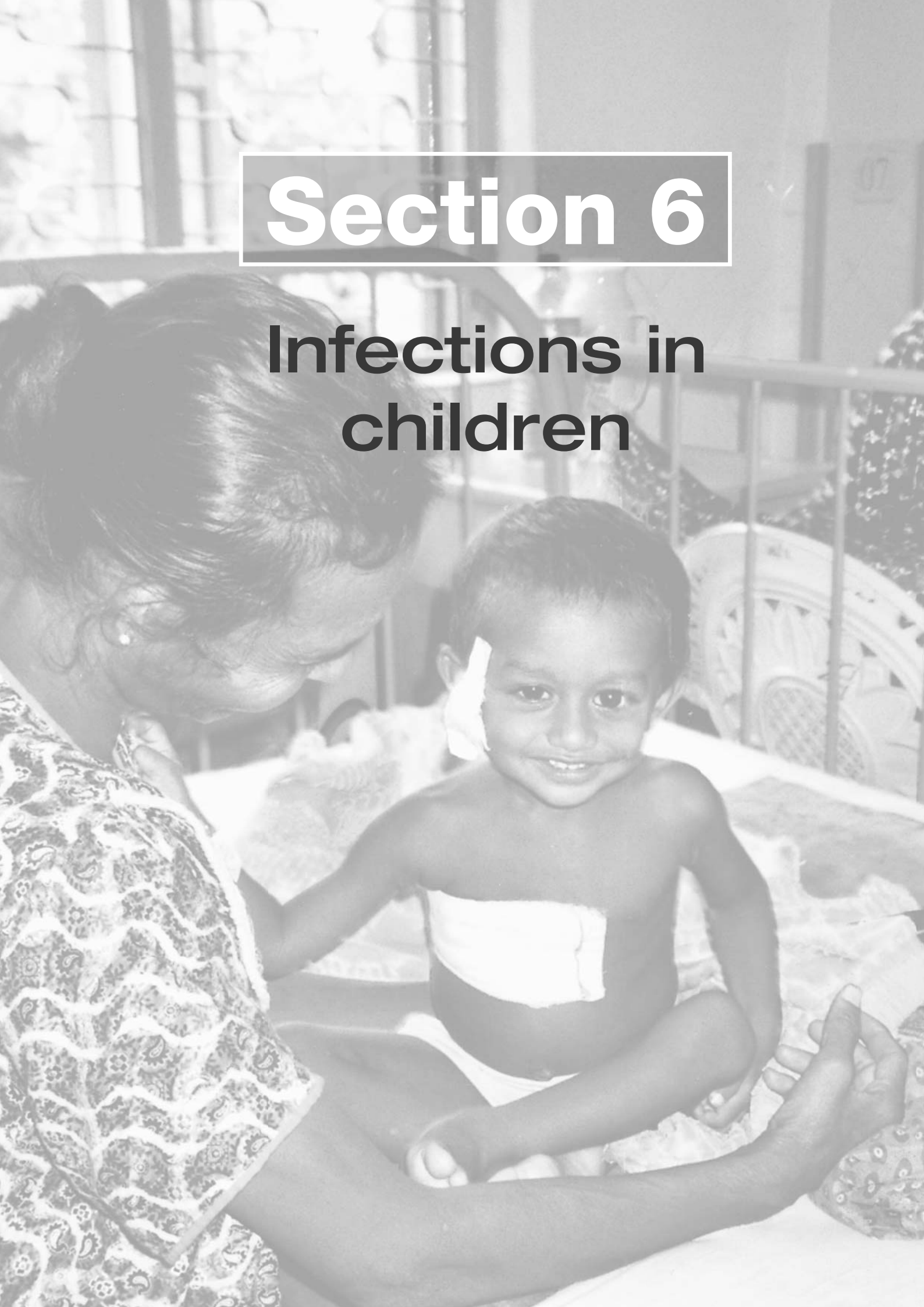


Section 6

Infections in children

6.1 Bacterial infections

6.1.A Botulism

BOX 6.1.A.1 Minimal standards
- Consider the diagnosis.
- Ideally give specific anti-toxin.
- Wound care when appropriate including antibiotics.
- High dependency care.

Introduction

Botulism intoxication is a rare, potentially fatal (5–10%) paralytic illness caused by botulinum toxin. The disease is caused by ingestion of the anaerobic *Clostridium botulinum* bacterium, which produces toxin in the intestinal tract or secretes the toxin directly into a wound. Person-to-person transmission of botulism does not occur.

Botulism can be prevented by killing the spores by pressure cooking or autoclaving at 121°C (250°F) for 3 minutes or providing conditions that prevent the spores from growing. Food-borne botulism results from contaminated foodstuffs in which *C. botulinum* spores have been allowed to germinate in anaerobic conditions. This typically occurs in home-canned food substances which have been inadequately heated and in fermented uncooked dishes. Given that multiple people often consume food from the same source, it is common for more than a single person to be affected simultaneously. Symptoms usually appear 12–36 hours after eating, but can also appear within 6 hours to 10 days.

Wound botulism results from the contamination of a wound with the bacteria, which then secrete the toxin into the bloodstream. Wounds may not be obviously or grossly infected but are usually deep and contain avascular areas.

The toxin, which is absorbed from the bowel or wound into the blood stream, causes paralysis by blocking the release of acetylcholine at the neuromuscular junction.

Signs and symptoms

Muscle weakness starts in the muscles supplied by the cranial nerves controlling eye movements, the facial muscles and the muscles controlling chewing and swallowing. Double vision, drooping of both eyelids, loss of facial expression and swallowing problems may occur, as well as difficulty with talking. The weakness then spreads to the arms (starting in the shoulders and proceeding to the forearms) and legs (again from the thighs down to the feet) (a symmetric descending flaccid paralysis in a proximal to distal pattern).

Severe botulism leads to reduced power in the muscles of respiration. There may be hypoventilation and difficulty coughing which when severe can lead to respiratory failure, coma from hypoxaemia and carbon dioxide retention and eventually death if untreated. Infants may present with prolonged apnoeic episodes.

Botulism can also cause disruptions to the autonomic nervous system. This is experienced as a dry mouth and throat (due to decreased production of saliva), postural hypotension (decreased blood pressure on standing, with resultant light-headedness and fainting), and eventually constipation (due to decreased bowel peristalsis). Some of the toxins (B and E) also precipitate nausea and vomiting.

The classic triad described is bulbar palsy and descending paralysis, lack of fever, and full consciousness.

Differential diagnosis

Botulism differs from other flaccid paralyses in that it always manifests initially with prominent cranial paralysis and its invariable descending progression, in its symmetry, and in its absence of sensory nerve damage.

In children the differential diagnosis is as follows:
- Guillain–Barré syndrome
- tick paralysis
- poisoning
- poliomyelitis
- psychiatric illness.

In infants it is as follows:
- meningitis
- electrolyte–mineral imbalance
- Reye's syndrome
- rare congenital abnormalities.

Infant botulism

Infants, especially those under 6 months of age, are susceptible to botulism. Infant botulism results from the ingestion of the *C. botulinum* spores, and subsequent colonisation of the small intestine. The composition of the intestinal microflora (normal flora) in infancy is insufficient to competitively inhibit the growth of *C. botulinum* and levels of bile acids (which normally inhibit clostridial growth) are lower than later in life. Ingestion of honey is a recognised source of botulism in infants.
- Typical symptoms of infant botulism include diminished suckling and crying ability (difficulty or poor feeding and an altered cry).
- Neck weakness progressing to generalised floppiness with a complete descending flaccid paralysis.
- Constipation. Although constipation is usually the first symptom of infant botulism, it is commonly overlooked.

Honey is the only known dietary reservoir of *C. botulinum* spores linked to infant botulism. For this reason honey should not be fed to infants under 1 year of age. Other

cases of infant and paediatric botulism are acquired from spores in the soil.

Complications

Botulism is very dangerous when affecting the respiratory system leading not only to respiratory failure, but also impaired clearing of secretions leading to pneumonia.

Laboratory confirmation is undertaken by demonstrating the presence of toxin in serum, stool, or food, or by culturing *C. botulinum* from stool, a wound or food.

However, laboratory testing may take hours or days. Initial diagnosis and appropriate treatment depend on clinical diagnosis through a thorough history and physical examination.

Diagnosis

Diagnosis is likely in resource-limited settings to be made on clinical grounds.

Consider diagnosing botulism if the patient's history and physical examination suggest botulism. However, other diseases such as Guillain–Barré syndrome, poliomyelitis and poisoning can appear similar to botulism, and special tests (when available) may be needed to exclude these other conditions. The presence of more than one affected family member is strongly suggestive of botulism.

A definite diagnosis can be made if botulinum toxin is identified in the food, wound or stool. Botulinum toxin can be detected by a variety of techniques, including enzyme-linked immunosorbent assays (ELISAs), electrochemiluminescent (ECL) tests and mouse inoculation or feeding trials.

Treatment

Botulinum antitoxin (if available) should be administered as soon as possible. Antitoxin does not reverse paralysis, but arrests its progression.

Before administration of antitoxin, skin testing should be performed for sensitivity to serum or antitoxin.

After skin testing, and ensuring that treatment for potential anaphylaxis is immediately available (adrenaline, IV fluids and bag-valve-mask), administration of one vial of antitoxin IV is recommended. There is no need to re-administer the antitoxin since the circulating antitoxins have a half-life of 5–8 days.

Close monitoring of respiratory function (including SpO_2 monitoring) is essential to detect respiratory failure. Physiotherapy to encourage deep breathing exercises may help to prevent retained secretions and pneumonia. When required, and available, artificial ventilation may be needed often for 2–8 weeks' duration in severe cases.

The treatment of children, pregnant women or immunocompromised patients with botulism does not differ from the above approach.

Antibiotics are required to remove the bacteria in cases of wound botulism. Oral (or intravenous) metronidazole (30 mg/kg per day, given at 6-hourly intervals; maximum 4 grams/day) is effective in decreasing the number of vegetative forms of *C. botulinum* and is the antimicrobial agent of choice. Penicillin V orally 25 mg/kg 6-hourly is an alternative treatment. Therapy for 10–14 days is recommended.

Other antibiotics may be required to treat secondary chest infections.

Remember that the child is fully conscious and can feel pain. Good nursing care is essential.

If a deep wound is thought to be responsible it should be treated to remove dead tissue and the source of the toxin-producing bacteria.

Each case of food-borne botulism is a potential public health emergency and it is important to identify the source of the outbreak and ensure that all persons who have been exposed to the toxin have been identified, and that no contaminated food remains.

6.1.B Buruli ulcer

BOX 6.1.B.1 Minimum standards

- WHO global public health initiative.
- Antibiotics: rifampicin, streptomycin and clarithromycin.
- Surgery.
- Dry reagent-based polymerase chain reaction (PCR) assay.

Introduction

Buruli ulcer is a highly destructive ulcerating condition caused by *Mycobacterium ulcerans*, which ranks third among mycobacterial infections affecting immunocompetent humans.

Any part of the body may be affected, particularly areas exposed to minor trauma. Management is a combination of medical treatment to eradicate the infective agent and surgical to excise the infected tissue.

Background and epidemiology

The disease occurs in several parts of Africa, Papua New Guinea, the Americas, South East Asia, China and Australia. The organism is found in soil or stagnant water and predominantly affects children in whom infection usually occurs following a minor penetrating injury.

Intercurrent helminthic infections may also predispose to ulceration. HIV infection, and other immunodeficiency states, can exacerbate Buruli ulcer and lead to severe complications.

Clinical features

A non-ulcerative lesion usually precedes ulceration. Four non-ulcerative presentations are recognised:

- **papule:** painless, may be itchy, non-tender intradermal lesion
- **nodule:** painless firm lesion 1–2 cm diameter in the subcutaneous tissue, usually attached to the skin

- **plaque:** painless well-demarcated elevated dry indurated lesion > 2 cm in diameter
- **oedematous:** diffuse extensive non-pitting swelling, ill-defined margin, firm, usually painful, with or without colour change over affected skin.

Subsequently an ulcer forms with central necrosis and often spreads very rapidly in all directions.

Characteristic features

- Ulcer is usually painless (hence delay in healthcare-seeking behaviour).
- Edge of ulcer is deeply undermined.
- Satellite ulcers often communicate with the original ulcer by subcutaneous tunnels.
- Skin between adjacent ulcers is often unattached to the underlying tissues.
- The extent of damage is always greater than it appears from the surface.
- Regional adenitis and systemic symptoms are unusual (and if present suggest primary or secondary bacterial infection).
- Erosion of underlying tissue may involve nerves, blood vessels and bone (in up to 15% of cases).

Complications

These include the following:

- tetanus
- osteomyelitis
- scarring
- ankylosis
- contractures.

Around 25% of patients develop long-term complications that may include amputation or loss of sight.

Differential diagnosis

- **Papule:** granuloma annulare, herpes, insect bites, leishmaniasis, acne, pityriasis, psoriasis.
- **Nodule:** boil, cyst, leishmaniasis, lipoma, lymphadenitis, mycosis, onchocerciasis.
- **Plaque:** cellulitis, haematoma, insect bites, leishmaniasis, leprosy, mycosis, psoriasis.
- **Oedema:** actinomycosis, cellulitis, elephantiasis, necrotising fasciitis, onchocerciasis, osteomyelitis.
- **Ulcer:** cutaneous diphtheria, guinea worm, leishmaniasis, necrotising fasciitis, neurogenic ulcer, tropical ulcer, tuberculosis, sickle-cell disease, squamous-cell carcinoma, syphilis, venous ulcer, cutaneous amoebiasis, yaws.

Investigations

- Slough from ulcer usually contains numerous acid-fast bacilli on Ziehl–Neelsen stain (sensitivity 40%).
- Culture unhelpful (sensitivity 20–60%, time consuming (8 weeks), expensive, frequently gives false-positive results).
- Biopsy and histopathology (sensitivity is 90%).
- Polymerase chain reaction (PCR) is increasingly used in diagnosis (it is rapid, only taking 2 days, and has a sensitivity of more than 95%). Recently, a highly sensitive dry reagent-based PCR assay has been developed that is better suited for use in most endemic countries.

Management

The current recommendation is for combined medical and surgical management.

1. **Small early lesion (e.g. nodules, papules, plaques, ulcers < 5 cm in diameter):** for papules and nodules, if immediate excision and suturing is possible, start antibiotics at least 24 hours before surgery and continue for 4 weeks. Otherwise, treat all lesions in this category with antibiotics for 8 weeks.
2. **Non-ulcerative and ulcerative plaque and oedematous form: large ulcerative lesions (> 5 cm in diameter): lesions in the head and neck region, particularly the face:** treat with antibiotics for at least 4 weeks, then surgery (if necessary), followed by another 4 weeks of antibiotics.
3. **Disseminated/mixed forms (e.g. osteitis, osteomyelitis, joint involvement):** treat with antibiotics for at least 1 week before surgery and continue for a total of 8 weeks.

Necrotic ulcers should be excised with care to remove all affected tissue by extending the margin into healthy tissue. Excision is followed by primary closure or split-skin grafting. Reconstructive surgery and physiotherapy may be required for patients with contractures and other permanent disabilities and disfigurements.

Antibiotics

Antibiotic combination treatment, by reducing ulcer size, makes larger ulcers more amenable to surgery and grafting.

Africa

Oral rifampicin (10 mg/kg) once daily plus intramuscular streptomycin (15 mg/kg) once daily for 8 weeks.

Overall treatment success rate 96% when used in conjunction with surgery depending on size of ulcer at presentation.

Note: for treatment of early (less than 6 months' duration) ulcers of limited size (< 10 cm), 4 weeks of streptomycin and rifampicin followed by 4 weeks of rifampicin and clarithromycin is as effective as 8 weeks of streptomycin and rifampicin.

Australia

Oral rifampicin plus one other oral antibiotic (either clarithromycin or ciprofloxacin) for 3 months:

1. when histology of resection margins shows either necrosis or acid-fast bacilli or granulomata, **or**
2. when initial lesion was large enough to require grafting, **or**
3. for complex recurrent disease.

Amikacin (IV) is recommended where surgical resection is necessarily incomplete.

Recommended antibiotics and doses for children are as follows:

- Rifampicin 10–20 mg/kg/day up to maximum 600 mg daily.
- Clarithromycin 15–30 mg/kg/day in two divided doses if under 12 years, up to a maximum of 500 mg twice daily if over 12 years.
- Ciprofloxacin 20 mg/kg/day in two divided doses, up to a maximum of 500–750 mg twice daily.

Prevention and public health aspects

Long trousers and other mechanical barriers.

BCG offers some protection.

The *Global Buruli Ulcer Initiative*, launched by the WHO in 1998, advocates the following:

- health education and staff training in the communities most affected
- development of educational materials adapted to the needs of the countries
- community-based surveillance system to increase early detection and referral for treatment in collaboration with diseases such as leprosy and Guinea worm
- assessment of local health services and resources currently available for the diagnosis and treatment of Buruli ulcer in endemic areas
- strengthening of the capacity of health systems in endemic areas by upgrading surgical facilities and improving laboratories
- rehabilitation of those already deformed by the disease.

6.1.C Diphtheria

BOX 6.1.C.1 Minimum standards

- ABC (especially airway protection).
- Immunisation and prophylaxis of contacts.
- Early parenteral antibiotics.
- Dexamethasone.
- Early antitoxin.
- Bed rest, close observation and ECG monitoring.
- Intubation/tracheostomy.

Introduction

In countries with adequate coverage of immunisation (over 70%), diphtheria is now uncommon. Epidemics still occur associated with a fall in level of immunisation, as happened in the mid-1980s and early 1990s in Russia and Ukraine and other republics of the former USSR. The disease affects all ages.

Epidemiology

- When levels of immunisation are low, children are the major group affected. Young infants are protected by maternal antibody.
- With improvement in immunisation rates, affected age groups shift to older children and adults. Boosters at school entry and school leaving are essential to provide adequate herd immunity.
- Mass movement of people, for example refugees or army personnel, are important sources of spread in epidemics.
- It is more common in autumn and winter.
- In tropical countries, skin infection by *Corynebacterium diphtheriae* provides a reservoir that results in natural immunity of the carrier and subclinical spread within the community.

Pathogenesis

C. diphtheriae invades the upper respiratory tract. The incubation period is 2–4 days.

TABLE 6.1.C.1 Clinical features of diphtheria

Site	Comments
Pharynx + + +	Affected in over 90% of cases
Tonsil ±	Yellow/white to grey/black (if haemorrhagic) thick membrane which extends beyond the tonsils and covers the adjacent pharyngeal wall. Bleeds when separated from underlying tissue. Pharyngeal membrane may extend to nares, palate or larynx. There may be distortion of soft palate, tonsils, etc. If confined to tonsils, little toxaemia
Nasal ±	Serosanguinous discharge, sore nose and lip Little toxaemia Highly infectious
Neck	Enlarged, tender cervical nodes, 'bull neck'
Skin 0– +	Any type of lesion (e.g. bites, impetigo) may be infected. May progress to ulcer with punched-out sharp edges. Important reservoir for transmission and natural immunisation. May result in respiratory colonisation
Other sites	Conjunctiva, ear and vulva
Levels of toxaemia 0, ±,+ +, + + +	Low-grade fever (rarely > 38.9°C) Weak, rapid pulse, limp, apathetic, restless Rarely haemorrhagic diathesis

- Diphtheria toxin causes necrosis and exudation in local tissue which results in formation of the 'membrane'. An attempt at removal of the membrane causes bleeding.
- Toxin is distributed by blood and lymphatic system resulting in toxaemia, and causing cardiac and neurological complications.
- Non-toxin-producing *C. diphtheriae* may cause focal disease but not cardiac and neurological complications. Vaccination does not protect against this organism.

TABLE 6.1.C.2 Complications of diphtheria

Complication	Weeks	Comments
Toxaemia	1	Related to extent of membrane and amount of toxin absorbed. May result in cardiovascular (CVS) collapse in first 10 days. Disseminated intravascular coagulation. Survivors of severe toxaemia usually have further CVS and neurological complications
Myocarditis	2–3 Range 1–6	Onset related to severity of toxaemia Soft first heart sound, apical systolic murmur ECG: conduction abnormalities, ST-T wave changes. **Echocardiogram:** left ventricular dilation, reduced contractility, hypertrophied left ventricle, sometimes pericardial fluid Biochemistry: **blood myoglobin levels elevated, elevated lactate dehydrogenase, elevated creatine phosphokinase** Mortality: high in early onset, severe carditis
Palatal paralysis	1	Probably due to local absorption of toxin: 'fluids come down nose' Resolves in a few days
Visual accommodation	4–5	Blurring of vision, sometimes strabismus
Bulbar, heart, respiratory and limb nerves	6–8	Bilateral, resolve completely if patient survives

Clinical features

Symptoms are initially due to disease of upper respiratory tract and associated toxaemia. Later symptoms relate to the level of toxin absorbed into the circulation. Cases with small membranes and low toxaemia recover spontaneously and most remain subclinical.

Diagnosis

- Unless all children with upper respiratory symptoms, including croup, have an appropriate examination, diphtheria will be missed.
- A portion of membrane or a swab taken from beneath it should be sent for Gram stain and culture. The laboratory should be informed of suspected diagnosis so that appropriate culture medium is used.

Management

See also Section 5.1.

The aim is to neutralise toxin released into blood by the bacillus and to kill the bacteria.

- Admit to isolation (on ICU if possible) cared for by staff who are fully immunised.
- Be prepared for intubation/tracheostomy, especially if laryngeal diphtheria is suspected.
- Dexamethasone (150 microgram/kg twice daily IV or orally) should be given in cases of moderate to severe airway obstruction and when there is swelling of the neck until airway obstruction resolves.
- Take great care when examining the throat or taking a sample of the membrane as it may precipitate complete airway obstruction.
- Give intravenous or nasogastric maintenance fluids if the child cannot drink.
- Give benzylpenicillin 50 mg/kg 4-hourly IV. Change to procaine benzylpenicillin 25 000–50 000 units/kg IM once daily (must not be given IV) when toxic symptoms have subsided or where toxicity is slight or, if the child can drink, to penicillin V 12.5 mg/kg 6-hourly. Erythromycin 40–50 mg/kg per day in four divided doses (maximum 2 grams/day) IV, and orally when child can swallow, is an alternative. Antibiotics should be given for 7–10 days.
- **Antitoxin must be given as soon as possible** (after the test dose). The dose is dependent on the severity of the disease rather than the site of the membrane, although the two usually coincide:
  - Nasal and tonsillar (mild disease): 20 000 units IM.
  - Laryngeal with symptoms (moderately severe): 40 000 units IM or IV.
  - Nasopharyngeal (moderately severe): 60 000–100 000 units IV depending on severity and combined sites/delayed diagnosis (malignant disease), also 60 000–100 000 units IV.
  - In practice, give 60 000 units to all cases with visible membrane and neck swelling.

Commercially available antitoxin is extremely expensive but highly purified. Some countries (e.g. Vietnam) make their own antitoxin but it is much **less purified** than the Aventis Pasteur vaccine for example, and **cannot be given intravenously**.

Test dose and desensitisation

See also *Section 5.1.B on anaphylaxis.*

- As antitoxin is from horse serum, a test dose with 0.1 mL of 1 in 1000 dilution in saline is given intradermally.
  - Positive reaction is 10 mm erythema occurring within 20 minutes.
  - If there is no reaction, give full-dose IV/IM as appropriate.
- Have adrenaline 1 in 1000 and syringe available to give IM if anaphylaxis occurs (10 micrograms/kg).
- Desensitisation: (if test dose is positive) give graduated doses of increased strength every 20 minutes commencing with:
  - 0.1 mL of 1 in 20 dilution in saline subcutaneously followed by 1 in 10 dilution
  - then 0.1 mL of undiluted subcutaneously, then 0.3 mL and 0.5 mL IM
  - then 0.1 mL undiluted IV.

Additional treatment

- Give oxygen if cyanosed or SaO_2 < 94%. Use nasal cannulae or a face mask held close to the child's face by the mother. **Do not use nasal or nasopharyngeal catheters** as these can precipitate complete airway obstruction. Be aware that giving oxygen does **not** compensate for hypoventilation which, if severe, will require intubation and cricothyroidotomy or tracheostomy (*see* Section 8.2). Note that intubation may dislodge the membrane, causing complete airway obstruction.
- Bed rest and observation for 2–3 weeks at least, depending on severity.
- Regular monitoring of cardiac function. Serial ECGs two or three times per week through the critical period from admission until towards the end of the second week of illness. Rhythm disturbances, particularly atrioventricular block sometimes going on to complete heart block are not uncommon, and are often the earliest evidence of cardiac involvement.
- With severe cardiac involvement (which often follows from severe local disease) the children develops a low-output state and may die from cardiac failure or arrhythmias. Poor urine output and rising creatinine are early indicators of poor prognosis and should be monitored, together with serum potassium which should be kept in the normal range (*see* Section 9.A). Strict bed rest is essential for all children until the critical period for cardiac complications has passed (minimum of 2 weeks from onset).
  - Captopril at the earliest sign of any cardiac involvement may be helpful (100 micrograms/kg once daily as a test dose with the child supine and monitoring blood pressure carefully, followed by 100–200 micrograms/kg 8-hourly).
  - Prednisolone 1.5 mg/kg/day for 2 weeks may be of value in reducing the incidence of myocarditis.
- Nasogastric feeds if palatal or bulbar paralysis occurs. Bulbar problems rarely become evident until several weeks later, so even if children come through the phase of upper airway obstruction and survive the cardiac problems, they should remain in close contact with the hospital for at least 6 weeks.
- Immunise on discharge.

Prevention

- Maintaining immunity at all age levels in the community is important. Additional immunisation at school entry and leaving (*see* Section 1.17).
- Give immunised household contacts a booster of toxoid.
- Give all unimmunised contacts one dose of IM benzathine benzylpenicillin (600 000 units for children under 5 years and 1.2 million units for those over 5 years). This drug must not be given IV. Immunise and check daily for signs of diphtheria.

6.1.D Leprosy

BOX 6.1.D.1 Minimum standards

- Public health measures.
- Clinical awareness.
- Multi-drug treatment (MDT) with rifampicin, dapsone and clofazimine.
- Protective footwear,
- Support and counselling.
- Reconstructive surgery.

Introduction

A campaign to eliminate leprosy below a prevalence of 1 in 10 000 greatly reduced total numbers, but new cases, especially in India and Brazil, are still being detected in worryingly large numbers. It remains the prototype of a disfiguring skin disease. It is caused by *Mycobacterium leprae*, an organism that invokes an immunological response in the skin and especially focusing on superficial cutaneous nerves, resulting in anaesthesia and paralysis of hand, foot and facial muscles. There is a range of disease from an effective immune response with few surviving bacteria termed paucibacillary leprosy, to a poor immune response with very large numbers of bacteria termed multibacillary leprosy. Unfortunately, the present public health picture of leprosy is that the majority of new cases are multibacillary and the percentage of children affected is greater than before. The incubation period is very long (up to 8–10 years) and disability is often present by the time it is diagnosed.

In countries where the prevalence is low, leprosy may be forgotten and those trained to recognise it disbanded. The expectation is that general health services will oversee the patient as he or she moves from an anxious family to a traditional health practitioner to a health centre. The latter will be overwhelmed by common skin disease such as impetigo, cutaneous fungus disease and scabies, and current policy is to train all health workers in health centres to manage these correctly and thereby increase the likelihood of detection and better management of rarer diseases such as leprosy. Conditions not diagnosed or not responding should be guided through an effective referral system to greater expertise.

The global registered prevalence of leprosy at the beginning of 2009 stood at 213 036 cases, while the number of new cases detected during 2008 was 249 007. The number of new cases detected globally has fallen by 9126 (a 4% decrease) during 2008 compared with 2007.

Pockets of high endemicity still remain in some areas of Angola, Brazil, Central African Republic, Democratic Republic of Congo, India, Madagascar, Mozambique, Nepal, and the United Republic of Tanzania.

Diagnosis

At one end of the clinical spectrum of leprosy is an early single lesion with very few bacilli which may resolve spontaneously and certainly responds well and quickly to antibiotics. It is hypopigmented, flat and insensitive to light touch, pinprick and hot and cold.

The spectrum passes through an increasing number of such lesions that are unlikely to resolve spontaneously, and

increasingly, over a period of years, infiltration and swelling which is often nodular, from asymmetry to symmetry, to greater numbers of bacilli, to eventual widespread infiltration of the skin. The bacteria are shed into the environment from the nose and wounds.

Early diagnosis requires a full examination of all the skin, tests of any suspicious lesion for numbness, and a biopsy of infiltrated lesions, especially nodules, the presence of a granuloma alerting to the need for bacterial stains.

Cutaneous nerves, ulnar, radial, posterior cervical, lateral popliteal and muscular cutaneous on the dorsum of the foot must be palpated for thickening. Early signs include flexion of the fourth and fifth finger, dropped foot, and reduction in blinking.

Differential diagnosis

Vitiligo is totally de-pigmented, whiter than leprosy and usually symmetrical. There is no sensory loss. It is long lasting.

Pityriasis alba is very common, mild, dry eczema, usually symmetrical on both cheeks and the extensor surface of both limbs. It varies over days or weeks and responds to moisturising ointments or hydrocortisone.

Pityriasis versicolor is a common infection of the skin from *Malassezia furfur* producing depigmentation and fine scaling especially of the upper trunk. The organism and the slight inflammation it causes accounts for a dull red to brown discolouration of white skin. Pigmented skin loses pigment due to exfoliation. It responds to selenium sulphide shampoo, Whitfields (benzoic acid and salicylic acid) ointment or ketoconazole, plus sun exposure for rapid re-pigmentation.

Post-inflammatory depigmentation is preceded by undisputed injury such as a burn, chickenpox, fungal infection or psoriasis. There may be loss of normal skin texture as in a scar.

Reactions

Reactions are immunological responses to *Mycobacterium leprae* or its antigen. There are two types.

Erythema nodosum-like with multiple tender, symmetrical red lumps anywhere in the skin due to immune complexes and accompanied by fever and malaise. It often responds to rest and non-steroidal anti-inflammatory drugs but persistent reactions will need oral steroids. There is usually a history of prior diagnosis of leprosy.

The other type of reaction is focused on a previous plaque or infected nerve. There is redness, swelling and tenderness. It is destructive of nerves. An early prescription of an initially high dose of prednisolone is necessary (1 mg/kg/day). Complete withdrawal of steroids should only occur after several weeks if nerve destruction is to be avoided

Treatment

Multidrug therapy cures leprosy. Multidrug therapy should be given under supervision by experts able to provide full advice on the preventive management of disability, who may confirm the diseases by skin smears or biopsies and can manage reactions. Standard drug therapy is available free from government programmes for the elimination of leprosy. WHO guidelines for multidrug therapy include a single dose for a single lesion, or two drugs for lesions which contain more than one bacteria. A daily regimen for 1 year of three drugs is necessary for more widespread multibacillary disease. Lepromatous leprosy is subject to reaction even after 1 year of therapy and patients must be educated to return for diagnosis and appropriate therapy promptly. Relapse after completion of therapy is uncommon but well documented.

WHO-recommended treatment for paucibacillary leprosy in children (10–14 years)

Once a month: On day 1, two capsules of rifampicin (300 mg + 150 mg) plus one tablet of dapsone (50 mg).

Once a day: On days 2–28, one tablet of dapsone (50 mg).

Full course: six blister packs over 6 months.

For children younger than 10 years, the dose must be adjusted according to body weight.

WHO recommended treatment for multibacillary leprosy in children (10–14 years)

Once a month: On day 1, two capsules of rifampicin (300 mg + 150 mg) plus three capsules of clofazimine (50 mg × 3) plus one tablet of dapsone (50 mg).

Once a day: On days 2–28, one capsule of clofazimine every other day (50 mg), plus one tablet of dapsone (50 mg) daily.

Full course: 12 blister packs over 12 months.

For children younger than 10 years, the dose must be adjusted according to body weight.

Children may be more troubled by the haemolytic side effect of dapsone, and are less tolerant to rifampicin. New drug regimens include ofloxacin, minocycline and clarithromycin. Several experimental and clinical studies have demonstrated that these drugs either alone or in combination with other anti-leprosy drugs have significant bactericidal activity. Patients presenting with single skin lesion paucibacillary leprosy can be treated with only one dose containing rifampicin 20 mg/kg, ofloxacin 15 mg/kg and minocycline 100 mg (only for children over 12 years).

Multibacillary leprosy patients who do not accept clofazimine can be treated with this combination given monthly for 24 months.

There is still a fear of the stigma of leprosy. The emphasis of therapy is that it is a cure and rapidly renders the patient non-infectious.

Support and counselling is necessary for the patient along with education for family and community, or else the cured patient may still not be acceptable to either family or community.

6.1.E Leptospirosis

BOX 6.1.E.1 Minimum standards
- Recognition and treatment of shock.
- Antibiotics: amoxicillin, penicillin (parenteral for severe disease), doxycycline.
- Public health measures.

Introduction

Leptospirosis is a zoonotic disease caused by *Leptospira* species with a worldwide distribution. It is endemic in the tropics and its incidence in these countries appears to be increasing. The possible reasons include an increase in the rat population and seasonal flooding. Transmission to humans is from infected animal urine. The onset is usually abrupt. It is an acute febrile disease with varied manifestations characterised by vasculitis. The severity of disease ranges from asymptomatic or subclinical to self-limited systemic illness (approximately 90% of patients) to life-threatening illness with jaundice, renal failure, and hemorrhagic pneumonitis. The clinical course is usually biphasic and with multisystemic involvement. The initial (septicaemic) phase lasts 4–7 days, the second (immune) phase 4–30 days. It can be lethal in the acute period, and is similar to diseases such as dengue, malaria, hepatitis and viral illnesses.

Risk factors for infection include occupational exposure (farmers, ranchers, abattoir workers, veterinarians, loggers, sewer workers, rice field workers, laboratory workers), recreational activities (fresh water swimming, canoeing, trail biking), household exposure (pet dogs, domesticated livestock, rainwater catchment systems, and infestation by infected rodents), and skin lesions (contact with wild rodents).

History and examination

- **Enquire about** headache, fever, abdominal pain, breathing difficulties and cough, diuresis, bleeding, diarrhoea or vomiting.
- **Assess** vital signs (blood pressure, pulse, respiratory rate), 'alarm signs', blood film for malaria parasite. Consider dengue fever.
- **Watch out for** 'alarm signs' of leptospirosis: abdominal pain, respiratory distress, jaundice, bleeding and oliguria.

Clinical manifestations

Leptospirosis is associated with a variable clinical course. The disease may manifest as a subclinical illness followed by seroconversion, a self-limited systemic infection, or a severe, potentially fatal illness accompanied by multiorgan failure. Physical examination is often unrevealing. An important but frequently overlooked sign is **conjunctival suffusion**.

Below are common clinical manifestations:

- **General symptoms:** headache, myalgia, vomiting and anorexia, arthralgia, macular rash.
- **Central nervous system:** CSF pleocytosis and elevated protein, meningism, neurological symptoms.
- **Renal system:** pyuria, haematuria, proteinuria, oliguria/anuria, dysuria, back pain.
- **Gastrointestinal system:** abdominal pain, diarrhoea, constipation, abnormal liver function tests, hepatomegaly, jaundice, gastrointestinal bleeding.
- **Respiratory system:** cough, pharyngitis, otitis media, chest pain, pneumonitis, pulmonary oedema and haemoptysis.
- **Cardiac system:** arrhythmias, conduction and other ECG abnormalities.
- **Haematology:** blood clotting disorder, petechiae, bruises, epistaxis, thrombocytopenia, lymphadenopathy, splenomegaly.
- **Eyes:** conjunctival bleeding, photophobia, retro-orbital pain, uveitis, papilloedema.

Classification

- **Mild disease:** headache, fever, myalgia, no evidence of bleeding.
- **Moderate disease:** headache, fever, myalgia, abdominal pain and jaundice.
- **Severe disease:** Weil's disease or icterohaemorrhagic fever: shock, abdominal pain, respiratory failure, pulmonary haemorrhage, acute renal failure, altered consciousness and bleeding.

Diagnosis

1 **Clinical:** Features that are significantly associated with leptospirosis include:
   - conjunctival suffusion
   - haemorrhage
   - abdominal pain
   - hepatosplenomegaly
   - oedema.

2 **Laboratory:**
   - **Cultures:** blood culture in initial phase and urine in the second phase. Blood (50% yield) and CSF specimens are positive during the first 10 days of the illness. Urine cultures become positive during the second week of the illness.
   - **Serology:** Serological tests (microscopic agglutination test (MAT), macroscopic agglutination test, indirect haemagglutination, and enzyme linked immunosorbant assay – ELISA) are most often used for confirmation.
     – The gold standard is considered to be the MAT. However, this test is cumbersome which requires live organisms, considerable expertise, and is performed only by reference laboratories. MAT is most specific when a fourfold or greater rise in titre is detected between acute and convalescent serum specimens. However, a single titre of > 1:800 is strong evidence of current or recent infection with leptospira.
     – Rapid diagnosis with specific IgM (ELISA) can be made by two commercially available rapid tests, the microplate IgM ELISA and an IgM dot-ELISA dipstick test. If one of these assays is positive, sera for MAT can be sent to a reference laboratory.
     – **Newer tests:** Polymerase chain reaction (PCR), not widely available, but shows considerable promise for a quick, accurate diagnosis.

- **Routine labs:** white blood cell (WBC) counts may range between 3000 and 26 000/microlitre; thrombocytopenia, raised serum bilirubin, hyponatremia, proteinuria, pyuria, microscopic haematuria, elevated creatine kinase and minimal to moderate elevations of hepatic transaminases may be seen.

3 **X-rays:** chest radiographs may show small nodular densities, confluent consolidation or a ground-glass appearance.

Differential diagnosis

Malaria, dengue fever, scrub typhus, acute viral illnesses including influenza, other rickettsial disease, typhoid fever and rare causes such as ehrlichiosis and hantavirus infections.

Complications

These include renal failure, uveitis, haemorrhage, acute respiratory distress syndrome, myocarditis and rhabdomyolysis. Vasculitis with necrosis of extremities may be seen in severe cases. Severe leptospirosis may require ICU admission. Multi-organ failure in 75% and mortality in over 50% of these patients may be seen.

Management

The majority of *Leptospira* infections are self-limiting. Many antibiotics have antileptospiral activity, and if the illness is severe and the diagnosis is recognised, antibiotic therapy should be given.

Mild disease:

- Discharge home with advice about hydration and 'alarm signs'.
- Antibiotics:
  - Children under 10 years of age: amoxicillin 15 mg/kg three times daily for 7 days or, if allergic, erythromycin 10–15 mg/kg/day three times daily for 7 days.
  - Children over 10 years: doxycycline 100 mg twice daily for 7 days.

Moderate disease:

- Observe for 48 hours, monitor vital signs 4-hourly.
- If abdominal pain and respiratory distress settle, discharge.
- Antibiotics: benzylpenicillin 25–50 mg/kg IV 6-hourly for 3 days, then change to oral penicillin. Amoxicillin is an alternative.

Severe disease:

- Give oxygen as required, IV fluids (*see* Section 5.5), and pass a nasogastric tube.
- Keep an accurate fluid-balance chart.
- Pulmonary haemorrhage may require assisted ventilation with PEEP.
- Pulmonary oedema: treat with fluid restriction, oxygen and diuretics.
- Management of disseminated intravascular coagulation, renal failure and myocarditis.
- Antibiotics: Intravenous therapy with benzylpenicillin (250 000 to 400 000 units/kg/day in four to six divided doses; maximum dose 6 million units daily: note 600 mg = 1 million units), or doxycycline (4 mg/kg/day in two equally divided doses; maximum dose 200 mg daily), or ceftriaxone (80–100 mg/kg once daily; maximum dose 4 grams daily), or cefotaxime (150–200 mg/kg/day in three to four equally divided doses; maximum dose 12 grams daily). Doxycycline should be avoided in children less than 8 years of age.
- For children less than 8 years of age with severe penicillin allergy, therapy with oral azithromycin (10 mg/kg once on day 1, maximum dose 500 mg/day, followed by 5 mg/kg/day once daily on subsequent days, maximum dose 250 mg/day) or oral clarithromycin (15 mg/kg/day divided into two equal doses, maximum dose 1 gram/day) may be given.
- The duration of treatment is usually 5–7 days.

Prevention

Vaccination of domestic animals against leptospirosis provides substantial protection. The major control measure is to avoid potential sources of infection such as stagnant water, water derived from run-off from animal farms, rodent control, and protection of food from animal contamination.

Currently no vaccine is available for human immunisation, but doxycycline prophylaxis during period of exposure has been shown to be protective.

6.1.F Lyme disease

BOX 6.1.F.1 Minimum standards
Antibiotics: doxycycline, amoxicillin and ceftriaxone.

Introduction

This disease is caused by the bacterium *Borrelia*. *Borrelia burgdorferi* is the main cause in North America, whereas *Borrelia afzelii* and *Borrelia garinii* cause most European cases. The prevalence of Lyme disease in sub-Saharan Africa is presently unknown, but cases have been reported. The abundance of hosts and tick vectors would support the presence of this infection in Africa where it is probably grossly under-diagnosed.

Transmission

Lyme disease is transmitted to humans from a natural reservoir among rodents by ticks that feed on both rodents and other animals, such as deer.

Tick bites often go unnoticed because of the small size of the tick in its nymphal stage, as well as tick secretions that prevent the host from feeling any itch or pain from the bite. However, transmission is quite rare, with only about 1% of recognised tick bites resulting in Lyme disease. This may be because an infected tick must be attached for at least a day for transmission to occur.

Days to weeks following the tick bite, the spirochetes spread via the bloodstream to joints, heart, nervous system,

and distant skin sites, where their presence gives rise to the variety of symptoms of disseminated disease.

If untreated, the bacteria may persist in the body for months or even years, despite the production of antibodies against *Borrelia* by the immune system.

Diagnosis

Lyme disease is diagnosed clinically based on symptoms, objective physical findings (such as erythema migrans (EM), facial palsy or arthritis) or a history of possible exposure to infected ticks, as well as serological blood tests. The EM rash is not always a bull's-eye (see below) (i.e. it can be red all the way across). When making a diagnosis of Lyme disease, healthcare providers should consider other diseases that may cause similar illness. Not all patients infected with Lyme disease will develop the characteristic bull's-eye rash, and many may not recall a tick bite.

Signs and symptoms

Many of the symptoms are not specific to Lyme disease.

The incubation period from tick bite to the onset of symptoms is usually 1–2 weeks, but can be much shorter (days), or much longer (months).

Early localised infection

The classic sign of early local infection with Lyme disease is a circular, outwardly expanding rash called erythema chronicum migrans (also erythema migrans or EM), which occurs at the site of the tick bite 3–30 days after the bite. The rash is red, and may be warm, but is generally painless. Classically, the innermost portion remains dark red and becomes thicker and firmer; the outer edge remains red; and the portion in between clears, giving the appearance of a bull's-eye. EM is thought to occur in about 80% of infected patients. Patients can also experience flu-like symptoms, such as headache, muscle soreness, fever, and malaise. Lyme disease can progress to later stages even in patients who do not develop a rash.

Early disseminated infection

Within days to weeks after the onset of local infection, the *Borrelia* bacteria begin to spread through the bloodstream. EM may develop at sites across the body that bear no relation to the original tick bite. Other discrete symptoms include migrating pain in muscles, joints, and tendons, and heart palpitations and dizziness.

Various acute neurological problems appear in 10–15% of untreated patients. These include facial palsy, arthritis and meningitis. Radiculoneuritis causes shooting pains that may interfere with sleep, as well as abnormal skin sensations. Mild encephalitis may lead to memory loss, sleep disturbances, or mood changes.

The disease may also have cardiac manifestations including cardiac arrhythmias.

Late disseminated infection

After several months, untreated or inadequately treated patients may go on to develop severe and chronic symptoms that affect many parts of the body, including the brain, nerves, eyes, joints and heart. Many disabling symptoms can occur.

Chronic encephalomyelitis, which may be progressive, can involve cognitive impairment, weakness in the legs, awkward gait, facial palsy, bladder problems, vertigo, and back pain. In rare cases untreated Lyme disease may cause frank psychosis, which has been misdiagnosed as schizophrenia or bipolar disorder. Panic attacks and anxiety can occur; there may also be delusional behaviour, including somatoform delusions, sometimes accompanied by a depersonalisation or derealisation syndrome, where the patients begin to feel detached from themselves or from reality.

Lyme arthritis usually affects the knees.

Treatment

In most cases, the infection and its symptoms are eliminated by antibiotics, especially if the illness is treated early. Delayed or inadequate treatment can lead to the more serious symptoms, which can be disabling and difficult to treat.

The antibiotics of choice for early infections are given orally for 10–28 days:

1. In children over 8 years: doxycycline, 4 mg/kg/day in two divided doses (maximum of 100 mg per dose).
2. In younger children (less than 8 years): amoxicillin 50 mg/kg/day in three divided doses. Doxycycline should not be given in pregnancy, instead use amoxicillin 250–500 mg three times daily for pregnant girls. If early infection is severe, ceftriaxone 50 mg/kg IV/IM once daily can be given at any age.

Late-diagnosed chronic Lyme disease is treated with oral or intravenous antibiotics for a minimum of 4 weeks, frequently ceftriaxone 50–75 mg/kg once a day IV.

6.1.G Meningococcal disease

BOX 6.1.G.1 Minimum standards

- Early parenteral antibiotics.
- Treatment of shock.
- Neurological assessment and cerebral protection.
- Frequent reassessment of clinical status.
- Electrolyte monitoring and replacement.
- Replacement of platelets, clotting factors and red cells.
- Follow public health procedures.

Introduction

Meningococcal disease is caused by *Neisseria meningitidis*, a Gram-negative diplococcus which is a commensal of the human nasopharynx. Endemic meningococcal disease primarily affects children under 5 years old. Some areas, in particular the meningitis belt in sub-Saharan Africa, suffer from epidemics of meningococcal disease. Temperate climates usually experience an increase in disease during winter months, whereas in sub-Saharan Africa, conditions during the dry season cause a sharp rise in incidence.

Predominant disease-causing organisms are serogroups A, B and C and W135, with other serogroups generally only causing infection in specific patient groups (e.g. complement deficiency and the immunocompromised). Serogroup A is associated with epidemic disease in the meningitis belt of Africa, Middle East and southern Mediterranean regions, and less commonly in other developing countries. Serogroups B and C are largely responsible for endemic disease in temperate countries, although serogroup C is now less common in countries where the serogroup C vaccine has been widely introduced.

TABLE 6.1.G.1 Signs and symptoms of meningococcal meningitis and septicaemia

Meningococcal meningitis	Meningococcal septicaemia
Symptoms	*Symptoms*
Fever	Fever
Headache	Petechial/purpuric rash
Nausea and vomiting	Shivering/rigors
Rash	Malaise and lethargy/ confusion
Drowsiness or irritability	Headache
Neck and back pain, and stiffness	Nausea and vomiting
Convulsions	Limb and joint pain
Signs	Absence of neck stiffness
Fever	Collapse
Non-blanching rash	*Signs*
Neck stiffness/positive Kernig's sign/opisthotonus	Fever
Decreased conscious level	Petechial/purpuric rash
Infants	Shock:
Signs of meningitis may be non-specific with neck stiffness frequently absent.	Tachycardia
Bulging fontanelle may be present.	Low pulse volume
Suspect meningitis in any febrile infant, especially where there is marked irritability, vomiting and poor feeding	Cool peripheries
Both meningitis and septicaemia can coexist in the same child.	Capillary refill time > 3 seconds
	Hypotension (late sign)
	Urine output reduced (< 1 mL/ kg/hour)
	Tachypnoea
	Hypoxaemia
	Decreased conscious level

Clinical features

In general, meningococcal disease presents either as **meningitis** or as **meningococcal septicaemia**, although many patients present with a mixed picture. In developed countries, the majority of cases may present with septicaemia and frequently with shock, whereas in African serogroup A epidemics, meningitis is the commonest presentation.

Meningococcal disease should be suspected in any patient who presents with a non-blanching (petechial or purpuric) rash. However, 13% of cases may present with a maculopapular rash and 7% may have no rash. Severity of rash does not correlate with severity of disease.

Life-threatening features of meningococcal disease

- **Shock:** particularly uncompensated shock (hypotension and tachycardia). Shock causes the majority of deaths due to meningococcal disease and is a medical emergency.
- **Raised intracranial pressure:**
  - Decreased conscious level (Glasgow Coma Scale score or Modified Children's Coma Score < 8 or deteriorating).
  - Focal neurological abnormalities, especially false localising signs (e.g. pupillary dilatation).
  - Abnormal postures (decorticate or decerebrate).
  - Convulsions.
  - Rising blood pressure with falling pulse rate.

CSF features consistent with meningococcal meningitis

- Turbid or purulent (may be clear or blood stained), white blood cell count > 500 cells/mm^3 (< 3 cells/mm^3 in normal CSF).
- Protein usually > 0.8 grams/litre (< 0.6 grams/litre in normal CSF).
- Glucose reduced compared with blood glucose concentration.
- Gram-negative diplococci (intra- or extracellular) in 72% of previously untreated cases.

When not to perform a lumbar puncture

Lumbar puncture may precipitate coning if there is significantly raised intracranial pressure. In septicaemia, lumbar puncture is unlikely to be helpful and may cause rapid deterioration in an unstable child.

Contraindications to lumbar puncture: suspected critically raised intracranial pressure

- Glasgow Coma Scale score/Modified Children's Coma Score < 8 (or if child is unresponsive to pain).
- Focal neurological signs, including pupillary abnormalities.
- Unexplained hypertension/bradycardia.
- Shock (see below).
- Significant clotting disorder or low platelet count (50 × 10^9/litre) is present.

Management of meningococcal disease

See Section 5.16.B for a discussion of isolated meningococcal meningitis.

Principles

In suspected cases, give an injection of benzylpenicillin before transfer of child to hospital. Recommended doses of benzylpenicillin by age group are as follows:

- < 1 year: 300 mg
- 1–10 years: 600 mg
- > 10 years: 1.2 grams.

On admission, early antimicrobial therapy should be given, such as benzylpenicillin with chloramphenicol (for dose and alternatives, *see* Table 6.1.G.3). Ideally this should be given intravenously, but if this is not possible it can be given intramuscularly.

Close monitoring and aggressive supportive therapy

TABLE 6.1.G.2 Investigations in meningococcal disease

Investigations		Comment
Microbiology	Lumbar puncture†	For Gram stain and culture (remember contraindications for performing lumbar puncture)
	Throat swab	Culture*
	Blood culture	Gold standard diagnostic test for septicaemia, positive in 30% or more of previously untreated cases
Special microbiology: advanced methods	Meningococcal serology: CSF or blood. Meningococcal PCR	Acute and convalescent blood samples required
Haematology	Full blood count	Low haemoglobin In early septicaemia or in lone meningitis usually high neutrophil count. Low white cell count with neutropenia in severe septicaemia. Low platelet count ($< 50 \times 10^9$/litre) in disseminated intravascular coagulation
	Coagulation screen	Prolonged PT, KCTT and TT Raised fibrin degradation products
Biochemistry	Urea, creatinine, electrolytes including calcium, magnesium, phosphate	Hypokalaemia Hypocalcaemia Hypophosphataemia Metabolic acidosis Raised urea and creatinine (if severe, suspect pre-renal failure)

* Meningococci should be cultured on Mueller–Hinton or chocolate agar to identify and serogroup with antibiotic sensitivities.

† Where laboratory facilities are scarce, diagnosis of meningitis is made on CSF alone: appearance, cell count, glucose sticks, Albustix.

are needed if features of shock or raised intracranial pressure develop.

Never delay antimicrobial therapy if facilities are not available for immediate lumbar puncture or blood culture.

The most appropriate available antibiotic should be used. In general, intravenous benzylpenicillin with intravenous chloramphenicol are the drugs of choice where meningococcal disease is the most likely diagnosis. Where the diagnosis is uncertain, or where there is a high prevalence of penicillin resistant meningococci, broad-spectrum antibiotics should be used (*see* Table 6.1.G.3), ideally including a third-generation cephalosporin.

Do not delay administration if cefotaxime or ceftriaxone are unavailable (use benzylpenicillin, ampicillin or chloramphenicol instead for the initial dose).

The risk of transmission disappears after 24–48 hours of antibiotic therapy. Isolation is not essential, but staff should maintain good hygienic practice and wear masks and gloves during invasive procedures such as intubation, airway and mouth care, and line insertion.

Parenteral antibiotic treatment should be given for 7–14 days if the diagnosis of meningococcal disease is certain. Once culture and sensitivity results are available, treatment should be modified appropriately.

TABLE 6.1.G.3 Antibiotic doses in meningococcal disease

Antibiotic	Route	Dose and frequency
Ampicillin	IV	400 mg/kg/24 hours in four divided doses (maximum single dose 3 grams)
Benzylpenicillin	IV	300 mg/kg/24 hours in six divided doses (maximum single dose 2.4 grams)
Cefotaxime	IV	200 mg/kg/24 hours in four divided doses (maximum single dose 4 grams)
Ceftriaxone	IV/IM	80 mg/kg/24 hours once daily (maximum single dose 4 grams)
Chloramphenicol	IV	100 mg/kg/24 hours in four divided doses*
	Oral	100 mg/kg/24 hours in four divided doses†

* Chloramphenicol should be used with caution in infants less than 3 months of age. Monitoring of serum levels is recommended, and lower doses with wider dosage intervals may be required.

† Oral chloramphenicol is usually used only following 3–4 days of parenteral antibiotics. Although not recommended for children less than 3 months of age or in malnourished children, the evidence for harmful effects is slight.

Important notes

- Early recognition of life-threatening disease (shock and raised intracranial pressure) is vitally important. There is a very high risk of death if patients are not resuscitated aggressively at presentation.
- Assess airway patency, breathing and circulation (ABC) and examine for signs of shock and raised intracranial pressure (see above). Management regimens differ for different presentations: shock; raised intracranial pressure; meningitis uncomplicated by either shock or raised intracranial pressure.
- Many children present with a mixed picture and may require treatment of shock as well as management of neurological complications.

- Meningococcal disease is often progressive and patients may continue to deteriorate after antibiotic and supportive therapy have been initiated. All suspected cases should be closely monitored for cardiovascular and neurological deterioration for at least 24 hours.
- Management of children with severe shock or raised intracranial pressure who do not respond fully to initial resuscitation is complex. Every effort should be made to admit these patients to an appropriate intensive-care facility.

Shock

This is a medical emergency (*see also* Section 5.5.A and 5.5.C)

- Assess **ABC** and give high-flow oxygen.
- Check blood glucose levels (e.g. using BM Stix).
- Obtain intravenous or intra-osseous access.
- Take blood for culture, full blood count, grouping and cross-matching, coagulation screen, and urea and electrolytes.
- Commence appropriate intravenous antibiotics.
- Do not perform a lumbar puncture.
- Commence fluid resuscitation immediately using 20 mL/kg of crystalloid or colloid given as fast as possible. Reassess and use further fluid boluses of 20 mL/kg if signs of shock persist. Use either Ringer-lactate or Hartmann's solution (or 0.9% saline if neither of these are available) or other non-glucose-containing crystalloid or a colloid such as 4.5% human serum albumin.
- Blood products such as packed cells, plasma and platelets may be required. Arrange for supplies if available.
- Patients who remain shocked after 40 mL/kg colloid/crystalloid will probably benefit from inotropic support (e.g. dopamine 10–20 micrograms/kg/minute IV by peripheral intravenous cannula).
- Shocked patients are at significant risk of developing pulmonary oedema as fluid therapy increases. Ideal therapy is mechanical ventilation for patients who require more than 40 mL/kg fluids.
  - In resource-limited countries, where facilities for mechanical ventilation are unavailable, further fluid boluses should be undertaken cautiously with repeated boluses of 5–10 mL/kg of crystalloid, colloid or blood products as appropriate.
  - If pulmonary oedema develops (with tachypnoea, hypoxia, cough and fine crackles, raised jugular venous pressure and hepatomegaly) further fluid administration should be withheld until the patient stabilises. Inotropic support, as described above, may be of benefit.
- Full neurological and cardiovascular assessment with regular (at least hourly) assessment of: pupillary responses, conscious level, pulse, blood pressure, capillary refill time, respiratory rate and effort, pulse oximetry (if available) and temperature.
- Regular (ideally 4-hourly initially) monitoring of electrolytes (sodium, potassium, **calcium and magnesium, phosphate**, urea and/or creatinine) and glucose and replacement of deficits.
- **Blood gases should be undertaken to detect metabolic acidosis from shock or respiratory acidosis due to ventilatory insufficiency.**
  - Severe metabolic acidosis (pH < 7.0), which does not respond to fluid therapy, may require cautious sodium bicarbonate correction (1 mEq/kg slowly IV).
  - Regular blood gas monitoring is essential for ventilated patients.
- Monitor full blood count and coagulation regularly if initially abnormal.
  - Blood or packed cell transfusion should aim to maintain haemoglobin levels around 7–10 g/dL in the early phases of shock.
  - Platelets and coagulation factors (usually fresh frozen plasma and cryoprecipitate) should be replaced as required in order to control bleeding.
- Hydration will usually be via the intravenous route, but nasogastric feeding is appropriate if tolerated.
  - Urine output should be monitored (by an indwelling catheter if the conscious level is depressed). Insert a nasogastric tube for gastric drainage if there is persistent vomiting or if the conscious level is decreased.

Suspected raised intracranial pressure

This is a medical emergency.

Actions

- Assess ABCD, give high-flow oxygen (10 litres/minute), and obtain intravenous or intra-osseous access.
- Treat shock (see above), if present.
  - Exercise caution with fluid therapy as there is a conflict of need between raised intracranial pressure (RICP) and shock. The former requires less fluid, and the latter needs more.
- Do not perform a lumbar puncture.
- Give mannitol 250–500 mg/kg IV (this should be repeated if signs of raised intracranial pressure persist, up to a maximum total dose of 2 grams/kg or if available a serum osmolality up to 325 mOsm/litre).
  - Hypertonic saline may be used as an alternative (e.g. 3% saline 3 mL/kg).
  - If mannitol or 3% saline is unavailable, give furosemide 1 mg/kg IV.

If signs of raised intracranial pressure persist, ideal management would include:

- Rapid sequence induction of anaesthesia and intubation for both airway protection (if Glasgow Coma Scale score is < 8 and/or the child is unresponsive to painful stimuli) and stabilisation of PCO_2.
- Mechanical ventilation with optimal sedation and maintenance of PCO_2 within the normal range (ideally 4.5–5.5 kPa).

Other useful techniques include the following:

- Place the patient supine in a 30-degree head-up position.
- Avoid placing a central venous catheter in the internal jugular vein.
- Give antipyretics to maintain normal temperature.
- Undertake a full neurological and cardiovascular assessment with regular (at least hourly) assessment of: pupillary responses, conscious level, pulse, blood pressure, capillary refill time, respiratory rate and effort, pulse oximetry (if available) and temperature.
- Monitor electrolytes, gases, clotting and full blood count as recommended for shock.

Prognosis

- Even with optimal intensive care, around 5–10% of patients with meningococcal septicaemia will die. Where intensive care is unavailable this may rise to more than 40%.
  - Mortality of other causes of acute meningitis is generally much lower (around 2%).
- The most frequent complication of meningitis is hearing impairment or deafness, which may affect up to 10% of survivors.
- Survivors of septicaemia may require skin grafting of necrotic lesions and amputation of necrotic digits or limbs.
- In general, most survivors make a virtually complete recovery, although subtle neurological abnormalities (e.g. behavioural and developmental problems, mild motor abnormalities) are not uncommon.

Prevention of meningococcal disease

Education

Increasing awareness of primary healthcare workers and general public about the presenting symptoms of meningococcal disease and emphasising the need for early presentation and treatment may have a major impact on mortality and morbidity.

Prophylaxis of contacts

Transmission is via droplet spread to close contacts. Around 4–25% of people are colonised at any one time, but outbreaks of disease are not generally related to colonisation rate. Household contacts of a case may be at 800 times increased risk of disease compared with the general population.

Chemoprophylaxis is used to prevent secondary cases by eliminating nasal carriage. Administer as soon as possible (within 48 hours after presentation of the index case).

Follow local public health guidelines when determining who should receive antibiotic prophylaxis. In general, only immediate family (or those sharing accommodation) and kissing contacts should be treated. Healthcare workers should receive prophylaxis only where they have experienced extensive contact with the patient's respiratory secretions (e.g. during intubation).

Drugs for prophylaxis

Give rifampicin for 2 days for all household contacts:

- adults: 600 mg twice daily
- children aged 1 month to 12 years: 10 mg/kg twice daily
- neonates: 5 mg/kg twice daily.

In many countries rifampicin is protected from use for any disease other than TB. In this case consider giving ciprofloxacin orally as a single dose: adults, 500 mg; children aged 5–12 years, 250 mg; children aged 1 month to 5 years, 125 mg.

Vaccination

Where the index case has proven serogroup A or C disease, consideration should be given to vaccinating close contacts with appropriate polysaccharide or polysaccharide conjugate vaccine.

During larger outbreaks or epidemics, wider-scale prophylaxis is occasionally used, but should only be carried out under guidance of local/national public health authorities. Public education regarding presenting symptoms of meningococcal disease and emphasising the need for early presentation may be more beneficial than wide-scale distribution of antibiotics.

Vaccines based on the **capsular** polysaccharide of serogroups A and C (±Y and W-135) have been available for several years, and have been used for vaccination of contacts (as above) and for protection of travellers to endemic areas. They are unable to reliably induce immunity in infants and young children as their duration of protection is short.

They are not generally used for population vaccination campaigns except in epidemic situations.

Conjugated polysaccharide vaccines for serogroups A, C, Y and W-135 are now available and offer the possibility of inducing long term immunity in all age groups.

A vaccine against serogroup B has recently received a license.

Where widespread epidemics of meningococcal disease occur (e.g. in the meningitis belt in sub-Saharan Africa), mass vaccination campaigns have proved useful in reducing attack rate. Such campaigns are administered by local public health authorities.

6.1.H Pertussis

BOX 6.1.H.1 Minimum standards

- Immunisation.
- Erythromycin.
- Oxygen.
- Close monitoring for apnoea and hypoxaemia.

Introduction

Infection with the organism *Bordetella pertussis* (a Gram-negative bacillus) causes a clinical syndrome commonly referred to as 'whooping cough'. The illness classically has three stages.

- Stage 1: **Catarrhal stage** (1–2 weeks). The symptoms are those of an upper respiratory infection.
- Stage 2: **Paroxysmal stage** (2–4 weeks). The child has severe episodes of coughing – usually up to 10 coughs without drawing breath, and then a sharp inspiration or 'whoop'. The prolonged coughing (often with vomiting) may lead to poor feeding, with weight loss and sometimes rectal prolapse. Other complications such as subconjunctival haemorrhages and ulceration of the frenulum may develop.
- Stage 3: **Convalescent stage** (1–2 weeks). The episodes of coughing subside. Occasionally the child may continue to cough for months.

Pertussis should be prevented by universal infant immunisation. In some countries, immunisation is also given to the

mother during pregnancy (28 to 38 weeks gestation) to prevent pertussis in infancy.

Effects on the young infant

Infants may become infected with pertussis before they have been immunised, or if immunisation is not available (or the parents have refused it). Young infants with pertussis have a different and serious clinical picture that includes the following:

- apnoea with hypoxaemia
- bradycardia
- seizures
- cough and poor feeding.

Diagnosis

The laboratory facilities needed to diagnose pertussis are not available in many hospitals. **Culture from a pernasal swab should be undertaken on Bordet–Gengou medium.** An absolute lymphocytosis (with a typical clinical picture) is highly suggestive (the total lymphocyte count may be over 30×10^9/litre).

Treatment

The following groups of children should be admitted to hospital

- infants under 6 months of age
- children with complications such as pneumonia, convulsions, dehydration or severe under-nutrition
- those with apnoea or cyanosis.

Supportive treatment

- Maintain nutrition and hydration.
- Give oxygen according to the criteria for acute lower respiratory infection (ALRI) (*see* Section 5.3.A).
- Give gentle suction of secretions (avoid triggering coughing).
- Low-dose continuous oxygen (0.5–1.0 litre/minute) via nasal cannulae may reduce apnoeic episodes in infants. Do not use nasopharyngeal cannulae, which can provoke coughing spasms.
- Do not give cough suppressants, sedatives or antihistamines.
- Encourage breastfeeding. If the infant cannot drink, pass a nasogastric tube.
- If there is severe respiratory distress, consider intravenous maintenance fluids to avoid aspiration, but avoid malnutrition.
- In some infants, the frequency of apnoeic episodes is high and requires ventilatory support.

Specific treatment

- Treat pneumonia that is complicating pertussis, according to the ALRI protocol in Section 5.3.A.
- Give DTP vaccine to any unimmunised siblings (*see* Section 1.17).
- Treat convulsions (*see* Section 5.16.E).
- Erythromycin will eradicate pertussis from the nasopharynx but has little effect on the severity or duration of clinical symptoms unless it is started very early in the disease. The oral dose of erythromycin is 12.5 mg/kg 6 hourly for neonates for 7 days and 125 mg 6 hourly for age 1 month to 2 years for 7 days. Azithromycin (10 mg/kg once daily) may also be given, and the course is shorter (3 days) but is not recommended under 6 months of age. Prophylaxis of other infants in the family is of no proven benefit, and has side effects.

6.1.I Relapsing fevers

BOX 6.1.I.1 Minimum standards

- Public health measures to kill lice.
- Antibiotics: erythromycin, ceftriaxone.
- Close observation for the Jarisch–Herxheimer reaction.

Epidemiology

Epidemic or louse-borne relapsing fever (LBRF), caused by *Borrelia recurrentis*, is transmitted by the human body louse (*Pediculus humanus*) (and occasionally the head louse (*P. capitis*) or, possibly, the crab louse (*Phthirus pubis*)), which becomes infected following a blood meal and remains infected for life. Humans are the reservoir host. The louse is crushed when the host scratches. *Borrelia* enters the new host via abrasions and mucous membranes. Bloodborne and congenital infections may also occur. Currently only endemic in Ethiopia, LBRF occurs in epidemics in situations of poor hygiene and overcrowding.

Endemic or tick-borne relapsing fever (TBRF) occurs in widespread endemic foci: central, eastern and southern Africa (*Borrelia duttonii*); north-western Africa and the Iberian peninsula (*B. hispanica*); central Asia and parts of the Middle East, India and China (*B. persica*); and various regions of the Americas (*B. hermsii*, *B. turicatae*, *B. venezuelensis*). Animal reservoirs include wild rodents, lizards, toads, owls, pigs and chickens. Transmission to humans occurs following the bite of an infected argasid (soft) tick of the genus *Ornithodorus* via tick saliva or coxal fluid. Human congenital infections may also occur. TBRF is a common and under-diagnosed cause of fever in many parts of Africa.

Pathology

Borreliae multiply in blood by simple fission. They have a predisposition for reticulo-endothelial system and CNS, causing widespread vascular endothelial damage and platelet sequestration in the bone marrow. Clinical severity tends to correlate with the level of spirochaetaemia and relapses result from antigenic variation.

Clinical features

- Incubation period usually 4 to 8 days (range 2–15 days).
- TBRF usually clinically milder, but may be associated with up to 11 relapses.
- LBRF more severe, and rarely gives rise to more than three relapses.

- Typical features include sudden-onset high fever, headache, confusion, meningism, myalgia, arthralgia, nausea, vomiting, dysphagia, dyspnoea and cough (which may be productive of sputum containing *Borrelia*).
- Hepatomegaly is common (associated with jaundice in 50% of patients with LBRF, and in less than 10% of those with TBRF). Splenomegaly is common and splenic rupture may occur.
- Petechiae, erythematous rashes, conjunctival injection and haemorrhages are more common in LBRF.
- Complications include myocarditis, pneumonia, nephritis, parotitis, arthritis, neuropathies, meningoencephalitis, meningitis, acute ophthalmitis and iritis.
- The case fatality rate (CFR) may reach 70% in epidemics of LBRF, and is lower in children than in adults.
- CFR is usually less than 10% in untreated cases of TBRF, but tends to be higher in children and pregnant women.

Differential diagnosis

Malaria, typhus, typhoid, meningococcal septicaemia/meningitis, dengue, hepatitis, leptospirosis, yellow fever, other viral haemorrhagic fevers.

Diagnosis

- Giemsa- or Field-stained blood films reveal spirochaetes.
- *Borrelia* is also visible on unstained blood films using dark-field or phase-contrast microscopy.
- Centrifuge anticoagulated whole blood to concentrate spirochaetes above the buffy coat.
- The acridine orange-coated quantitative buffy coat (QBC) technique is also useful.
- Polymerase chain reaction (PCR) assays are now available for diagnosis and speciation.
- Serology is unreliable.
- Examination of the vector may be useful.

Treatment

- A single dose of antibiotic is effective in about 95% of cases of LBRF, and in up to 80% of cases with TBRF.
- Single-dose treatment is recommended in LBRF epidemics.
- TBRF relapses are less likely with a 5- to 10-day course of treatment.

Effective antibiotics include tetracycline, doxycycline, penicillin, erythromycin, chloramphenicol and ciprofloxacin. Choice will depend on the patient's age, contraindications and drug availability.

Ceftriaxone is recommended for patients presenting with meningitis or encephalitis.

In epidemics of LBRF, treatment of close contacts may also be recommended.

Usual dosage recommendations:

- LBRF: a single dose of one of the following:
  - doxycycline, 100 mg (non-pregnant adults)
  - tetracycline, 500 mg (non-pregnant adults)
  - erythromycin, 500 mg in adults and children over 5 years
  - erythromycin, 250 mg in children up to 5 years.
- TBRF: a 5-day course of one of the following:
  - doxycycline, 100 mg twice daily (non-pregnant adults)
  - erythromycin, 2 grams divided into two to four doses daily (adults)
  - erythromycin, 50 mg/kg divided into two to four doses daily (children).

Complications

A Jarisch–Herxheimer reaction (JHR) may occur in up to 80–90% of patients treated for LBRF, and in up to 50% of those treated for TBRF. This may be fatal in around 5% of cases.

- The reaction usually commences within 2 hours of the first dose of antibiotic.
- Symptoms include rigors, restlessness and anxiety, then a sharp rise in temperature, tachycardia and initial rise blood pressure, followed by marked vasodilation and sweating, which may result in collapse and shock.
- All patients must be closely monitored for a JHR. Intravenous fluids may be required to maintain blood pressure.
- Steroids are of no benefit.

Prevention and control

LBRF: improve hygiene, reduce crowding, delouse (DDT, permethrin or malathion powder to skin and clothing), heat treat/destroy clothing. Antibiotic prophylaxis may be recommended in high-risk situations.

TBRF: avoid tick habitats.

6.1.J Sexually transmitted diseases

BOX 6.1.J.1 Minimum standards

- Health education programmes.
- Child protection in cases of abuse.
- Antibacterial drugs.
- Antiviral drugs.
- Podophyllin/trichloroacetic acid.

Introduction

Anogenital infections in childhood are most commonly acquired through sexual contact or abuse, but may also arise as a result of close personal contact within the family or on the playground, and some systemic infections may be transmitted by sexual means without being considered venereal illnesses.

The diagnosis of sexually transmitted disease is considered in the following circumstances:

- a history of recent sexual abuse
- the isolation of sexually transmitted organisms in cases without obvious trauma leading to a diagnosis of chronic sexual abuse
- specific syndromes and diseases usually transmitted by the sexual route in adults
- congenital syphilis or perinatally acquired chlamydia

or gonorrhoea transmitted from the mother *in utero* or postnatally (*see* Section 3.4)
- HIV infection not acquired perinatally, through transfusion or another known mechanism.

There are more than 20 different infections that may be spread by the sexual route. These range from the classic sexually transmitted diseases (e.g. syphilis, gonorrhoea), through conditions that are mainly sexually transmitted (e.g. genital herpes, human papillomavirus), to those infections that can also be transmitted by sexual means (e.g. hepatitis B and C).

Sexual abuse

Children known to have been abused recently

Sexually abused children are at risk of acquiring an infection from the perpetrator. In relation to the high frequency of sexual abuse, the typical sexually acquired infections are fairly rare, but the risk depends on a number of epidemiological factors.

The diagnosis of potential infection of a child presenting with sexual abuse includes an active microbiological search by culture of vulval, perineal or anal swabs. Bacterial infections such as gonorrhoea, syphilis or chlamydia are usually manifested soon after the assault, with the development of local ulcers and infected vaginal or vulval discharge.

The sexually transmitted viral diseases such as herpesvirus type 2 can also become evident soon after the incident, but diseases with a longer latency period such as human papillomavirus are more difficult to link directly to the episode of sexual abuse.

The management of the child potentially infected after sexual abuse consists of the following:
- management of the sexual abuse (*see* Section 7.6)
- local management of injuries, including tetanus toxoid if applicable
- bacteriological swabs
- serological tests for syphilis, hepatitis B and HIV, repeated 6 weeks later
- prophylactic broad-spectrum antibiotics: ceftriaxone 50 mg/kg IM as a single dose (maximum dose 4 grams) plus erythromycin 20–40 mg/kg/day in three divided doses for 7 days
- post-exposure hepatitis B vaccination if not previously vaccinated; follow-up doses at 1–2 and 4–6 months after the first dose
- assessment of the risk of HIV transmission and prophylaxis if indicated.

Children are at higher risk because episodes of assault are often multiple and mucosal trauma is likely.

Factors that should be assessed include the following:
- assailant's HIV status or likelihood of having HIV
- time elapsed since incident (< 72 hours)
- exposure characteristics
- possible benefits and risks associated with post-exposure prophylaxis (PEP).

PEP is generally well tolerated in children. The choice of antiretroviral drugs will depend on local availability and policy. An example is a combination of zidovudine, lamivudine and lopinavir/ritonavir. Follow-up and appropriate treatment of identified infection (see below) should be undertaken.

The presence of a sexually transmissible infection in a child alerting to the possibility of sexual abuse

This group of children presents with symptoms and signs suggestive of genital, urinary or lower intestinal infection. In children aged around 2–10 years, the finding of genital, anal or pharyngeal infection with *Neisseria gonorrhoeae*, *Treponema pallidum* or *Chlamydia trachomatis* should prompt a search for evidence of sexual abuse. However, herpesvirus type 2, *Trichomonas vaginalis*, *Mycoplasma* species and bacterial vaginosis are not so commonly acquired as a result of sexually transmitted infection in this age group. Although human papillomavirus types 6, 11, 16 and 18 are also usually transmitted by sexual means and may present with condylomata, a long latency in the onset of clinical signs means that these may have been transmitted from mother to child during birth, and close domestic contact other than sexual abuse has also been shown in such cases.

Specific syndromes or diseases usually associated with sexual transmission in adolescent children

These conditions occur particularly in sexually active adolescents. In view of the rampant spread of HIV infection, the approach to the management of sexually transmitted diseases in children and adolescents must include the following aspects:
- Treatment of the symptoms and causes in a typical syndromic approach to STDs, as described below.
- Identification of those without symptoms. There is a recognised risk of co-infection, and as both syphilis and HIV may be asymptomatic, serological tests for syphilis (VDRL or RPR) and HIV (ELISA) should be offered with appropriate counselling in all patients.
- Prevention of new infection by education about safe sex practices and condom use.
- Motivation to engage in health-seeking behaviour.

Genital ulcers and lymphadenitis

The infections presenting with genital ulcers with or without inguinal adenopathy and bubos are most often acquired as a result of voluntary or involuntary sexual activity, but may occur as a result of non-sexual inoculation through close domestic or play contact or indirect transmission. The patient should be carefully examined to determine the site, number, size and appearance of the ulcers, the type of exudate, the presence of associated pain, erythema and swelling, or of draining lymphadenopathy.

Regional epidemiological factors determine the relative frequency and likelihood of genital herpes (herpesvirus type 2), syphilis, chancroid, lymphogranuloma venereum or granuloma inguinale.

Genital herpes

This causes painful vesicular or shallow ulcerative lesions on the genitals. Grouped or single lesions occur on a thin erythematous base but with generally uninflamed intervening epithelium. These regress spontaneously but may recur. Oral aciclovir 200 mg five times daily for 5 days does not

prevent future recurrences, but if started early, will reduce the intensity and duration of symptoms. Locally, anaesthetic and antiseptic creams help to relieve symptoms.

Chancre of primary syphilis

This is a painless ulcer with a serous exudate which is highly infectious. The diagnosis can be made by direct dark-field examination or immunofluorescent antibody stains. At this stage, serological tests for syphilis are usually still negative. The treatment in children over 12 years consists of benzathine benzylpenicillin, 50 000 U/kg IM as a single dose (50 000 U = 37.5 mg). Benzathine benzylpenicillin must not be given IV.

Chancroid

This is caused by *Haemophilus ducreyi*. Painful papulovesicles or ulcers on the genitals are associated with suppurative inguinal adenopathy. In the absence of adenopathy, the condition has to be differentiated from herpes or syphilis, the latter of which is usually painless. In treatment of children over 12 years of age, the following are satisfactory: azithromycin 1 gram orally as a single dose, ceftriaxone 250 mg IM as a single dose, or erythromycin base 500 mg orally four times daily for 7 days.

Lymphogranuloma venereum

Patients with lymphogranuloma venereum (LGV) commonly present with unilateral tender inguinal and/or femoral lymphadenopathy. Genital ulcers are usually less obvious and have often disappeared by the time of presentation. LGV is caused by *Chlamydia trachomatis.* Treatment for children over 12 years of age is with doxycycline 100 mg orally twice daily or erythromycin 500 mg orally four times daily, and should be continued for 21 days.

Granuloma inguinale

Klebsiella granulomatis is the cause of this ulcerative disease. The lesions are painless and slowly progressive. Subcutaneous granulomas often occur on the genitals and perineum, but regional lymphadenopathy is absent. Treatment is with doxycycline or erythromycin, as for LGV. Alternatively azithromycin, ciprofloxacin or trimethoprim-sulfamethoxazole can be used.

Urethritis and vulvovaginitis

These patients present typically with a discharge from urethra or vagina. The character of the discharge may be non-specific or it may have typical features allowing a presumptive diagnosis concerning its aetiology. Together with the discharge, there may be other features such as itching, discomfort or dysuria. There may be inflammatory erythema and swelling of the tissues. Where pruritus is a major symptom, *Trichomonas* or *Candida albicans* should be suspected. The appearance of the discharge may be typically white cheesy in *Candida*, or creamy-purulent and frothy in *Trichomonas* infection, but often is fairly non-specific.

The organisms responsible for this mode of presentation include *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas*, *Candida* species, *Gardnerella vaginalis* and *Ureaplasma* species. In the syndromic approach to the management of patients with surface epithelial infection, broad-spectrum treatment aimed at gonorrhoea, *Chlamydia* and *Trichomonas* or *Candida* is given at the same time as bacterial swabs are taken for culture. Where laboratory resources are scarce, bacteriological investigations may be reserved for those not responding appropriately to the first course of therapy.

Recommended treatment for children over 12 years of age includes ceftriaxone 250 mg IM as a single dose, or cefixime 400 mg orally in a single dose, against *Neisseria gonorrhoeae*. Azithromycin, 1 gram orally as a single dose, or doxycycline 100 mg orally twice daily for 7 days (alternatively, erythromycin 40–50 mg/kg/day given as 4 divided doses 6 hourly for 14 days for children under 12 years) should be added for *Chlamydia*. If *Trichomonas* or bacterial vaginosis due to *Gardnerella vaginalis* is identified or strongly suspected, metronidazole is added as 15–30 mg/kg/day in three divided doses for 7 days. *Candida* infection can be treated with a short course (3 days) of topical azoles such as clotrimazole, miconazole or butoconazole cream. An alternative is treatment with local nystatin (100 000 U/mL three to four times daily), but this is less effective.

Acute balanoposthitis

Inflammation of the glans and prepuce can have a large number of infectious and also non-infectious causes. In the usual case, there is erythema and swelling of the glans and prepuce together with local exudate. Most such cases are not due to sexually transmitted infection, but are caused by beta-haemolytic streptococci, *Staphylococcus aureus* or *Candida albicans*. These may arise secondary to local trauma including ritual circumcision. Allergic contact dermatitis and rarer causes such as psoriasis or pemphigus should also be considered. Sexually transmitted organisms include *Chlamydia*, *Gardnerella vaginalis*, *Trichomonas*, *Candida albicans*, syphilis, herpes virus and papillomavirus. If 'milking' along the length of the urethra produces a purulent discharge, STDs are also more likely.

Accordingly, the evaluation of a boy presenting with balanoposthitis includes examination for the presence of urethral discharge and a urine dipstick. A swab should be sent for microbiological confirmation. A suggested treatment for children over 12 years is azithromycin 1 gram orally in one dose, or erythromycin 40–50 mg/kg per day in four divided doses for 14 days, plus metronidazole 15–30 mg/kg per day in three divided doses for 7 days. In the presence of urethral discharge, treatment should also include antibiotic cover for gonorrhoea.

Genital warts

Condylomata acuminata are fleshy, soft, pedunculated or flat warty lesions that may sometimes have quite a narrow base. They occur singly or in clusters. In sexually active adolescent boys, they may occur on the shaft or corona of the penis, and in girls on the genital mucosal surface both inside and outside the vagina. Perineal cutaneous condylomata are not always acquired sexually. Human papillomavirus (HPV) types 6 and 11 cause these warts. Apart from the visible wart, the infection may be quite asymptomatic, particularly where lesions occur intravaginally. They must be differentiated from the flat papular condylomata lata of syphilis, skin tags and molluscum contagiosum.

Local treatment is satisfactory in most instances, although recurrences occur. Trichloroacetic acid or 10–25% podophyllin may be applied to external lesions, taking care not to involve normal skin. Other precautions to avoid the development of complications include limiting the

application to less than 0.5 mL of podophyllin and an area of over 10 cm^2 of warts per session. The preparation should be washed off 1–4 hours after application to reduce local irritation. The process can be repeated in 7 days. Other treatment modalities include cryotherapy, surgical excision, curettage or electrocautery. An alternative is not to treat, and to await possible spontaneous resolution.

The association with genital dysplasia and carcinoma should be remembered, and therefore Pap smears and regular follow-up are indicated in girls with human papillomavirus infection.

Two HPV vaccines are now available. They offer protection against HPV types that cause a large percentage of carcinomas as well as genital warts.

Pelvic inflammatory disease (PID) and epididymitis

The deep infections of the upper female genital tract present with features of infection, such as fever and leucocytosis, together with lower abdominal pain and a vaginal discharge. There may be signs of pelvic peritonitis or a tender mass on vaginal or rectal examination. Epididymitis in males presents typically with unilateral pain, swelling and tenderness of the testis, together with urethral discharge. This can be distinguished from testicular torsion by means of an ultrasound examination. In sexually active adolescents, these infections are most often caused by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Such patients may be very ill and require hospitalisation including possible surgical drainage. General supportive therapy is given as required. The antibiotic therapy aims at the above two organisms and outpatient treatment typically includes a third-generation cephalosporin like ceftriaxone plus doxycycline. Metronidazole may be added to treat bacterial vaginosis which frequently accompanies PID.

In severe cases, or where there is no response to the above treatment within 72 hours, intravenous broad-spectrum antibiotics including an aminoglycoside and clindamycin should be given.

6.1.K Streptococcal disease

BOX 6.1.K.1 Minimum standards
- Antibiotics: penicillin and erythromycin.
- For resistant pneumococci: cefotaxime/ceftriaxone, vancomycin.
- Pneumococcal vaccine post-splenectomy and in sickle-cell disease.

Introduction

Streptococci are Gram-positive bacteria, of which the most important are:
- Group A streptococcus
- Group B streptococcus
- *Streptococcus pneumonia*.

Group A streptococci (GAS) *Streptococcus pyogenes*

This is a common commensal in the throat. It causes many diseases, as described below.

Head and neck

- Acute pharyngitis, retropharyngeal abscess and otitis media (*see* Section 5.1.C).
- Tonsillitis: GAS likely if exudate, tender anterior cervical lymph nodes, fever, no cough. Penicillin V for 10 days is the treatment of choice, but amoxicillin may be better tolerated in liquid form. GAS is always sensitive to penicillin. In penicillin allergy use a macrolide (although there is resistance to this group of antibiotics).
- Sinusitis: follows otitis media: coryza, postnasal drip, headache, fever.
- Brain abscess: this is a rare complication resulting from direct extension of an ear or sinus infection, or from haematogenous spread (*see* Section 5.16.K).

Skin and soft tissue

- Impetigo: purulent, yellow-crusted skin lesions (*see* Section 5.18).
- Pyoderma: papule becomes vesicular then pustular with a thick crust and surrounding erythema.
- Erysipelas: erythematous warm painful skin lesions with raised borders associated with fever.
- Cellulitis: local pain, tenderness, swelling and erythema associated with fever.

Skin infections are commonly co-infected with *Staphylococcus aureus*, which should be treated with flucloxacillin. Treat invasive disease with IV flucloxacillin, benzylpenicillin and clindamycin.

Necrotising fasciitis

- Pain disproportionate to physical findings: erythema may be absent or rapidly progress to purple with haemorrhagic fluid-filled blisters or bullae. Fever, malaise, myalgia, diarrhoea, anorexia. Spread through fascial planes requires early surgical exploration and resection. Give intravenous immunoglobulin (IVIG) (if available).

Myositis

- CT or MRI (if available) is useful for diagnosis.

Scarlet fever

- This presents with tonsillitis and a characteristic rash, circumoral pallor and strawberry tongue. Rash starts with generalised blanching erythema which is punctate (i.e. like sandpaper) and palpable, followed by desquamation.

Pneumonia

- Invasive GAS can rapidly progress to necrotising pneumonia with empyema (*see* Section 5.3.B).

Septicaemia

- Risk factors include burns and chickenpox. The main symptoms are fever, tachycardia, tachypnoea and hypotension.

Mediastinitis

- Rare but serious, frequent fatalities as often diagnosed late.

Toxic shock syndrome

- Systemic shock with multi-organ failure. Give IVIG (if available) (*see* Section 5.5.C).

Rheumatic fever

Acute rheumatic fever

- **Major criteria:** carditis, Sydenham chorea, polyarthritis, erythema marginatum, subcutaneous nodules.
- **Minor criteria:** fever, arthralgia, raised ESR or CRP, prolonged PR interval on ECG.

Two major or one major and two minor criteria with evidence of preceding GAS throat infection confirm a diagnosis of rheumatic fever (*see* Section 5.13).

Rheumatic heart disease results in chronic valvular damage, predominantly of the mitral valve.

Glomerulonephritis

- Acute renal failure with haematuria and proteinuria days after streptococcal pharyngitis (*see* Section 5.6.A).

Group B streptococci (GBS) *Streptococcus agalactiae*

This species colonises 15–45% of healthy women and can cause severe infections in the puerperium and in the neonate.

Postpartum infection (*see* Section 2.5.G).

Neonatal infection

- Early onset (first week of life) (*see* Section 3.4) associated risk factors: prematurity, prolonged rupture of membranes, maternal intrapartum fever, chorioamnionitis, maternal UTI, previous baby with GBS disease.
- Late onset (1 week to 3 months of age) causes sepsis and meningitis: not prevented by peripartum antibiotics.

Empirical IV treatment with ampicillin and gentamicin for 5 days. Then, once GBS is confirmed, treat sepsis with benzyl penicillin for 7 days if meningitis is excluded by lumbar puncture. If meningitis is not excluded, treat for 14 days.

Maternal

- Septic abortion, puerperal sepsis, urinary tract infection.

Streptococcus pneumoniae

Gram-positive diplococcus (lancet shaped). At least 85 pathogenic serotypes are known. Types 1, 3, 4, 6, 7, 8, 9, 12, 14, 18, 19 and 23 are the most virulent.

- Common infections include pneumonia, meningitis, peritonitis, otitis media, sinusitis, arthritis and conjunctivitis.
- Pneumococcal infections are more common in children with defective splenic function (e.g. sickle-cell anaemia, splenectomy); also nephrotic syndrome, chronic renal failure, diabetes mellitus, malabsorption, heart failure, skull fracture, neurosurgery and those with congenital or acquired immunodeficiency such as agammaglobulinaemia, and HIV infection.
- Patients with white blood cell counts of more than 15×10^9/litre are likely to have bacteraemia.
- Culture of *Streptococcus pneumoniae* from the respiratory tract is not useful because many people are asymptomatic carriers.

Treatment

- In the last two decades, resistance of *S. pneumoniae* to antibiotics such as penicillin and chloramphenicol has emerged.
- In many countries, up to 5–40% of isolates may be resistant to penicillin G.
- If resistance to chloramphenicol or penicillin is suspected, give either cefotaxime or ceftriaxone. If resistance to these two drugs is considered, add vancomycin to ceftriaxone or cefotaxime. If results of sensitivity confirm susceptibility to penicillin G, ceftriaxone or cefotaxime should be given and vancomycin should be stopped.

TABLE 6.1.K.1 Antibiotic doses for streptococcal disease

Disease	Antibiotic	Dose and route	Dose interval	Duration/comments
Otitis media	Amoxicillin (oral)	12.5 mg/kg orally	8 hours	5–7 days
	Amoxicillin – clavulanic acid	12.5 mg/kg orally	8 hours	5–7 days
	Cefaclor	12.5 mg/kg orally	8 hours	5–7 days
	Erythromycin	12.5 mg/kg orally	6 hours	5–10 days
Sinusitis	As for otitis media	As for otitis media	As for otitis media	As for otitis media
Meningitis	Penicillin G	50 mg/kg IV	4–6 hours	10–14 days for all antibiotics below
	Chloramphenicol	Load 50 mg/kg IV, then 25 mg/kg	6 hours	
	Cefotaxime	50 mg IV	6–8 hours	Maximum single dose 4 grams
	Ceftriaxone	100 mg IV	24 hours	Maximum single dose 4 grams/day
	Vancomycin	Load 15 mg/kg IV then 10 mg/kg IV	6 hours	Total daily dose not more than 2 grams Drug levels needed
	Meropenem	10–20 mg/kg slow IV injection over 5 minutes	8 hours	Maximum single dose 2 grams

Pneumococcal vaccine

- Give pneumococcal conjugated vaccine (e.g. Prevenar 13), two doses starting at 2 months of age, with 2 months between doses, with a reinforcing dose at 12–13 months, or if over 1 year old give a single dose.
- At-risk groups (see above) should have conjugate vaccine (any age) followed by polysaccharide vaccine (23 serotypes) over 2 years of age with a repeat dose every 5 years.

Chemoprophylaxis

- Daily oral penicillin V (125 mg twice daily for children under 5 years, 250 mg twice daily for older children) is recommended for children at risk (see above).

Other groups of streptococci (C, D, E, F, G, H, K, L, M, N, O and V)

- These cause diseases such as infective endocarditis, urinary tract infection and pneumonia. Susceptibility to penicillin is variable, and treatment with an aminoglycoside (e.g. gentamicin) and penicillin G or ampicillin is recommended.

TABLE 6.1.K.2 Streptococci and related conditions

Streptococci	Group Lancefield	Reaction (Haemolytic)	Disease caused
S. pyogenes (GAS)	A	J	Tonsillitis, pyoderma, impetigo, scarlet fever (subsequent rheumatic fever, acute glomerulonephritis) Necrotising fasciitis, toxic shock syndrome
S. agalactiae (GBS)	B	J	Neonatal sepsis/meningitis
S. equisimilis (GCS)	C	J	Endocarditis, pneumonia, cellulitis, septicaemia
S. faecalis (GDS)	D	J or none	Normal gut flora. May cause peritonitis, urinary tract infection, endocarditis and septicaemia
S. viridians	–	I	Mouth commensal. May cause endocarditis, dental caries
S. pneumoniae	–	–	Pneumonia, meningitis, otitis media, sinusitis

6.1.L Tetanus

BOX 6.1.L.1 Minimum standards

- Immunisation and prevention.
- ABC, especially airway protection.
- Anti-tetanus immunoglobulin and tetanus toxoid.
- Wound care.
- Diazepam, magnesium sulphate and phenobarbitone for acute spasms.
- Morphine.
- Early IV penicillin and/or metronidazole.
- Close observational care in a high-dependency area.

Introduction

Generalised tetanus (lockjaw) is a neurological disease manifesting as trismus and severe muscular spasms. It is caused by a neurotoxin produced by the anaerobic bacterium *Clostridium tetani* in a contaminated wound. The different forms of tetanus include the following:

- **Neonatal tetanus** is a form of generalised tetanus occurring in newborn infants lacking protective passive immunity because their mothers are not immune.
- **Localised tetanus** manifests as local muscle spasms in areas contiguous to a wound.
- **Cephalic tetanus** is a dysfunction of cranial nerves associated with infected wounds on the head and neck. Both of the latter conditions may precede generalised tetanus.

Tetanus continues to cause thousands of deaths per year worldwide (*see* Figure 6.1.L.1). The World Health Organization estimates that 59 000 newborns worldwide died in 2008 as a result of neonatal tetanus.

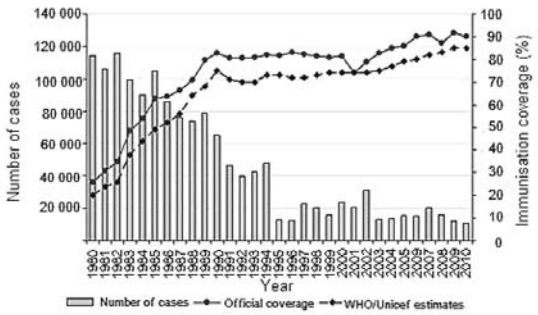


FIGURE 6.1.L.1 Total tetanus global annual reported cases and coverage, 1980–2010. Source: WHO/IVB Database, 2011.

For infection to occur, two conditions must be met:

1 a wound with a degree of necrosis
2 a wound contaminated with material containing *Clostridium tetani* (a Gram-positive obligate anaerobe widely distributed in the environment).

The umbilical stump is a common site of entry for neonatal tetanus, which carries up to 60–80% mortality. Ear piercing in neonates is also a common cause (e.g. in Vietnam). In up to 30% of infected children no wound can be found. Cases

of tetanus in older children follow small puncture wounds, accidents and trauma in the partial or unvaccinated child.

Pathogenesis

Once the *C. tetani* spore is inoculated into necrotic tissue with a low oxygen concentration it changes into a vegetative form, which elaborates the powerful toxin, tetanospasmin, which ascends peripheral nerves to the spinal cord where it binds to cerebral gangliosides and impairs inhibitory synapses. This causes muscle rigidity, spasm and autonomic overactivity.

Clinical presentation

A previously well neonate presents at 3–20 days with irritability, decreased sucking, trismus, muscle spasms or convulsions. An older child presents following a minor injury or bite. Some infections follow chronic otitis media.

The clinical presentation depends upon the distance the injury is from the spinal cord. The incubation period ranges from 3 to 21 days. The shorter the incubation period and the time from onset of symptoms to the first spasm, the worse the outcome.

More than 90% of patients develop trismus ('locked jaw') due to the short pathway of the fifth cranial nerve. As the disease progresses, spasm of muscle groups supplied by other cranial nerves occurs, including the seventh cranial nerve, resulting in facial muscle rigidity and risus sardonicus. Spasm of the pharyngeal muscles may result in dysphagia, and spasm of the laryngeal muscles may result in asphyxia. The **generalised muscle spasms are extremely painful**, and may be prolonged, giving rise to opisthotonus. The sympathetic system can be affected, causing lability of temperature, blood pressure and cardiac function.

Early signs will be helpful in making the diagnosis. The mother may complain of an abnormal cry ('baby cannot cry well'), because she has noticed that trismus prevents the mouth from opening. This happens before suckling is affected. If one is uncertain, a slight touch stimulus may initiate spasm or rigidity. History of the birth (usually at home) and of how the cord was cut is informative, although not particularly discriminating. Contamination at birth (e.g. being born on to the floor with or without cord cutting with an unsterile instrument) is more likely to result in tetanus than for example contamination following a circumcision, but either could be responsible.

The diagnosis of tetanus is made clinically by excluding other causes of tetanic spasms, such as hypocalcaemic tetany, phenothiazine reaction, strychnine poisoning, and hysteria in the older child.

Management of established tetanus

The approach to treatment given in this subsection is appropriate for both neonatal and childhood tetanus.

The aims of management are as follows:

- neutralising existing toxin and preventing its further production
- control of spasms
- prevention of complications
- providing adequate nutrition.

On admission

- Secure and maintain the airway, and ensure adequacy of ventilation.
- Insert an intravenous line. IV infusions, even slow IV administration of drugs, may not be possible, because of lack of a suitable IV giving set (even as simple as a burette type) equipment or skilled time. However, an IV cannula should be left *in situ* for drug and antibiotic administration.
- **IM injections must be avoided at all costs, as they will provoke spasms.**
- If the baby or child is in **acute spasm**, this should be terminated by giving **diazepam by bolus IV infusion over 15 minutes (dose 300 micrograms/kg) or rectally (400 micrograms/kg)**. Ensure that for intravenous infusion, diazepam is diluted to 100 micrograms/mL and that extravasation does not occur (very irritant).
- Also give an IV loading dose of 25–40 mg/kg of magnesium sulphate over 20–30 minutes (maximum loading dose is 2 grams).
- **Always have a bag-mask available in case the patient stops breathing as a result of the diazepam and/or magnesium.**
- When the patient is stable, a nasogastric tube, ideally passed by an anaesthetist, will allow fluids, food and drugs to be given with minimal disturbance. Feeds need to be given frequently (ideally hourly) and in small amounts due to reduced gut motility. **In the neonate, regular breast milk feeds via a nasogastric tube are essential.**
- Any obvious wound should be debrided and cleansed, especially if extensive necrosis is present, and previously ill-advised sutures should be removed. In neonatal tetanus, wide excision of the umbilical stump is not indicated.
- Finally, the disease itself does not induce immunity, so after recovery tetanus vaccine must be given for future prevention.

Antibiotics

- Oral (or intravenous) metronidazole (30 mg/kg per day, given in divided doses at 6-hourly intervals; maximum dose 400 mg) is effective in decreasing the number of vegetative forms of *C. tetani* and is the antimicrobial agent of choice.
- IV benzylpenicillin 100–200 mg/kg/day, given in divided doses at 4- to 6-hourly intervals; (75 mg/kg/day in the neonate in 3 divided doses) for the first 48 hours then oral penicillin V 25 mg/kg 6 hourly is an alternative treatment. Therapy for 10–14 days is recommended. Oral therapy can be given after the initial period.

Associated septicaemia is not uncommon in the neonate, and additional broader-spectrum antibiotics will often be required (*see* Section 3.4 for treatment of neonatal sepsis). Hospital-acquired infections are also common, especially pneumonia, and should be appropriately treated.

Neutralisation of toxin

Antitetanus human immunoglobulin (HTIG) is the preparation of choice for neutralising unbound tetanospasmin. It is given by intravenous infusion over 30 minutes at a dose of **5000–10 000 units immediately on admission.** Adverse reactions are rare. **Local instillation is of no benefit.**

For neutralisation of the toxin, HTIG is not available in most countries where it is needed. An equine immunoglobulin may be available and is used (500–1000 units/kg IM; maximum dose 20 000 units). There is a risk of anaphylaxis (*see* Section 5.1.B for management), so adrenaline must be immediately available if equine immunoglobulin is given. Immune globulin intravenous (IGIV) contains antibodies to tetanus and can be considered for treatment in a dose of 200–400 mg/kg if HTIG is not available.

Management of spasms and hypertonicity

- Spasms can usually be controlled by slow IV injection of diazepam, 200 micrograms/kg followed by IV 25–40 mg/kg of magnesium sulphate over 20–30 minutes (maximum loading dose 2 grams).
- Subsequently give IV diazepam (200 micrograms/kg every 4–6 hours) and magnesium sulphate (10–20 mg/kg 2- to 4-hourly IV).
- Stop diazepam if magnesium alone controls the spasms.
- Reduce the dose of diazepam if apnoeic episodes occur.
- **Always have a bag-mask available in case the patient stops breathing as a result of the diazepam and/or magnesium.**
- Give paracetamol 25 mg/kg 6-hourly for pain (20 mg/kg in the neonate). If this is insufficient, the WHO pain ladder approach should be adopted. Oral or IV morphine may be needed (*see* Section 1.15).

Alternative antispasmodic or sedative drugs

- Phenobarbitone (15 mg/kg in one or two divided doses) as a loading dose then 5 mg/kg given once daily can be used for breakthrough spasms.

Ventilation and prevention of complications

Hospitals in regions with a high prevalence of neonatal tetanus may not have appropriate facilities for ventilation, or even for emergency intubation of neonates; bag-and-mask ventilation, when apnoeic attacks occur, may be the only alternative.

Many patients have major problems with pharyngeal spasms/upper airway obstruction and are sometimes best managed with a tracheostomy and pharmacological control of the spasms (sometimes the tracheostomy may need to be undertaken as an emergency procedure). Up to a third of those who need a tracheostomy do not require ventilation.

- Intubation can be very difficult because of pharyngeal/laryngeal spasm, and often a mini-tracheostomy without prior intubation may be appropriate, provided experts for the procedure and anaesthesia are present.
- Infusions of morphine are essential to minimise suffering due to severe pain. Under no circumstances should paralysing drugs be given to children who are intubated and ventilated without infusions of morphine.

Neonates rarely receive ventilation. Also, few places where tetanus occurs will have appropriate ventilators, or staff who are skilled in intubation and ventilation of children. An alternative way to support breathing is by bag-and-mask ventilation as often as necessary for the apnoeas that occur secondary to bouts of spasms and/or the drugs given to treat the spasms.

Good nursing and frequent monitoring, with particular attention to gentle suction under direct vision of secretions from the airway, maintenance of adequate hydration, temperature, mouth hygiene, turning of the patient to avoid orthostatic pneumonia and bed sores, will reduce complications.

- The child should be nursed in a quiet environment with low-level lighting. Sudden loud noises should be avoided.
- It will be helpful to involve the mother in management to call the staff if the baby goes into spasm or stops breathing. She can also be taught to feed the baby by tube (including checking position by suction of the tube before each feed) and taught minimal handling techniques. She could also count minor spasms, although she may not be able to chart them.
- Invasive procedures should be kept to a minimum and preceded by appropriate analgesia. There must be **continuous** observation by experienced personnel.
- In a high-dependency care unit, cardiac function should ideally be monitored by ECG to detect toxin-induced arrhythmias and autonomic instability.

TABLE 6.1.L.1 Guide to tetanus prophylaxis in routine wound management in children

History of absorbed tetanus toxoid (doses)	Clean, minor wounds		All other wounds[a]	
	Td or Tdap[b]	HTIG[c]	Td or Tdap[b]	HTIG[c]
Less than 3 or unknown	Yes	No	Yes	Yes
3 or more[d]	No[e]	No	No[f]	No

Td = adult-type diphtheria and tetanus toxoid vaccine, Tdap = booster tetanus toxoid, reduced diphtheria toxoid and acellular pertussis, HTIG = human tetanus immune globulin.

[a] Such as, but not limited to, wounds contaminated with dirt, faeces, soil and saliva, as well as puncture wounds, avulsions, and wounds resulting from missiles, crushing, burns and frostbite.

[b] Tdap is preferred to Td vaccine for adolescents who never have received Tdap vaccine. Td is preferred to tetanus toxoid (TT) vaccine for adolescents who have received Tdap vaccine previously, or when Tdap vaccine is not available.

[c] Immune globulin intravenous should be used when HTIG is not available.

[d] If only three doses of fluid toxoid have been received, a fourth dose of toxoid, preferably an adsorbed toxoid, should be given. Although licensed, fluid tetanus toxoid rarely is used.

[e] Yes, if 10 years or more have elapsed since the last tetanus-containing vaccine dose.

[f] Yes, if 5 years or more have elapsed since the last tetanus-containing vaccine dose. More frequent boosters are not needed, and can accentuate adverse effects.

- High-dependency care of severe cases of tetanus may be necessary for up to 3–4 weeks.

It is important to realise that the child/baby has unimpaired consciousness and is aware of what is taking place. Prescribe regular and frequent analgesia, as antispasmodics alone do not prevent the suffering resulting from painful spasms or painful procedures. The spasms are also very frightening and distressing for the parents.

Rigidity will take longer to resolve than the spasms.

Monitoring

Only absolutely essential blood tests should be performed, to avoid precipitating spasms.

- Glucose, urea and electrolytes.
- A chart of the occurrence of spasms can be helpful.
- Cardiac monitoring.
- Pulse oximetry.
- Fluid input/output.
- Calorific intake.

Prognosis

The prognosis for neonatal tetanus is poor, especially with a short incubation period (< 7 days) or with rapid evolution of symptoms. Pyrexia, tachycardia and frequent spasms (> 20 spasms in 24 hours) also indicates a poor prognosis. Quality of nursing care and the **availability of high-dependency care facilities greatly affect the outcome, and where these facilities are available mortality may be as low as 20%**.

In children who survive neonatal tetanus, motor difficulties may be permanently present. Older children may have muscle weakness and atrophy, and difficulties with speech, balance and memory.

Prevention

Every child should receive tetanus vaccine according to the expanded programme of immunisation (EPI). All pregnant women should receive two doses antenatally, as this will protect the baby for the first 4–6 months of age.

Tetanus toxoid should be given, combined with diphtheria and pertussis, to infants according to national schedules. Note that both HIV infection and placental malaria reduce the transplacental transfer of anti-tetanus antibodies *in utero*. Sterile handling of the umbilical cords by midwives or appropriately trained traditional birth attendants should also reduce the incidence of neonatal tetanus. Sterilisation of hospital supplies will prevent the rare instances of tetanus that may occur in a hospital from contaminated sutures, instruments or plaster casts.

A booster tetanus toxoid vaccine with or without tetanus immune globulin (TIG) in the management of wounds depends on the nature of the wound and the history of immunisation with tetanus toxoid (*see* Table 6.1.L.1).

Further reading

World Health Organization (2014) *Immunisation Surveillance, Assessment and Monitoring*.
www.who.int/immunization_monitoring/diseases/tetanus/en/

6.1.M Trachoma

BOX 6.1.M.1 Minimum standards

- Bilamellar tarsal rotation.
- Oral azithromycin.
- Ocular tetracycline.
- The WHO SAFE strategy: Surgery for trichiasis, Antibiotics to clear infection, and Facial cleanliness and Environmental improvement.

Introduction

Trachoma is the most common infectious cause of blindness worldwide. It is caused by *Chlamydia trachomatis*, certain serotypes of which preferentially infect the conjunctival epithelium. The organism is transmitted from person to person by direct contact, fomites (objects capable of carrying infectious organisms), and eye-seeking flies. Disease clusters in families; the greatest risk factor for infection is sharing a bedroom with an active case. Repeated episodes of infection over many years cause an accumulation of scar tissue in the tarsal plate and tarsal conjunctivae of the upper lids. Contraction of the scar may produce trichiasis and/or entropion, and the resulting corneal abrasion by in-turned lashes leads to corneal scarring. This eventually causes blindness. In paediatric practice in endemic areas, active trachoma is seen frequently. Blinding complications may start to appear in the second and third decades of life.

Clinical features

These are best presented using the framework of the WHO simplified clinical grading system. Examination for trachoma involves inspection of the lashes and cornea, followed by eversion of the upper eyelids to examine the tarsal conjunctivae (*see* Figure 6.1.M.1). A ×2.5 magnifying loupe and torch (or daylight) should be used. These tools are sufficient to determine the presence or absence of signs that are considered in this grading scheme. Each eye is graded separately.

Trachomatous inflammation – follicular (TF): the presence of five or more follicles at least 0.5 mm in diameter in the central part of the upper tarsal conjunctiva. Follicles appear as white or yellow-grey semitransparent patches or swellings beneath the conjunctiva. Fewer than five follicles, or follicles at the nasal or temporal margin, may be normal.

Trachomatous inflammation – intense (TI): pronounced inflammatory thickening of the upper tarsal conjunctiva obscuring more than half of the normal deep tarsal blood vessels.

TF and TI are both forms of 'active trachoma'; they are associated with infection with *Chlamydia trachomatis*, **although not all infected individuals exhibit these signs, and not all individuals with these signs are infected**. Patients with active trachoma may be asymptomatic or complain of irritable red eyes or a whitish discharge.

Trachomatous scarring (TS): the presence of easily visible scars in the tarsal conjunctiva. Scars appear as white bands, lines, or sheets. TS is the result of repeated cycles of inflammation and resolution over many years and itself is virtually asymptomatic, although scarring of eyelid glands may produce symptoms of dry eye.

Trachomatous trichiasis (TT): at least one eyelash rubs on the eyeball, or there is evidence of recent removal of in-turned eyelashes. TT is intensely irritating to the sufferer, and they may choose to pull out their eyelashes in an attempt to reduce the discomfort. There may be discharge from superadded bacterial infection of the abraded cornea. Except in hyperendemic areas, it is unusual to observe TT in children.

Corneal opacity (CO): easily visible corneal opacity over the pupil, so dense that at least part of the pupil margin is blurred when viewed through the opacity. Such corneal opacities cause significant visual impairment.

It is important to remember that these grades are not mutually exclusive. A patient with active trachoma (TF and/or TI) may also show signs of the late complications of the disease.

There are other signs of trachoma that are not included in the simplified grading scheme:

- Papillae are often visible in individuals with active trachoma, but are not specific for trachoma. These are small elevations of the conjunctival surface that give the conjunctiva a velvety appearance. They are more easily seen using a slit lamp.
- Fibrovascular connective tissue may grow inwards from the limbus to invade the anterior layers of the superior cornea in response to infection. The ingrowth is known as pannus. The new blood vessels may persist after resolution of infection.
- Sometimes follicles are found under the bulbar conjunctiva at the limbus as well as deep to the tarsal conjunctiva. Scarring of limbal follicles may subsequently leave small depressions known as Herbert's pits.

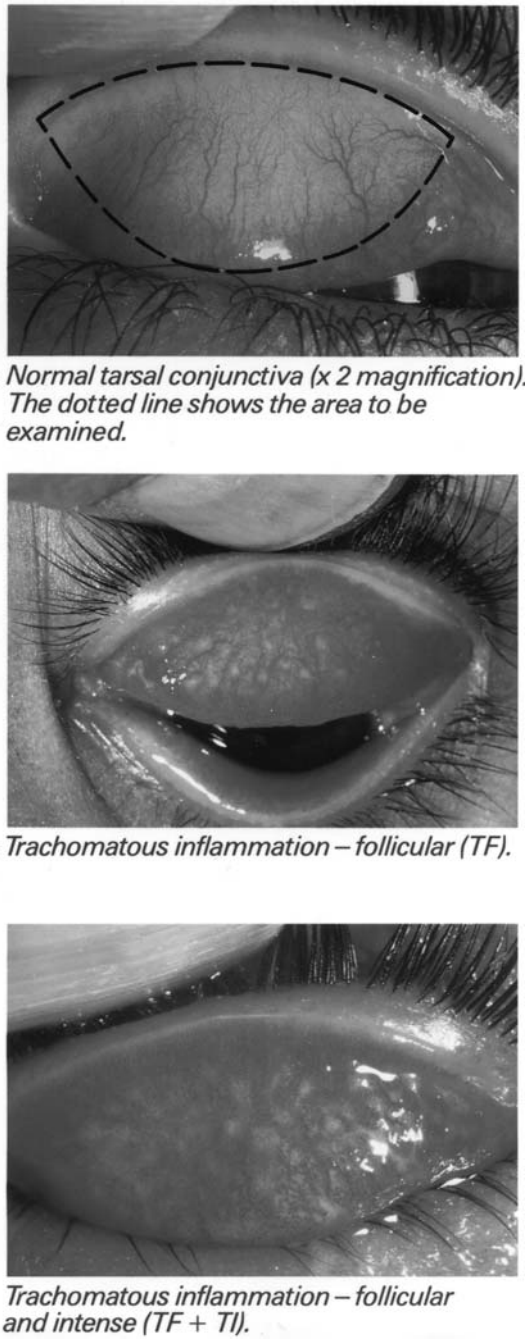
Treatment

For active trachoma (TF and/or TI), antibiotics are required. Topical tetracycline eye ointment 1% is effective when applied to both eyes twice daily for 6 weeks. A single dose of oral azithromycin (20 mg/kg, up to a maximum dose of 1 gram) is just as effective, is better tolerated than topical tetracycline, and can be directly observed, so is associated with higher compliance rates.

Trichiasis or entropion requires surgical management to restore the margin of the eyelid to its normal position, so that contact between the lashes and globe is interrupted. Bilamellar tarsal rotation is the procedure currently recommended by the World Health Organization; it is performed under local anaesthetic and can be undertaken at the village level by trained ophthalmic nurses or ophthalmic assistants.

Corneal opacity can theoretically be managed by corneal graft. Unfortunately, few endemic countries have the resources to establish a transplant programme, and because of new vessel growth from the limbus and abnormalities of the tear film in the trachomatous eye, the risk of graft rejection or failure is very high.

The identification of signs of trachoma in an individual should prompt screening of other members of that individual's community. Antibiotic treatment of individuals presenting to healthcare facilities is unlikely to have any impact on the incidence of blindness from trachoma in the communities from which those individuals come. Comprehensive community-based management of trachoma is necessary wherever the prevalence of disease is high.



a *Normal tarsal conjunctiva (x 2 magnification). The dotted line shows the area to be examined.*

b *Trachomatous inflammation – follicular (TF).*

c *Trachomatous inflammation – follicular and intense (TF + TI).*

FIGURE 6.1.M.1 (a) Normal tarsal conjunctiva (×2 magnification). The dotted line shows the area to be examined. (b) Trachomatous inflammation – follicular (TF). (c) Trachomatous inflammation – follicular and intense (TF + TI).

Prevention

Blindness from trachoma is preventable. The acronym SAFE has been adopted by the WHO and partners to encapsulate the recommended approach to controlling trachoma. It comprises Surgery for trichiasis, Antibiotics to clear infection, and Facial cleanliness and Environmental

improvement (provision of water and acceptable means for disposal of human faeces) to reduce transmission. Surgery should be offered to all individuals with trichiasis. The 'A', 'F' and 'E' components should be implemented district-wide wherever the prevalence of TF in 1- to 9-year-olds is 10% or higher. The WHO plans to use the 'SAFE' strategy to achieve the elimination of trachoma as a public health problem by the year 2020.

6.1.N Tuberculosis

BOX 6.1.N.1 Minimum standards

- All children with suspected TB should be tested for human immunodeficiency virus (HIV).
- All children with HIV should have a chest X-ray to look for TB.
- Children who cannot expectorate spontaneously should have induced sputum or gastric aspirate.
- Specimens should be sent for both microscopy for acid-fast bacilli and TB culture or Xpert MTB/RIF test.
- Drug-resistant TB needs expert supervision.
- Tracing, screening and prophylaxis of contacts.

Introduction

The global incidence of tuberculosis (TB) has been falling since 2002. However, in 2009 there were still almost 10 million children who were orphans as a result of parental deaths caused by TB. About 13% of TB cases occur among people living with HIV. India and China accounted for 40% of notified cases and Africa accounted for another 24%. Treatment for smear-positive pulmonary TB was 87% in 2009.

Major factors in the global increase in tuberculosis since the mid-1980s include the HIV pandemic, migration of people from countries with a high prevalence of tuberculosis to industrialised countries (particularly refugees), poverty, overcrowding and failure of investment in tuberculosis control programmes. Multi-drug resistance is a major concern.

Epidemiology

- In low-income countries, the risk of developing infection is up to 2.5% per annum.
- The age group at highest risk of developing disease is 0–5 years, with risk up to 30–40% (especially under 1 year) and at puberty.
- Spread is by untreated smear-positive adults who may infect up to 10–15 people per year.
- Children are generally non-infectious, except for older children and adolescents with cavitatory TB.
- Children with untreated tuberculosis contribute to the pool of adults with reactivated disease.
- The WHO estimates that TB in children contributes to 1.3 million annual cases (or 15%) in low-income countries and 450 000 deaths worldwide.

Factors that predispose tuberculosis-infected children to develop systemic disease

- Age under 5 years, and especially under 1 year.
- Household contact with smear-positive disease.
- Malnutrition.
- Tuberculosis infection in previous 2 years.
- Immunosuppression, especially HIV infection.

Tuberculin skin test

- The tuberculin skin test (TST), also called the Mantoux test, is useful for screening contacts. The TST is less useful for diagnosing active TB because a negative result does not exclude TB. If TB is clinically suspected, efforts should be made to collect diagnostic specimens, exclude other causes, and then treat if TB is the most likely diagnosis (do not treat as a diagnostic test).
- Use either 5 TU of tuberculin (PPD-S) or the 2 TU of tuberculin (PPD RT2 3).
- Inject tuberculin (PPD-S) **intradermally** into the upper third of the flexor surface of the forearm with a 1-mL syringe and a short bevel gauge 25–27 needle producing a wheal of at least 5 mm. Read the transverse diameter of induration at 48–72 hours. Regard induration of 0–5 mm as negative, 6–9 mm as indeterminate, and likely to be associated with environmental mycobacteria, and 10 mm or more as indicative of infection with *Mycobacteria tuberculosis*, except in the child who has had BCG in the previous few years, when induration of 15 mm is required.
- In resource-limited countries where BCG is given at birth, most children will have a negative tuberculin test by 10 years of age, and thus an induration of 10 mm in children this age or older may be regarded as supportive of *M. tuberculosis* infection.
- Negative or reduced response to tuberculin occurs in malnutrition, immunosuppression associated with HIV or other immunodeficiency states, recent viral or some bacterial diseases such as pertussis, overwhelming tuberculosis and non-respiratory tuberculosis. Thus with these conditions an induration of 6–9 mm may be indicative of tuberculosis.
- Remember that a negative tuberculin does not exclude tuberculosis, and additional work-up may be warranted in any suspected child.
- Tuberculin skin test interpretation must be undertaken bearing in mind the age, epidemiology and underlying illness, if any.

Serology

Antibody tests are inconsistent and imprecise. They do not improve outcomes for patients and should not be used. The WHO recently gave guidelines recommending against the use of serology tests for TB. It is the first negative recommendation to be made by the WHO, describing it as 'inaccurate and useless', after 'overwhelming' evidence that suggested it produced an 'unacceptable level' of false-positive or false-negative results.

Pathogenesis

- Inhalation of the tubercle bacillus into an alveolus establishes the primary (Ghon) focus. In the 4- to 8-week period before the cell-mediated immune (CMI) response develops, there is spread to regional lymph nodes, and small numbers of bacilli disseminate throughout the body in the lympho-haematogenous system.
- Certain organs favour survival of tubercle bacilli, including regional nodes, epiphyseal lines of bones, cerebral cortex, renal parenchyma and apical regions of the lungs (Simon focus).
- Establishment of an adequate CMI response (which coincides with the appearance of sensitisation to tuberculin) in most cases results in control or eradication of proliferating tubercle bacilli at these sites.
- The primary focus is seldom detected on chest X-ray; enlarged hilar/paratracheal nodes or parenchymal complications are the usual evidence of the primary complex.
- **Primary tuberculosis of the lung** is usually a manifestation of lympho-bronchial disease, with local compression or erosion of the bronchi. **Extrathoracic disease** is due to local spread of disease at metastatic sites (e.g. lymph nodes, brain, bone, kidney and abdomen).
- Dissemination of large numbers of tubercle bacilli may result in acute miliary disease or, less commonly, a chronic disseminated (cryptic) tuberculosis.
- Erythema nodosum and phlyctenular conjunctivitis are hypersensitivity reactions which may occur during primary tuberculosis.
- The risk of developing symptomatic disease following primary tuberculosis is highest (around 50%) in the first 1 to 2 years after infection and the rest in the individual's lifetime.

Tuberculosis in adolescence

This may result from reactivation of a primary infection, exogenous infection, or both. There is a strong hypersensitivity reaction in the lungs with local infiltration and often cavity formation. Pulmonary lymph node enlargement and extra-thoracic dissemination is uncommon.

Clinical features

In well-resourced countries, the majority of children with respiratory tuberculosis are asymptomatic and are picked up through contact tracing and will generally have early primary disease. In resource-limited countries, only children with symptomatic disease present, and they are therefore only 'the tip of the iceberg'.

The following are some of the key features of tuberculosis in children:

- Fever, cough, anorexia, weight loss, wheezing, night sweats and malaise are common.
- Extrapulmonary disease may involve other tissues and organs, such as the central nervous system, lymph nodes and gastrointestinal tract.
- Findings can include lung findings (dull resonance) or involvement of other organs in extrapulmonary tuberculosis, such as hepatosplenomegaly, lymphadenopathy, mass, etc. (*see* Table 6.1.N.1).

TABLE 6.1.N.1 Typical features of common forms of extrapulmonary TB in children

Type of extrapulmonary TB	Key clinical findings
TB lymphadenitis (most common)	Enlargement and swelling of lymph nodes
Pleural/pericardial TB	Cough and shortness of breath
TB meningitis	Headache, vomiting, fever, neck stiffness, seizures, confusion and coma
Miliary TB	Very sick, respiratory distress, hepatosplenomegaly, diffuse lymphadenopathy
Gastrointestinal TB	Abdominal pain, diarrhoea, mass or ascites
Spinal TB	Backache with or without loss of function in lower limbs
TB arthritis	Pain and swelling of joints (usually monoarthritis)

HIV and tuberculosis

Children living with HIV who have poor weight gain, fever or current cough, or contact history with a TB case, may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, children should be offered isoniazid preventive therapy (IPT) regardless of their age.

Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB. Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening and have no contact with a TB case should receive 6 months of IPT (10 mg/kg/day, maximum 300 mg/day) as part of a comprehensive package of HIV prevention and care services.

With regard to children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive 6 months of IPT if the evaluation shows no TB disease. All children living with HIV after successful completion of treatment for TB disease should receive isoniazid for an additional 6 months.

- Features of tuberculosis in children with perinatally acquired HIV infection are not well defined.
- Many HIV-infected infants probably succumb to bacterial infections and *Pneumocystis jirovecii* pneumonia before contracting tuberculous infection.
- In older children, there is difficulty in diagnosis due to the following reasons:
  - The tuberculin reaction is positive in only 20% of cases.
  - There is confusion with HIV-related respiratory disorders, including lymphocytic interstitial pneumonitis (LIP), superimposed viral/bacterial infections, chronic interstitial pneumonitis, Kaposi's sarcoma and bronchiectasis.
  - There is often a lack of facilities for culturing *M. tuberculosis.*
- Atypical clinical and radiological features of TB are much more common in children with HIV with more severe and complicated disease.
- HIV/tuberculosis co-infected children are more likely to develop disseminated tuberculosis and meningitis, have cavitary pulmonary disease and may have a poor response to treatment and a higher mortality if not started on ART.

- Because of the difficulty in confirming tuberculosis in symptomatic HIV-infected children, many children probably receive unnecessary tuberculous chemotherapy.
- Finger clubbing may be seen in chronic tuberculosis, and is common in HIV-related pulmonary disorders.
- Standard 6-month chemotherapy is given in uncomplicated pulmonary tuberculosis.

Respiratory tuberculosis

- Most respiratory tuberculosis results from complications of lympho-bronchial disease and includes segmental lesions, consolidation, collapse and obstructive emphysema.
- In young children, small cavities may develop during the course of primary (especially progressive) tuberculosis, but they are classically seen in the adolescent period.
- Large pleural effusions usually occur in older children and adolescents.
- Radiological features of pulmonary tuberculosis may be atypical in HIV infection, other immunosuppressed states and/or malnutrition.

Pericarditis

Tuberculosis should be considered in all cases of pericarditis. *M. tuberculosis* may be cultured from a pericardial tap in over 50% of the cases.

Lymph node disease

- This may result from a focus in the upper lung fields or from haematogenous spread.
- Diagnosis may be made by biopsy or fine-needle aspiration.
- Swelling and softening of nodes may continue for months after treatment has been completed.
- In well-resourced countries, environmental mycobacteria are now a far commoner cause of chronic granulomatous disease of cervical lymph nodes than tuberculosis in indigenous young children.

Miliary tuberculosis

- This is commonest in young children and in those who are immunosuppressed, usually occurring within 3–12 months of primary infection.
- Chest X-ray (except in the early stages) will demonstrate a 'snowstorm' or miliary appearance.
- Meningitis is a common complication. Therefore a lumbar puncture should be performed in all cases.
- The WHO advises 9–12 months of anti-TB chemotherapy.

Meningitis

- This is commonest in children under 5 years, and often occurs within 6 months of infection.
- The onset is usually insidious and the diagnosis is often delayed. Late diagnosis is invariably complicated by neurological dysfunction or death.
- Prolonged fever, irritability, headache, vomiting, mental status changes, visual symptoms, focal neurological deficits or cranial nerve palsies, and seizure are some of the common presentations in children with tuberculous meningitis.
- CSF: cell count is usually less than 500/mm^3 and mainly lymphocytic, but polymorpho-neutrophils may be prominent early on, which may cause confusion with partially treated bacterial meningitis. Protein levels are usually raised (0.8–4 grams/litre) and glucose levels are low. However, on admission CSF values may be within normal limits and lumbar puncture must be repeated if there is any doubt.
- **Brain imaging, such as CT or MRI (if available)**, should be undertaken at diagnosis and at 3–4 months, and at any time when there is neurological deterioration, to detect complications such as hydrocephalus and tuberculomata.

Management

- A four-drug regimen in the upper range of drug doses is recommended for 2 months, followed by a two-drug regimen for 10 months in uncomplicated tuberculosis meningitis. It consists of the following four drugs given for first 2 months:
  - H: isoniazid 20 mg/kg once daily orally, or by IM or slow IV injection; (maximum 300 mg daily) **plus**
  - R: rifampicin 15–20 mg/kg once daily orally or by IV infusion over 2–3 hours; (maximum 600 mg daily) **plus**
  - Z; pyrazinamide 40 mg/kg once daily orally; (maximum 2 grams daily) **plus**
  - E: ethambutol 20 mg/kg once daily orally (maximum 1.5 grams daily).

Thereafter, isoniazid **plus** rifampicin alone are continued for 10 months. The WHO also now advises 12 months of therapy, although shorter regimens have been shown to be adequate in some studies.

Corticosteroids must be given in all cases with initiation of therapy. Dexamethasone 0.6 mg/kg/day in two divided doses or prednisolone 2–4 mg/kg/day is given for 4 weeks and tapered over 2 weeks for a total duration of 6 weeks.

A ventriculo-peritoneal shunt may be required for obstructive hydrocephalus (if available).

Bone and joints

- These are frequently missed in the early stages because of a low index of suspicion.
- The spine is affected in 50% of the cases, followed by knee, hip and ankle. The most serious complication is spinal compression.
- The diagnosis is made by histology, Ziehl–Neelsen (ZN) stain and mycobacterial culture of tissue that may be positive, and **if in doubt specimens should be sent for polymerase chain reaction (PCR)**.
- **The WHO advises the standard 12 months of anti-TB chemotherapy, similar to that for TB meningitis.**

Abdominal tuberculosis

- This may present with ascites, abdominal nodes or masses, or diarrhoea with or without abdominal pain, or as gastrointestinal obstruction.
- The diagnosis is usually made on bacteriological examination of ascitic fluid or a biopsy.
- The standard three- to four-drug regimen is used for therapy for a total of 6–9 months in uncomplicated cases.
- Ultrasound and **CT or MRI (if available) may be required in evaluation and to detect any complications**.

Perinatal tuberculosis

- Congenital tuberculosis is rare but should always be

considered in sick neonates or infants, especially in areas where HIV/tuberculosis co-infection is common.
- If a mother has completed tuberculosis chemotherapy during pregnancy or has inactive disease, her infant should be given BCG at birth.
- If she has active disease or is still requiring treatment, the infant should be given isoniazid 10 mg/kg once daily for 3–6 months.
- Once the mother and infant are both on appropriate treatment, the infant may breastfeed unless the mother has multi-drug-resistant TB. A tuberculin test and chest X-ray is then performed on the infant. If they are negative, BCG is given; if it is positive, full investigations for tuberculosis are undertaken. If no evidence of disease is detected, isoniazid is continued for another 3–4 months. If tuberculosis is suspected, full treatment with 4 drugs is given at standard doses (*see* Table 6.1.N.2 and Table 6.1.N.3 on management).

Danger signs for TB
- Suspicion of tuberculous meningitis.
- Extensive pulmonary or miliary TB.
- TB in an infant or a child with HIV.
- Symptoms and signs such as seizures, coma, severe respiratory distress, gastrointestinal obstruction or severe malnutrition.

Diagnosis of TB

Diagnosis depends on eliciting key points that may increase the yield of TB cases. A high index of suspicion in a child who has prolonged or unexplained illness should warrant investigation for TB. Sputum or gastric aspirate for acid-fast bacilli (AFB) stain and culture should always be attempted.

Standard methods for diagnosis are the tuberculin test and a chest X-ray. Even in resource-limited countries, every effort should be made to obtain a diagnostic specimen from gastric aspiration or sputum induction (see below). In poor communities the tuberculin test is often negative (or unavailable) and the chest X-ray might not be available, easy to interpret or have films of good enough quality. Many children are often over-diagnosed, especially in areas with high HIV prevalence.

TB infection is diagnosed using the tuberculin skin test. It is considered positive if there is Mantoux induration of ≥ 10 mm in children who have not received BCG vaccination or ≥ 15 mm in children who have received BCG recently. Interferon-gamma release assays (IGRA) detect latent and active infection but cannot differentiate between the two. They may be positive in some cases of HIV infection and malnutrition when the tuberculin test is negative, but in these circumstances there is also a higher rate of false-negative IGRA results. However, they are currently too expensive for resource-limited countries, and their routine use is not advised by the WHO.

Key features suggestive of pulmonary TB

Three or more of the following should strongly suggest a diagnosis of TB:
- chronic symptoms suggestive of TB (prolonged fever, cough, night sweats weight loss)
- physical signs suggestive of TB (chronic lymphadenopathy, abdominal mass, gibbus or monoarthritis)
- a positive tuberculin skin test (induration > 10 mm)
- chest X-ray suggestive of TB (hilar adenopathy, cavitation, pleural effusion, infiltrate; see below for pictures).

Investigations
- Tuberculin test > 10 mm or > 5 mm in malnutrition or HIV.
- Chest X-ray: lymphadenopathy, collapse/consolidation with or without persistent opacity, cavitation, miliary appearance.
- Histology: lymph node or other tissue biopsy.
- Smear/culture: gastric aspirate, induced sputum, nasopharyngeal aspirate, laryngeal swab, bronchoscopy or body fluids.
- Ultrasound: chest, abdomen, lymph nodes, pericardium and brain.
- **CT or MRI (if available).**
- HIV antibody tests (if relevant).

Except in adolescents with cavitary disease, most tuberculosis in children is paucibacillary (low number of mycobacteria). Young children cannot expectorate.

Tuberculosis may be evident on chest X-ray, especially in older children.
- Gastric aspiration should be undertaken in the early morning while the child is lying down. Ziehl–Neelsen (ZN) staining of gastric aspirate is positive in only about 10% of children with advanced pulmonary tuberculosis, and culture is positive, under optimal conditions, in only 30–50% of cases.
- Alternative methods are sputum induction using nebulised 3% hypertonic saline, nasopharyngeal aspiration and laryngeal swabs. None of these has a sensitivity of more than 25–30%. Sputum induction requires a nebuliser and appropriate equipment, and must be undertaken in a room with adequate ventilation.
- **The polymerase chain reaction (PCR) on histological specimens may be useful if the ZN stain is negative.** In CSF it has similar sensitivity (around 50%) to culture. It is reserved for special cases where an urgent diagnosis is required.
- Young children, especially those who are sick, malnourished or deteriorating, or where tuberculous meningitis is suspected, should be considered for treatment even though investigations are inconclusive. In other cases with pulmonary disease where the diagnosis is not clear, a course of appropriate antibiotics should be given for 7–10 days and the chest X-ray repeated after 2 weeks or so. If there is no improvement or deterioration, a full course of anti-tuberculosis chemotherapy may be given and progress carefully monitored to document the response. If the tuberculin test is negative initially it should be repeated after 3 months, when the patient's immune system has normalised, and it may become reactive at that time.
- Increase in weight (measured daily or weekly) and loss of fever (measured twice daily) indicate a response to treatment. If treatment is given for suspected rather than proven tuberculosis, and no resolution or improvement in symptoms occurs within 4 weeks, this suggests that tuberculosis is unlikely. However, the course should still be completed and an alternative diagnosis sought, such as drug-resistant tuberculosis, fungal infection or malignancy.

Xpert MTB/RIF test

The Xpert MTB/RIF is a test for rapid diagnosis of TB and drug-resistant TB. It is a TB-specific automated, cartridge-based nucleic amplification assay, and it detects *Mycobacterium tuberculosis*, as well as mutations conferring resistance to rifampicin, directly from sputum in an assay that provides results within 100 minutes.

Results from field demonstration studies found that a single Xpert MTB/RIF test can detect TB in 99% of patients with smear-positive pulmonary TB and more than 80% of patients with smear-negative pulmonary TB. The co-existence of HIV does not significantly affect the performance of Xpert MTB/RIF.

Furthermore, Xpert MTB/RIF can detect rifampicin resistance with 95.1% sensitivity and exclude resistance with 98.4% specificity. The WHO endorsed the Xpert MTB/RIF assay in December 2010. It should be used as the initial test in individuals with suspected multi-drug-resistant TB (MDR-TB) or HIV/TB. It may be used as a follow-on test to microscopy where MDR-TB and/or HIV is of lesser concern, especially in smear-negative specimens. It is effective in children where sputum may need to be obtained by induction via nasopharyngeal aspirate after salbutamol and then saline nebuliser.

Management of TB in children

With the exception of CNS and osteo-articular disease (see below), both pulmonary and extra-pulmonary tuberculosis may be treated with standard 6-month chemotherapy. The standard treatment regimen for all patients with drug-susceptible, uncomplicated TB is made up of an intensive phase lasting 2 months and a continuation phase lasting 4 months. During the intensive phase 4 drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) are used to rapidly kill the tubercle bacilli. Infectious patients become less infectious within approximately 10–14 days of starting treatment and symptoms abate. In the continuation phase, 2 drugs (isoniazid, rifampicin) are used, over a period of 4 months.

For non-HIV-infected children with a low risk of isoniazid resistance, ethambutol can be omitted. Ethambutol should not be given in a dose higher than 20 mg/kg/day to children under 5 years, as they may be unable to report visual disturbance associated with optic neuritis.

TABLE 6.1.N.2 Regimens for treatment of uncomplicated susceptible pulmonary tuberculosis

Regimen	Total duration
Standard daily	
Isoniazid, rifampicin, pyrazinamide ethambutol* for 2 months, then isoniazid, rifampicin for 4 months†	6 months
Intermittent three times weekly	
Isoniazid, rifampicin, pyrazinamide, ethambutol for 2 months, then isoniazid, rifampicin three times weekly for 4 months	6 months

* In HIV-uninfected children with a low risk of isoniazid resistance, ethambutol can be omitted.

† For central nervous system and osteo-articular disease, the continuation phase should be 10 months (total duration 12 months).

Thiacetazone is no longer used as a first-line drug. Thiacetazone may cause severe reactions in HIV-infected patients.

Presently DOTS (directly observed treatment, short course) is not generally practised for children, as it is assumed that parents will supervise treatment, but where DOTS is practised in the community it may be appropriate to include children.

During the continuation phase of treatment, thrice-weekly regimens can be considered for children known to be HIV-uninfected and living in an area of low HIV prevalence and settings with well-established directly-observed therapy (DOT). However, our advice is that in low resource settings, all children with TB should be treated with daily regimes (for dosage *see* Table 6.1.N.4).

For central nervous system and osteo-articular disease, the continuation phase should be 10 months (total duration 12 months).

Adverse reactions to tuberculosis chemotherapy are uncommon and if they occur it is usually within 6–8 weeks of starting treatment. Liver transaminases may increase two- to threefold during treatment with isoniazid and rifampicin, but drug therapy may be continued if there is no jaundice or symptoms of liver toxicity (e.g. nausea, vomiting, malaise or liver tenderness). Viral hepatitis (especially hepatitis A) should be considered if jaundice occurs. Adjunct treatment with corticosteroids in meningitis is indicated at initiation of therapy (see above) and may enhance resolution of disease in lympho-bronchial disease, pericarditis, pleural effusion and severe miliary disease with alveolar capillary block. Prednisolone 1.5–2.0 mg/kg/day is given for 2–3 weeks and then tailed off over 2 weeks (see treatment of meningitis).

Follow-up

All children who are started on anti-tuberculous therapy must be followed closely, preferably every month. Clinical, radiologic and mycobacteriologic improvement and adverse effects of drugs must be monitored. In children, weight gain and resolution of signs and symptoms are indicators of a good response to treatment. Routine laboratory tests such as liver function tests and X-rays are rarely needed in children. Those children with severe disease, poor response,

TABLE 6.1.N.3 Summary of treatment of pulmonary or peripheral lymph node TB

Area of low HIV prevalence with low levels of isoniazid resistance and child HIV-negative	*2-month intensive phase* Isoniazid Rifampicin Pyrazinamide *4-month continuation phase* Isoniazid Rifampicin
Area of high HIV prevalence or high levels of isoniazid resistance or extensive pulmonary disease	*2-month intensive phase* Isoniazid Rifampicin Pyrazinamide Ethambutol *4-month continuation phase* Isoniazid Rifampicin

TABLE 6.1.N.4 Daily dosage schedule for anti-tuberculous drugs and side effects

Drug	Children: once daily dose	Adolescents under 50 kg: once daily dose	Adolescents over 50 kg: once daily dose	Side effects
Isoniazid daily	10 mg/kg range 7–15 mg/kg Maximum 300 mg 15–20 mg/kg for meningitis	5 mg/kg Maximum 300 mg	5 mg/kg Maximum 300 mg	Hepatic enzyme elevation, hepatitis, peripheral neuropathy, hypersensitivity
Rifampicin	15 mg/kg range 10–20 mg/kg Maximum 600 mg 15–20 mg/kg in meningitis	10 mg/kg Maximum 600 mg	10 mg/kg Maximum 600 mg	Orange discoloration of urine and secretions (and contact lenses), nausea, vomiting, hepatitis, febrile reactions, thrombocytopenia
Pyrazinamide	35 mg/kg range 30–40 mg/kg 40 mg/kg in meningitis	25 mg/kg Maximum 1.5 gram	25 mg/kg Maximum 2.0 gram	Hepatotoxicity, hyperuricaemia, gastrointestinal upset, arthralgia, skin rash
Ethambutol	20 mg/kg range 15–25 mg/kg 20 mg/kg in meningitis	15 mg/kg Maximum 2.5 grams	15 mg/kg Maximum 2.5 grams	Optic neuritis, skin rash

Higher range of isoniazid applies to young children. Use mean dosage and round up rather than round down when prescribing except when prescribing ethambutol.

TABLE 6.1.N.5 Three times weekly dosage schedule for anti-tuberculous drugs (from the WHO)

Drug	Children: three times weekly dose given once daily	Adolescents under 50 kg: three times weekly dose given once daily	Adolescents over 50 kg: three times weekly dose given once daily
Isoniazid	20–40 mg/kg Maximum 900 mg	10 mg/kg Maximum 900 mg	10 mg/kg Maximum 900 mg
Rifampicin	10–20 mg/kg Maximum 600 mg	10–20 mg/kg Maximum 600 mg	10 mg/kg Maximum 600 mg
Pyrazinamide	50–70 mg/kg Maximum 3 gram	35 mg/kg Maximum 3 gram	35 mg/kg Maximum 2.5 gram
Ethambutol	25–30 mg/ kg	25–30 mg/kg	25–35 mg/kg

unusual presentations or suspected resistant TB must be referred to an expert.

Multi-drug-resistant TB (MDR-TB) and extreme-drug-resistant TB (XDR-TB)

Rapid drug susceptibility testing of isoniazid and rifampicin should be done at the time of diagnosis (if available). After treatment is started for MDR-TB, further sputum (induced or gastric aspirate) should be obtained monthly to ensure successful treatment. An expert in the management of paediatric TB must be involved in choosing the optimal regimen for a child with drug-resistant TB.

Fluoroquinolones may be used in treatment of MDR-TB in children. Theoretical concerns about cartilage damage from early trials in young dogs have not been evident in children, and these are far outweighed by the benefits in treatment of TB. Later-generation fluoroquinolones (see below) are more effective than earlier ones. Four second-line anti-tuberculous drugs should be used and the intensive phase should include ethionamide or prothionamide, pyrazinamide, a parenteral agent, and cycloserine (or para-aminosalicylic acid (PAS) if cycloserine cannot be used).

The intensive phase should be at least 8 months and the total duration at least 20 months if there was no previous MDR-TB treatment. The continuation phase is usually given as the same oral drugs while stopping the injectable drugs. In children with HIV and MDR-TB, antiretrovirals should be started as soon as possible following initiation of anti-tuberculous therapy, irrespective of CD4 count. The preferred regimen is zidovudine, lamivudine and efavirenz, but if already on antiretrovirals, continue the same regimen. Co-trimoxazole should be added for pneumocystis prophylaxis.

Treatment should be ambulatory rather than in hospital as much as possible.

Groups of second-line anti-tuberculosis agents

Second-line parenteral agent (injectable anti-tuberculosis drugs)

- Kanamycin (Km), 15–30 mg/kg/day (maximum 1000 mg).
- Capreomycin (Cm), 15–30 mg/kg/day (maximum 1000 mg).
- Streptomycin (S) 15–20 mg/kg/day (maximum 1.0 gram).

Fluoroquinolones

- Levofloxacin (Lfx), 15–25 mg/kg/day (maximum 1000 mg).
- Moxifloxacin (Mfx), 7.5–10 mg/kg/day (maximum 400 mg).
- Ofloxacin (Ofx), 15–20 mg/kg/day (maximum 800 mg).

Oral bacteriostatic second-line anti-tuberculosis drugs

- Ethionamide (Eto), 15–20 mg/kg/day (maximum 1000 mg).
- Cycloserine (Cs), 10–20 mg/kg/day (maximum 1000 mg).

TABLE 6.1.N.6 Recommended anti-tuberculous drugs according to resistance pattern of TB culture from list above

Resistance pattern	Change to:
Pan-susceptible	Category 1 (HREZ) (Isoniazid: H Rifampicin: R Ethambutol: E Pyrazinamide: Z)
H (with or without Streptomycin (S))	R – E – Z (6–9 months)
Polyresistant but not MDR	Continue the empirical second-line regimen. Consult with a specialist. Patient may require a combination of first- and second-line drugs
HR HRE	Z – S – Lfx – Eto – Cs – PAS
HREZ	S – Lfx – Eto – Cs – PAS
HRS HRES HREZS	Km – Lfx – Eto – Cs – PAS
Resistance to any second-line drug	Continue the empirical second-line regimen. Consult with a specialist

- Terizidone (Trd), 10–20 mg/kg/day (maximum 1000 mg).
- *p*-aminosalicylic acid (PAS), 150 mg/kg/day (maximum 8 grams (PASER)).

Prevention of TB

- Diagnosis and treatment of 'smear-positive' tuberculosis in adults combined with contact tracing is the key to prevention of childhood tuberculosis.
- Tuberculin-positive children with normal chest X-rays should be given prophylaxis, either isoniazid (10 mg/kg/day, maximum dose 300 microgram) alone for 6 months or in low-incidence countries, isoniazid and rifampicin for 3 months. The age limit for prophylactic therapy depends on national policy, for example, under 5 years in low-income countries as per WHO recommendations.
- HIV-infected infants and children exposed to tuberculosis infection but without active disease should receive isoniazid prophylaxis as described above. The WHO advises that HIV-infected children over 1 year old who are unlikely to have tuberculosis, even in the absence of exposure to tuberculosis, should receive a routine course of isoniazid for 6 months. There must be facilities for investigation of tuberculosis and regular follow-up. However, a recent double-blind, randomised, placebo-controlled trial (*see* Further reading below) of pre-exposure isoniazid prophylaxis against tuberculosis showed that this does not work for primary prophylaxis. It did not improve tuberculosis-disease-free survival among HIV-infected children or tuberculosis-infection-free survival among HIV-uninfected children immunised with BCG vaccine.
- Neonatal BCG may reduce the risk of tuberculosis meningitis and disseminated disease by 60–80%, especially in children under 5 years of age. However, it has a limited efficacy against pulmonary disease. Because of the increased risk of disseminated BCG infection in HIV-infected infants, the WHO advises that all infants **known to be HIV-infected** should **not** receive BCG. However, this has practical implications in resource-limited countries where PCR is not usually available to detect HIV infection in infants under 18 months of age.

Further reading

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6.1.O Typhoid or paratyphoid

BOX 6.1.0.1 Minimum standards

- Blood culture and full blood count.
- Antibiotics: chloramphenicol, amoxicillin, ceftriaxone, ciprofloxacin.
- Public health measures.
- Sanitation, hygiene and preventive vaccines.

Typhoid

Epidemiology

Despite major advances in public health and hygiene in much of the developed world, typhoid fever continues to plague many resource-limited countries. Although accurate community-based figures are unavailable, it is estimated that over 30 million cases occur annually, with the vast majority of cases in Asia leading to an estimated 200 000

deaths. Population-based incidence rates are estimated at 500–1000 cases per 100 000 population in endemic areas. However, there is a paucity of information from Africa, and preliminary data indicate that the burden in Africa, in urban settings, may also not be far behind that of Asia.

In recent years, typhoid fever has been notable for the emergence of drug resistance. The first cases of chloramphenicol-resistant typhoid emerged in the early 1970s, followed by the emergence of multi-drug-resistant (MDR) typhoid in the mid-1980s. This organism is resistant to ampicillin, chloramphenicol and trimethoprim-sulphamethoxazole (co-trimoxazole)). Over the last few years, however, the development of quinolone and third-generation cephalosporin resistance in *Salmonella typhi* from various parts of Asia has raised the extremely worrying prospect of a 'super-resistant' variant of typhoid in addition.

In contrast to classic descriptions of milder disease, because of increasing drug resistance in *Salmonella paratyphi*, paratyphoid fever is now of comparable severity and virulence to typhoid fever. Both types of illness will therefore be described.

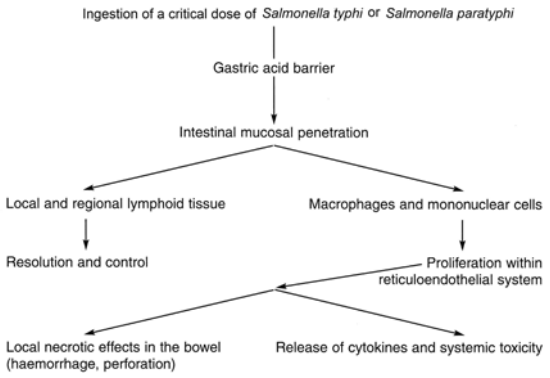

FIGURE 6.1.0.1 The pathogenesis of typhoid.

Pathogenesis

The disease is spread by the ingestion of a Gram-negative flagellar organism, *Salmonella enterica* serovar Typhi (*S. typhi*). A larger infecting dose leads to a shorter incubation period and a more severe infection.

The organism crosses the intestinal mucosal barrier after attachment to the microvilli by an intricate mechanism involving membrane ruffling, actin rearrangement and internalisation in an intracellular vacuole. Once inside the intestinal cells, *S. typhi* bacteria find their way into the circulation and reside within the macrophages of the reticulo-endothelial system.

The clinical syndrome is produced by the release of pro-inflammatory cytokines (the interleukins IL-6 and IL-13 and tumour necrosis factor-α, TNF-α) from the infected cells, leading to fever, rigors, inanition (the exhausted condition that results from lack of food and water) and anorexia. Local effects such as intestinal haemorrhage and perforation are comparatively rare in childhood, as there is relative lymphoid hyperplasia of the intestinal wall. However, malnourished children, especially adolescents, may be at greater risk of these complications.

Clinical features

The classic stepladder rise of fever is relatively rare in childhood. Much of the presentation of typhoid fever in various geographical locations and populations is modified by coexisting morbidities and early administration of antibiotics. In malaria-endemic areas and in parts of the world where schistosomiasis is common, the presentation of typhoid may also be atypical. Data in Table 6.1.O.1 from a consecutive series of 2000 cases show the common clinical features of typhoid in endemic areas.

TABLE 6.1.0.1 Common clinical features of typhoid fever in childhood (Karachi, Pakistan)

High-grade fever	95%
Coated tongue	76%
Anorexia	70%
Vomiting	39%
Hepatomegaly	37%
Diarrhoea	36%
Toxicity	29%
Abdominal pain	21%
Pallor	20%
Splenomegaly	17%
Constipation	7%
Headache	4%
Jaundice	2%
Obtundation (reduced alertness)	2%
Ileus	1%
Intestinal perforation	0.5%

Although data from South America and parts of Africa suggest that typhoid may present as a mild illness in young children, this may vary in different parts of the world. There is emerging evidence from South Asia from both community and health facility settings that the presentation of typhoid may be more dramatic in children under 5 years of age, with comparatively higher rates of complications and hospitalisation. Diarrhoea, toxicity and complications such as disseminated intravascular complications are also more common in infancy, with higher case-fatality rates. However, some of the other features of typhoid fever seen in adults, such as relative bradycardia, are rare, and rose spots may only be visible at an early stage of the illness in fair-skinned children.

It must also be recognised that MDR typhoid appears to be a more severe clinical illness with higher rates of toxicity, complications and case-fatality rates. This appears to be a consistent finding and potentially related to the increased virulence of MDR *S. typhi* as well as higher rates of bacteraemia. In endemic areas, therefore, it may be prudent to treat all severely ill toxic children, especially those requiring hospitalisation, with second-line antibiotics.

Acute perforation of the intestine with haemorrhage and peritonitis can occur. This presents with severe abdominal pain, vomiting, abdominal tenderness, severe pallor and shock. An abscess may form together with enlargement of the liver and spleen. Management of peritonitis is described in Section 5.19.

Diagnosis of typhoid

The sensitivity of blood cultures in diagnosing typhoid fever in many parts of the developing world is limited, as microbiological facilities may be basic, and widespread antibiotic prescribing may render bacteriological confirmation difficult. Although bone marrow and **duodenal fluid cultures** may increase the likelihood of bacteriological confirmation of typhoid, these are difficult to obtain and they are invasive.

The serological diagnosis of typhoid is also fraught with problems, as a single Widal test may be positive in only 50% of cases in endemic areas, and serial tests may be required in cases presenting in the first week of illness. **Newer serological tests such as a dot-ELISA, co-agglutination and the Tubex® are promising**, but are comparatively expensive, may not be effective in primary care settings and have yet to find widespread acceptability.

The mainstay of diagnosis of typhoid in endemic areas therefore remains clinical. **Thus any high-grade fever of more than 72 hours' duration associated with any of the above-mentioned features, especially with no localising upper respiratory signs or meningitis or malaria, must be suspected as typhoid and managed accordingly.** While leucopenia (white blood cell count < 4 × 10^9/litre) with a left shift in neutrophils may be seen in a third of children, young infants may also commonly present with a leucocytosis.

Typhoid treatment

Making an early diagnosis of typhoid fever and instituting appropriate supportive measures and specific antibiotic therapy is the key to the appropriate management of typhoid fever. The following are the important principles of management:

- Adequate rest, hydration and attention to correction of fluid-electrolyte imbalance.
- Antipyretic therapy (paracetamol) as required if fever is > 39°C.
- A soft, easily digestible diet should be continued unless the child has abdominal distension or ileus.
- Regular monitoring for clinical recovery and potential complications.
- Antibiotic therapy: the right choice, dosage and duration are critical to curing typhoid with minimal complications. Traditional therapy with either chloramphenicol or amoxicillin is associated with relapse rates of 5–15% and 4–8%, respectively.
- **If drug resistance is not locally a problem**, start with oral chloramphenicol and/or oral amoxicillin/ampicillin (initially intravenous if vomiting).
- **If drug resistance is prevalent**, use cefixime or ceftriaxone or ciprofloxacin (associated with higher cure rates).

Although epidemics are usually associated with a single dominant clone of *S. typhi*, in endemic situations there may be several coexistent strains of *S. typhi*, and a clinical judgement may need to be made when instituting antibiotic therapy before culture results become available. This is particularly important as delay in the institution of appropriate second-line antibiotic therapy in resistant cases of typhoid leads to a significant increase in morbidity and mortality. Despite the availability of newer orally administrable drugs such as quinolones and third-generation cephalosporins, blanket administration of these agents to all cases of suspected typhoid is expensive and will only lead to the rapid development of further resistance.

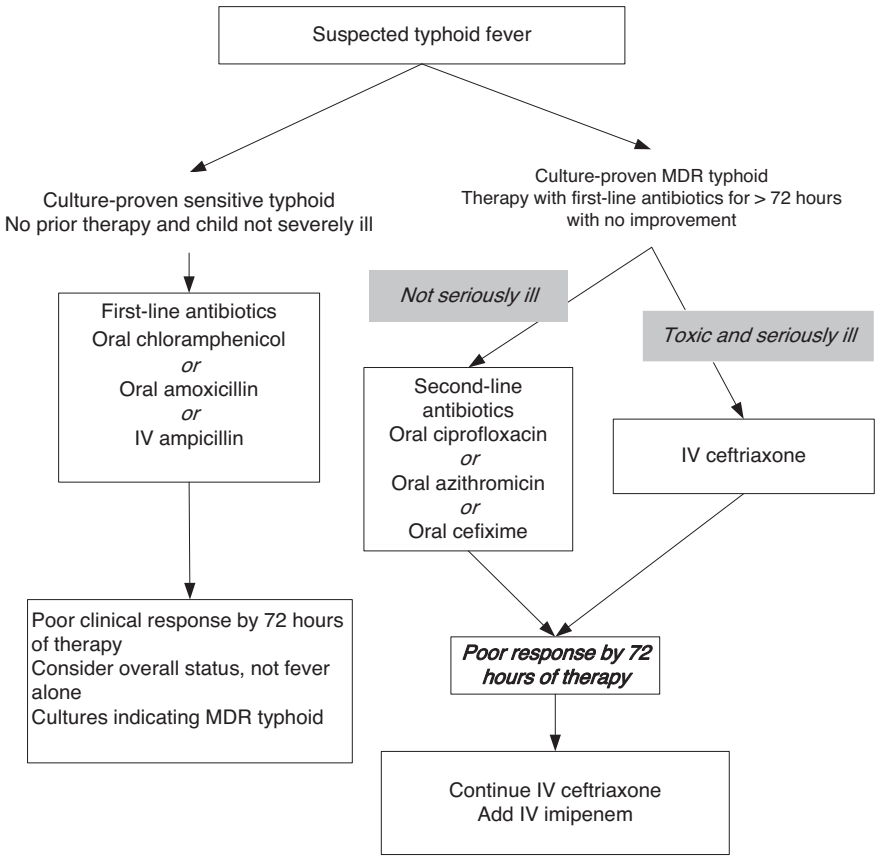

FIGURE 6.1.0.2 Algorithm for the treatment of typhoid. MDR, multi-drug-resistant.

Given the recent evidence that MDR typhoid is a more severe clinical illness from the outset, the algorithm in Figure 6.1.O.2 may be acceptable for selection of antibiotics and management of typhoid.

Table 6.1.O.2 shows the main antibiotics that can be employed for the treatment of both sensitive and MDR infections with *S. typhi.*

Corticosteroids

In severely ill and toxic children with typhoid requiring hospitalisation, past studies have shown that **dexamethasone IV** (0.5–1 mg/kg/day 8-hourly for up to six doses) **may be life-saving in some contexts**. However, **avoid using steroids in ambulatory settings**, as they mask abdominal complications and peritonitis.

Preventive measures for typhoid

The continued presence of typhoid in much of the developing world is an indication of the poor state of public health and sanitation. It is important therefore to be aware of the important risk factors for developing typhoid, in order to institute preventive measures during outbreaks.

There is some epidemiological evidence that prior usage of antibiotics is associated with an increased risk of subsequent development of typhoid. The precise reasons for this are unclear, but may be related to alterations in intestinal flora, increasing the predisposition to colonisation and infection with pathogenic strains of *S. typhi.* Thus controlling indiscriminate use of antibiotics may not only reduce the emergence of drug-resistant strains, but also reduce the risk of development of typhoid.

Of the major risk factors for outbreaks of typhoid, contamination of water supplies with sewage is the most important. Therefore during outbreaks a combination of central chlorination and domestic water purification is important. In endemic situations, consumption of street foods, especially ice cream and cut fruit, has been recognised as an important risk factor. The human-to-human spread by chronic carriers is also important, and attempts should therefore be made to target food handlers and high-risk groups for *S. typhi* carriage screening. There is an urgent need to define the extent of carriage among food handlers in areas of high burden.

Of the available vaccines against typhoid, the classic heat-inactivated whole-cell vaccine is associated with an unacceptably high rate of side effects and is no longer in use. There are two newer vaccines which offer protection in older school-age children, but these are not recommended for use in children under 2 years of age:

- The Vi polysaccharide (Vi-CPS) vaccine can be administered in two doses at any stage, and has a 60–70% protective efficacy for at least 5 years. Recent large-scale demonstration projects in South Asia indicate that the Vi-CPS vaccine has considerable potential for use in school-age populations. The protective efficacy in children under 5 years of age has varied between studies.
- The oral attenuated ty-21a vaccine has also been evaluated and found to be comparably effective. However, it is generally available in capsule form and therefore difficult to administer to young children, especially those of preschool age.

Given the high rates and morbidity of typhoid in young children, there is a clear need for the development of a Vi-conjugate vaccine, which could be potentially employed within the Extended Programme of Immunisation vaccination schedule. Studies in Vietnam confirm the protective efficacy of such candidate vaccines, and several candidates are in an advanced stage of clinical development.

TABLE 6.1.0.2 Antibiotics in *S. typhi* infections

Drug	Route	Dose (frequency)	Duration (days)
Chloramphenicol	Oral	60–75 mg/kg/day (6-hourly)	14 days
Ampicillin/amoxicillin	IV/oral	100 mg/kg/day (6- to 8-hourly)	14 days
Ciprofloxacin	Oral/IV	20–30 mg/kg/day (12-hourly)	7–10 days
Gatifloxacin	Oral	10 mg/kg/day (once daily)	7 days
Ceftriaxone	IV/IM	65–100 mg/kg/day (once daily)	7–14 days
Cefixime	Oral	8 mg/kg/day (12-hourly)	14 days
Azithromycin	Oral	10–20 mg/kg/day (once daily)	5–7 days

Non-typhoidal salmonella infections

These infections usually give rise to a self-limiting gastroenteritis. This is manifested as diarrhoea with abdominal cramping pains, nausea and vomiting. There is usually a fever and there may be blood and mucus in the stools (*see* Section 5.12.A for treatment of this level of infection). A reactive polyarticular arthritis may develop 2 weeks after the diarrhoea.

Occasionally, particularly in the neonate and in the immunosuppressed, the malnourished, or children with sickle-cell disease, these infections can become very serious by spreading to the following sites: meninges (meningitis), bones (osteomyelitis) and joints (septic arthritis), lungs (pneumonia and empyema) and soft tissues (giving abscesses). This is a particular problem in children with HIV infection.

Treatment for metastatic infections should be urgently given by intravenous or intramuscular injection. Initial treatment should ideally be with the broad-spectrum antibiotics cefotaxime or ceftriaxone, and if later sensitivity tests become available the organisms may be sensitive to amoxicillin (usually resistant now), co-trimoxazole and ciprofloxacin. Chloramphenicol may be effective in the absence of the above.

Drug dosage schedules

- Cefotaxime:
  - Neonates less than 7 days old: 50 mg/kg every 12 hours.
  - Neonates over 7 days old: 50 mg/kg every 8 hours.
  - Infants and children: 50 mg/kg every 6 hours.
- Ceftriaxone: All ages 50 mg/kg once daily. In very severe infections 80–100 mg/kg once daily may be given (maximum dose 4 grams/day).
- Co-trimoxazole: 18 mg/kg by IV infusion 12-hourly. In very severe infections, 27 mg/kg co-trimoxazole IV 12-hourly (maximum dose 1.44 gram).
- Ciprofloxacin: 10–15 mg/kg twice daily by IV infusion.

6.1.P Rickettsial diseases

BOX 6.1.P.1 Minimum standards

- Supportive care and hydration.
- Early treatment with doxycycline or chloramphenicol.
- Public health measures and vector control.

Introduction

Rickettsial diseases are caused by obligate intracellular Gram-negative coccobacillary forms that multiply within eukaryotic cells. They take on a characteristic red colour when stained by the Giemsa or Gimenez stain.

- Illnesses are restricted by geography to places where both the natural animal host and its insect vector are present, and the vector has contact with humans.
- These diseases affect all ages, including children.

Aetiology and types

Rickettsial illnesses can be divided into the following biogroups:

1 **Spotted fever biogroup:**
   - Rocky Mountain spotted fever (RMSF), caused by *Rickettsia rickettsia*.
   - Rickettsial pox, caused by *Rickettsia akari*.
   - Boutonneuse fever (i.e. Kenya tick-bite fever, African tick typhus, Indian tick typhus, etc.).
2 **Typhus group:**
   - The causative organisms (*Rickettsia prowazekii* and *Rickettsia typhi*) are similar to those of epidemic typhus.
   - Examples include Brill–Zinsser disease (i.e. relapsing louse-borne typhus) and murine (endemic or flea-borne) typhus.
3 **Scrub typhus biogroup (Tsutsugamushi disease):**
   - These are a heterogeneous group of organisms that differ strikingly from rickettsial species and have a single taxonomic name, *Orientia tsutsugamushi* (*see* Section 6.1.Q).
4 **Other rickettsioses and closely related illnesses:**
   - New or re-emerging rickettsioses have been described, including tick-borne lymphadenopathy (TIBOLA) and *Dermacentor*-borne-necrosis-eschar-lymphadenopathy (DEBONEL).
   - *Ehrlichia* organisms (the cause of human monocytic ehrlichiosis and *Ehrlichia ewingii* infection), *Anaplasma phagocytophilum* (the cause of human granulocytic anaplasmosis), and *Bartonella* species (the cause of catscratch disease, relapsing fever and trench fever) are organisms related to the rickettsiae.
   - Q fever is a disease caused by *Coxiella burnetii*, which has recently been removed from the Rickettsiales.

Clinical presentation

There are so many clinical similarities among the diseases caused by rickettsiae that certain clinical and epidemiological features should suggest their presence:

1 Most of these infections are spread through ticks, mites, fleas or lice.
2 All rickettsial infections cause fever, headache and intense myalgias.
3 All rickettsial infections are arthropod-borne, so exposure to ticks or mites is an important clue to their early diagnosis.
4 Rash and/or a localised eschar occur in most patients.
   - Illnesses are generally characterised by fever, rash and malaise. They are often misdiagnosed as measles, meningococcaemia, typhoid or rheumatic fever, or investigated as pyrexia of unknown origin.
   - Disease is caused by a vasculitis of small blood vessels, which on the skin is seen as a petechial or haemorrhagic rash. The vasculitis may affect many organ systems, and explains the wide range of symptoms seen.
   - There are features specific to individual rickettsia, including meningoencephalitis (in Rocky Mountain spotted fever), myocarditis and cough (in Q fever) or lymphadenopathy and hepatosplenomegaly (in scrub typhus).
   - An eschar at the site of the infecting bite is helpful in the diagnosis of tick-borne and mite-borne rickettsial infections, and is recognised as a necrotic black papule.
   - The severity of illness varies with the organism, and the age of the patient. For example, in Rocky Mountain spotted fever, the untreated acute illness has a case fatality rate of 20%, with two-thirds of cases occurring in children under 15 years of age. In contrast, louse-borne typhus may only cause mild symptoms in children, with deaths occurring mainly in adults.
   - Other manifestations may occur, such as gastrointestinal, conjunctival, hepatic and pulmonary manifestations, that are more common in some illnesses than in others.

Differential diagnosis

Depending on local diseases, the combination of clinical manifestations, laboratory data and geographical areas, other causes to consider include the following:

- malaria
- measles
- typhoid

- dengue haemorrhagic fever
- Kawasaki disease
- leptospirosis
- meningococcal infections
- rubella
- group A streptococcal infection
- syphilis
- toxic shock syndrome
- vasculitis and thrombophlebitis.

Diagnosis

Confirmation of diagnosis of rickettsial infections is usually clinical, with the following methods used for confirmation as appropriate:

1 **Isolation:**
   - Rickettsiae can be isolated following inoculation into animals, such as guinea pigs in special reference laboratories.

2 **Serology:**
   - Serological detection of convalescent antibodies is the mainstay of diagnosis of rickettsial infection. The following serologic tests can be used:
     - the Weil–Felix (WF) agglutination test; **this is not used for rickettsial pox, Q fever or ehrlichiosis, for which specific diagnostic serological tests are available**
     - microimmunofluorescent (MIF) antibody test
     - enzyme-linked immunosorbent assay (ELISA)
     - Western blot immunoassay.

   The WF test is neither specific nor sensitive, and is not helpful. None of these methods are normally useful in the initial clinical management of patients with acute illness. A modification of the ELISA test has been developed to serologically confirm the specific species of rickettsiae.

3 **Immunologic detection of rickettsiae in tissue:**
   - Biopsies of skin rash, an eschar, or other tissues can be useful but are rarely performed, as these require specialised laboratories.

4 **PCR amplification of rickettsial DNA:**
   - PCR amplification, especially by the new 'suicide PCR' primers from rickettsial genes from blood, skin biopsy samples and other tissues can be performed in reference laboratories for detection of rickettsial DNA. It has estimated sensitivity and specificity of 68% and 100%, respectively.

5 **Routine blood examinations:**
   - These are unhelpful but are required to rule out other diseases, such as malaria, typhoid, dengue haemorrhagic fever and leptospirosis.

Treatment

- Treatment should not await serological diagnosis, as this is often delayed.
- In children over 8 years of age, give tetracyclines, particularly doxycycline (2.2 mg/kg twice daily up to a maximum of 100 mg twice daily). The use of these drugs is not advised in children under 8 years of age because of dental staining. Under 8 years give co-trimoxazole 24 mg/kg twice daily for 2 weeks.
- Oral chloramphenicol (25 mg/kg four times daily up to a maximum of 3 grams/day) is also effective.
- For scrub typhus (*see* Section 6.1.Q), rifampicin and azithromycin have been used successfully in areas where the rickettsia is resistant to conventional treatment.
- Treatment should be for 7–14 days.
- Fluoroquinolones (e.g. ciprofloxacin) may be effective and are being evaluated.
- Supportive care for complications affecting the cardiac, renal and pulmonary systems may be necessary in patients with severe disease.

Control

- Insect vector control is important for human louse-borne typhus, which occurs in cold mountainous areas where people live close together, or in internally displaced or refugee populations. In these situations, delousing of individuals with insecticides prevents and controls epidemic typhus.
- For scrub typhus, mite bites can be prevented by using topical insect repellents.
- A vaccine is also available for Rocky Mountain spotted fever.

Health education

This may include the following:

- community education on the risks of living in very close proximity to animals
- the need for regular re-facing of mud walls and floors
- for human louse-borne typhus, the importance of washing and sunning clothes and bedding.

TABLE 6.1.P Some major rickettsia and their distribution

Disease	Agent	Vector	Reservoir	Distribution
Rocky Mountain spotted fever	*R. rickettsii*	Ticks	Rodents, dogs, rabbits	USA, South America, Canada
Rickettsial pox	*R. akari*	Mite	Mouse	Worldwide
Louse-borne typhus	*R. prowazekii*	Lice	Human	Worldwide
Murine typhus	*R. typhi*	Flea	Mouse (urban)	Worldwide
Scrub typhus	*Orientia tsutsugamushi*	Mite	Rodents	Australia, India, SE Asia
Q fever	*Coxiella burnetii*	None	Cattle, goats	Worldwide

6.1.Q Scrub typhus

BOX 6.1.Q.1 Minimum standards
- Serology.
- Chest X-ray.
- Doxycycline and tetracycline.

Epidemiology

- Geographical distribution: Asia, Australia and Pacific Islands.
- Agent: *Orientia tsutsugamushi* (Rickettsia tsutsugamushi).
- Hosts: Rodents are reservoir hosts, and humans are accidental hosts. The most commonly affected age group is 5–14 years, and the disease is more common in boys.
- Vector: Larva of trombiculid mite. Mites live on jungle grass and become infectious by biting and sucking tissue fluid of infected rodent or by transovarian transmission to the next generation of mites.

Clinical manifestations

- Incubation period is 5–18 days.
- Abrupt onset of fever, severe headache, myalgia, cough, suffused conjunctivae, dark red papular or maculopapular rash (5–7 days after fever) on the trunk, arms and thighs.
- Eschar (19–28% in children, 46–82% in adults) may be seen at the site of the mite bite, especially in the perineum, axilla or trouser-belt region. Eschar is a firmly adherent black scab, 3–6 mm in diameter, with a raised red margin.
- There is regional or generalised lymphadenopathy, hepatomegaly and sometimes a maculopapular rash. Moderate leucocytosis may be seen, and occasionally thrombocytopenia.
- **In severe cases**, complications include meningoencephalitis, myocarditis, pneumonitis, respiratory distress syndrome or (rarely) renal failure.
- **In non-severe cases**, fever subsides within 2 weeks. Indigenous people in endemic areas usually have mild illness without rash or eschar.

Diagnosis

- Diagnosis is based on clinical manifestations, geographical distribution and history of contact with jungle-grass exposure in the bush.
- Confirmation is by serology or polymerase chain reaction (PCR). Weil–Felix test titres of 1:160 (or a fourfold rise after 2–4 weeks) occur in only 50% of cases. **More sensitive serological tests are the indirect immunoperoxidase test and the indirect immunofluorescent tests. For individuals living in endemic areas the positive titre is ≥ 1:400 or a fourfold rise in acute and convalescent sera. The positive titre indicating infection may be lower in non-endogenous children. PCR on the eschar material is more sensitive than on the blood.**
- Routine blood examinations are unhelpful, but are required to rule out other diseases such as dengue haemorrhagic fever, malaria and leptospirosis.
- Blood culture to exclude septicaemia (e.g. typhoid).
- Chest X-ray is indicated if there is cough and dyspnoea to detect pneumonitis, pleural effusion or respiratory distress syndrome.
- Perform lumbar puncture if there is meningism or severe headache to rule out other causes of CNS infection. CSF commonly shows a picture of aseptic meningitis.
- A fall in body temperature usually occurs within 24–48 hours after treatment.

Management

- The drug of choice is doxycycline orally 2.2 mg/kg initially followed by 2.2 mg/kg 12 hours later, then 1.1 mg/kg every 12 hours until the patient is afebrile for 2–3 days, **or** continue treatment for 5–7 days.
- Alternative drugs are tetracycline 250 mg orally four times a day for 7 days (in children over 8 years) or chloramphenicol 15–25 mg/kg orally four times a day for 7 days, depending on severity.
- In a few cases, fever returns 5–7 days later. If this happens, repeat the dose of antibiotic.
- Tetracycline should not be given to oliguric patients. Doxycycline is safe in renal impairment.
- Rifampicin and azithromycin have been used successfully in areas where the rickettsia is resistant to conventional treatment.
- In severe cases, the risk of dying outweighs the risk of tooth discoloration from doxycycline or tetracycline.
- **Remember that antimicrobial agents only suppress infection. Cure depends on host immunity.**
- Treatment should not be withheld pending laboratory confirmation for a clinically suspected infection.

6.1.R Yaws

BOX 6.1.R.1 Minimum standards
- Azithromycin.
- Benzathine penicillin.

Introduction

Yaws is caused by the bacterium *Treponema pallidum* subspecies *pertenue*. It is closely related to the bacterium that causes syphilis, but this disease is not sexually transmitted. Yaws mainly affects children in rural tropical areas, such as the Caribbean Islands, Latin America, West Africa, India,

and South-East Asia. Yaws is transmitted by direct contact with the skin sores of infected people.

Symptoms

About 2–4 weeks after infection, the child develops a sore called a 'mother yaw' where bacteria entered the skin. The sore is reddish and looks like a berry. It is usually painless but does cause itching.

These sores may last for months. More sores may appear shortly before or after the mother yaw heals as the person scratches or spreads the bacteria from the mother yaw to uninfected skin. Eventually the skin sores heal.

Some patients develop destructive ulcerations of the nasopharynx, palate and nose (termed gangosa), painful skeletal deformities, especially in the legs (termed saber shins), and other soft-tissue changes (gummas, inflammatory cell infiltration). In the advanced stage, sores on the skin and bones can lead to severe disfigurement and disability.

Signs and tests

A sample from a skin sore is examined using a dark-field microscope. There is no blood test for yaws. However, the blood test for syphilis is usually positive in children with yaws, because the bacteria that cause these two conditions are closely related.

Treatment

Recently a single dose of oral azithromycin (30 mg/kg) has been shown to be as effective as a single IM injection of benzathine benzylpenicillin 50 000 units/kg (37.5 mg/kg) with less risk of a dangerous anaphylactic response and the need for needles. If the child vomits within 30 minutes of the oral dose of azithromicin, a repeat dose should be given. Benzathine benzylpenicillin must not be given IV.

Anyone who lives in the same house with someone who is infected should be examined for yaws and treated if they are infected. Skin lesions may take several months to heal. By its late stage, yaws may have already caused damage to the skin and bones. It may not be fully reversible, even with treatment for the infection.

6.1.S Other bacterial infections

BOX 6.1.S.1 Minimum standard

- Anthrax: ciprofloxacin, doxycycline, rifampicin, vancomycin, gentamicin, chloramphenicol, penicillin, amoxicillin, imipenem, meropenem and clindamycin.
- Brucellosis: co-trimoxazole.
- *Chlamydia*: erythromycin.
- *Haemophilus influenzae*: amoxicillin, Hib vaccine.
- Plague: streptomycin, tetracycline, chloramphenicol.
- *Staphylococcus*: cloxacillin, flucloxacillin, sodium fusidate.

Anthrax

This is an infection from animals caused by *Bacillus anthracis*.

Cutaneous

Major features:

- surrounded by extensive oedema
- painless and non-tender (although may be pruritic or accompanied by a tingling sensation).

Minor features:

- development of black eschar
- progresses over 2–6 days through papular, vesicular and ulcerated stages before eschar appears
- most commonly affects the hands, forearms, face and neck
- discharge of serous fluid
- local erythema and induration
- local lymphadenopathy
- associated with systemic malaise including headache, chills and sore throat, but afebrile.

Take initial diagnostic tests:

Swab from lesion for stain and culture.

Blood cultures (prior to antimicrobial use, if possible).

Start antibiotic treatment to cover *B. anthracis.*

Ciprofloxacin orally is given under 8 years of age. In children older than 8 years doxycycline can be given. Either drug is combined with one or two other antibiotics (such as amoxicillin, benzylpenicillin, or chloramphenicol). When the condition improves and the sensitivity of the *Bacillus anthracis* strain is known, treatment may be switched to a single antibiotic. Treatment should continue for 60 days because germination may be delayed.

Features of inhalation anthrax

- Rapid onset of severe unexplained febrile illness (fever, chills, fatigue, non-productive cough).
- Rapid onset of severe sepsis not due to a predisposing illness.
- Abrupt onset of respiratory failure and the presence of widened mediastinum or pleural effusions on chest X-ray.
- Nausea.
- Sweats (often drenching).
- Confusion or altered mental status.
- Vomiting.
- Pallor or cyanosis.
- Dyspnoea.
- Tachycardia.
- Abdominal pain.
- Pleuritic chest pain.
- Sore throat.

Take initial diagnostic tests:

- Chest X-ray: **mediastinal widening**, pleural effusion, pulmonary infiltrate.
- Full blood count: to look for raised haemocrit, raised white cell count, especially neutrophilia.
- Liver function tests: to look for high transaminase activity.
- CT of chest (if available) if high suspicion and normal chest X-ray.

- Blood culture.

Start antibiotic treatment to cover *B. anthracis*.

Give ciprofloxacin intravenously in combination with one or two other antibiotics (agents with *in-vitro* activity include rifampicin, vancomycin, gentamicin, chloramphenicol, penicillin, amoxicillin, imipenem, meropenem and clindamycin) until sensitivity testing is available. Treatment should continue for 60 days because germination may be delayed.

It is important to notify public health authorities if such an infection is identified.

Brucellosis

This is an infection from animals caused by *Brucella* species, usually through infected milk. It causes a chronic illness with fever, pain and swelling of the joints, and anaemia.

Treatment is with co-trimoxazole for 4 weeks: give 18–24 mg co-trimoxazole/kg twice daily.

- **Or** give paediatric liquid 240 mg/5 mL (200 mg sulfamethoxazole plus 40 mg trimethoprim):
  - Age 6 weeks to 6 months: 2.5 mL twice daily.
  - Age 6 months to 6 years: 5 mL twice daily.
  - Age 6–12 years: 10 mL twice daily.

Campylobacter infection

This causes acute gastroenteritis with **considerable abdominal pain**, fever and bloody diarrhoea (*see* Section 5.12.A). Most children recover without treatment with antibiotics, although erythromycin and ciprofloxacin are both effective.

Chlamydia infections

Chlamydia trachomatis causes trachoma (*see* Section 6.1.M), infections of the genital tract (*see* Section 6.1.J), and conjunctivitis in the newborn which is less severe than that due to the gonococcus (*see* Section 3.4).

Chlamydia pneumoniae produces a chronic pneumonitis in the infant. It is important not to forget this cause of acute respiratory infection, which responds well to erythromycin.

Haemophilus influenzae infections

Haemophilus influenzae causes serious infections in infants and young children, including:

- pneumonia (*see* Section 5.3.A)
- middle ear infections (*see* Section 5.1.C)
- acute epiglottitis (*see* Section 5.1.A)
- meningitis (*see* Section 5.16.B).

Infections can be prevented by an extremely effective conjugate vaccine. **Every country should attempt to immunise their infants against this cause of many serious illnesses, deaths and handicap.**

Plague

Yersinia pestis is transmitted to children by the fleas of infected rats. It occurs in epidemics.

It presents with an acute fever and painful tender large swollen lymph nodes (buboes). It can cause pneumonia and septicaemia.

Prompt treatment on suspicion is essential.

- Streptomycin is the treatment of choice for severe cases (15 mg/kg IM daily, maximum dose 1 gram) for 7 days.
- Tetracycline (in children over 8 years, 250–500 mg 6-hourly) and chloramphenicol (15–25 mg/kg 6-hourly) are alternative drugs, which are also given for 7 days.

Shigellosis

- This causes an acute gastroenteritis, which particularly affects the large bowel. There is blood and mucus in the diarrhoea.
- There is often a high fever.
- Shigellosis may cause seizures.
- There may be tenesmus (a continuous feeling of wanting to defecate).
- Septicaemia may occur.

See Section 5.12.A for advice on treatment.

Staphylococcal infections

The most common presentation is with a pus-forming skin infection (impetigo) (*see* Section 5.18).

However, this bacterium can be transported in the blood to other parts of the body, where it produces serious infections:

- Pneumonia is particularly dangerous (*see* Section 5.3.A).
- Osteomyelitis is also dangerous and difficult to diagnose (*see* Section 5.17).
- Pyomyositis can occur.
- Occasionally staphylococcal infections cause mastoiditis (*see* Section 5.1.C) and laryngotracheitis (*see* Section 5.1.A).

The two groups of antibiotics most effective against this organism are flucloxacillin or cloxacillin and sodium fusidate (fucidin).

Treatment with sodium fusidate/fusidic acid

Use in combination with another antistaphylococcal agent if possible, to avoid the development of resistance.

Oral route

Absorption is not as good as with the IV route, but the oral route should be used when possible. Doses as fusidic acid:

Neonate to 1 year	15 mg/kg	3 times daily
1 year to 5 years	250 mg	3 times daily
5 years to 12 years	500 mg	3 times daily
12 years to 18 years	750 mg	3 times daily

The suspension usually contains 250 mg of fusidic acid in 5 mL.

Intravenous infusion

Give 6–7 mg/kg of sodium fusidate 8-hourly (for children over 50 kg in weight, give 500 mg IV 8-hourly).

The dose may be doubled in severe infections.

Dilute in 5% glucose to a concentration of 1 mg/mL, and give slowly over at least 6 hours.

See Section 5.12.A for further information on *Campylobacter* and cholera infections.

6.2 Viral infections

6.2.A Chickenpox

BOX 6.2.A.1 Minimum standards
- Antipyretics and antipruritus treatment (e.g. chlorpheniramine/promethazine).
- Antibiotics for secondary infection.
- Aciclovir in immunosuppressed, neonates and other at-risk groups.
- VZIG IM (if available) for immunocompromised patients.
- Live attenuated varicella vaccine (for susceptible groups when in remission).

Introduction

Chickenpox is caused by varicella zoster virus (VZV), a member of the herpesvirus family. It is spread by direct contact, droplet or airborne transmission, and is very contagious.

Chickenpox manifests as a generalised pruritic vesicular rash typically consisting of crops of lesions in varying stages of development and resolution (crusting), mild fever, and other systemic symptoms. Varicella tends to be more severe in adolescents and adults than in young children.

The peak age for infection is 5 to 9 years. In immunocompetent children it is usually a mild disease, and lifelong immunity follows an infection.

Groups at increased risk include those with immunodeficiency (mainly those with HIV infection), those on chemotherapy or long-term steroids (defined as those who within the previous 3 months received prednisolone, or its equivalent, at a daily dose of 2 mg/kg/day or more than 40 mg/day for at least 1 week or 1 mg/kg/day for 1 month), and neonates whose mothers have had chickenpox just before or just after the birth. Patients on lower doses of steroids plus another immunosuppressant drug and patients with an additional medical problem (e.g. nephrotic syndrome) should be included, plus those on salicylate therapy or with chronic lung or skin problems, including eczema. Acyclovir should be used in these groups.

Children with chickenpox are at increased risk of developing Reye's syndrome if given aspirin and other non-steroidal anti-inflammatory drugs.

Clinical presentation

- The incubation period is 14–21 days. There is low-grade fever and headache, followed by the rash, which is mostly on the trunk and face. The rash develops into successive small single oval vesicles with an erythematous base which break within 2 days to develop into scabs and heal. It is very itchy, and scratching may result in secondary bacterial infection and scar formation.
- The course of the disease is about 1 week. Children are infectious from 1 or 2 days before the rash appears until 1 or 2 days after all of the lesions have formed scabs.
- Complications include septicaemia, bronchopneumonia, hepatitis, thrombocytopenia, purpura, pericarditis, myocarditis, endocarditis, arthritis, myositis, glomerulonephritis, ascending mediastinitis and post-infectious encephalitis, especially with cerebellar involvement. Any fever or other symptom occurring within a few days of apparently resolving chickenpox must be taken seriously.
- Guillain–Barré syndrome, facial nerve palsy, transverse myelitis, hypothalamic involvement, optic neuritis and transient loss of vision have been reported.
- Intrauterine infection, especially in the first two trimesters, may result in a congenital varicella syndrome (i.e intrauterine growth retardation, scarred skin, limb atrophy, mental retardation, CNS and eye complications). Only 1–2% of infants with intrauterine exposure develop complications.
- In mothers, chickenpox but not shingles, occurring between 5 days before and 2 days after delivery, may result in a **severe infection in the neonate**. This is probably due to lack of formation of VZV IgG antibodies that would have crossed the placenta and would be protective for the newborn baby. The infant should be treated as soon as possible with **varicella-zoster immunoglobulin** (if available) and with **IV aciclovir** as well if infection manifests (see below and Section 2.8.1).

Management

- Keep the child clean, and cut and clean under their nails to discourage scratching and prevent secondary skin infection.
- Baking soda baths or calamine lotion may relieve the itching.
- Antihistamines, such as chlorpheniramine 1 mg twice daily (1 month to 2 years of age), 1 mg three to six times a day; maximum 6 mg daily (2–6 years), 2 mg three to four times a day; maximum 12 mg daily (6–12 years), or 4 mg three to six times a day; maximum 24 mg daily (over 12 years) may reduce scratching.
- Give paracetamol for fever.
- Appropriate antibiotics should be given for secondary bacterial infection, which is mostly due to *Staphylococcus aureus* or *Streptococcus pyogenes.*
- Aciclovir IV 10 mg/kg 8-hourly or 250 mg/m^2 8-hourly for 7–10 days is recommended for immunocompromised children who develop chickenpox. Oral aciclovir (20 mg/kg four times a day) is given for HIV-infected patients whose **CD4+ counts** are relatively normal. It should

be considered for HIV-infected children with a CD4+ T-lymphocyte percentage of 15% or greater.
- If available, IM varicella-zoster immunoglobulin (VZIG) should be given at the following doses: birth to 5 years, 250 mg (one vial); 6–10 years, 500 mg (two vials); 10–15 years, 750 mg (three vials) and 15–18 years, 1 gram. This may modify the disease if given shortly (not more than 4 days) after exposure. Indications include immunocompromised children, such as HIV-infected pregnant women and premature infants born at less than 28 weeks' gestation, who have had intimate contact (face to face) with chickenpox or herpes zoster. Neonates whose mothers develop varicella between 7 days before and 28 days after delivery are offered VZIG 250 mg as a single IM injection.
- If VZIG is not available, oral or IV aciclovir (at the above doses) may be given.
- In addition to standard precautions, airborne and contact precautions are recommended for patients with varicella for a minimum of 5 days after the onset of rash and until all lesions are crusted, which in immunocompromised patients can be 1 week or longer.

Prevention

- Live attenuated varicella vaccine (monovalent varicella vaccine or measles, mumps, rubella, varicella: MMRV) given as two subcutaneous or intramuscular injections confers over 95% protection against severe disease. Both have been licensed for use in healthy children from 12 months to 12 years of age. Children in this age group should receive two 0.5-mL doses of varicella vaccine administered subcutaneously, separated by at least 3 months.
- Susceptible children aged 13 years or older without immunocompromise should receive two 0.5-mL doses of varicella vaccine separated by at least 28 days.
- Patients in whom vaccine is contraindicated include those who are immunocompromised children and those receiving aspirin.
- Patients who are receiving immunosuppressive treatment (including steroid therapy) are generally immunised when in complete remission. The total lymphocyte count should be > 1.2×10^9/litre and there should be no other evidence of a lack of cellular immune competence.
- The vaccine should not be given within 3 months of VZIG.

6.2.B Dengue

BOX 6.2.B.1 Minimum standards
- Airway, Breathing and Circulation assessment and management.
- Recognition and treatment of shock.
- Blood transfusion and replacement of clotting factors and platelets.
- High-dependency/intensive care.
- Vector control.

Introduction

Dengue infection is caused by an RNA virus of the Flaviviridae family. The disease first appeared in an epidemic in the Philippines in 1957, subsequently in Thailand, and then in other South-East Asian countries. It is now an important health threat in most Asian and South American countries, with an estimated 50–100 million dengue infections worldwide every year and a fatality rate of about 2.5% in hospitalised cases, although this could be reduced by earlier detection and access to good medical care.

Epidemics occur every year during the rainy season, and the mosquitoes *Aedes aegypti* and *Aedes albopictus* are the main vectors.

The dengue virus comprises four serotypes (type 1, 2, 3 and 4) which cause lifelong specific antibody responses. Unusually, a second infection with a different serotype of the virus puts the sufferer at greater risk of more severe illness.

Dengue hemorrhagic fever or severe dengue is the

TABLE 6.2.B.1 Increasing signs of severity in dengue

Dengue: diagnosis	Warning signs of severity	Severe dengue
Probable dengue	*Require close observation and medical care*	*Any of the following:*
Live in or travel to dengue endemic area	Persistent vomiting	Severe plasma leakage showing as shock or respiratory distress
	Clinical fluid accumulation	
Fever and two of the following:	Mucosal bleed	
Nausea, vomiting	Lethargy, restlessness	Severe bleeding as evaluated by clinicians
Rash	Liver enlargement > 2 cm	
Aches and pains	Laboratory: increase in haematocrit concurrent with rapid decrease in platelet count	Severe organ involvement: • liver (AST, ALT ≥ 1000) • CNS: impaired consciousness • heart and other organ failure
Tourniquet test positive		
and either		
Supportive serology	Abdominal pain and tenderness	
or		
Occurrence at the same location and time as other confirmed dengue cases		

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CNS, central nervous system.

severe clinical illness, and involves plasma leakage, significant bleeding and shock with a significant fatality rate, especially where intensive-care facilities are lacking. There are no available vaccines for dengue and no specific antiviral treatment. Treatment is supportive. Control is currently by control of the vectors.

Diagnosis

In 2009, the WHO classification of dengue infection was revised to simplify diagnosis and management. Table 6.2.B.1 shows the warning signs that severe dengue may develop.

This new WHO guideline classifies the infection either as dengue or as severe dengue. The old definition of (non-severe) dengue is the same as that of dengue fever (A90 according to the ICD code) and severe dengue means dengue hemorrhagic fever (A91 according to the ICD code).

The alternative differential diagnosis of acute febrile illness with non-specific symptoms is as follows:

- septicaemia
- scrub typhus
- viral infection
- enteric fever
- leptospirosis.

Pathogenesis of severe dengue or dengue haemorrhagic fever (DHF)

Infection with one dengue serotype gives specific lifelong antibody with only partial protection against other serotypes. Therefore, unusually, severe dengue or DHF occurs predominantly in patients with second infections who have a different serotype in their second infection from their first (previous dengue fever). Antibody-dependent enhancement, immune enhancement and T-cell (T8) proliferation and apoptosis are important in the development of disease.

Hypotheses for severe dengue or DHF include the following:

- Non-neutralising antibodies to dengue virus enhance viral uptake and replication in target cells (monocytes).
- Enhanced viral replication in the presence of T-cell apoptosis, resulting in large antigen load in the face of massive T-cell activation, releasing cytokines that lead to tissue damage and vascular leakage.

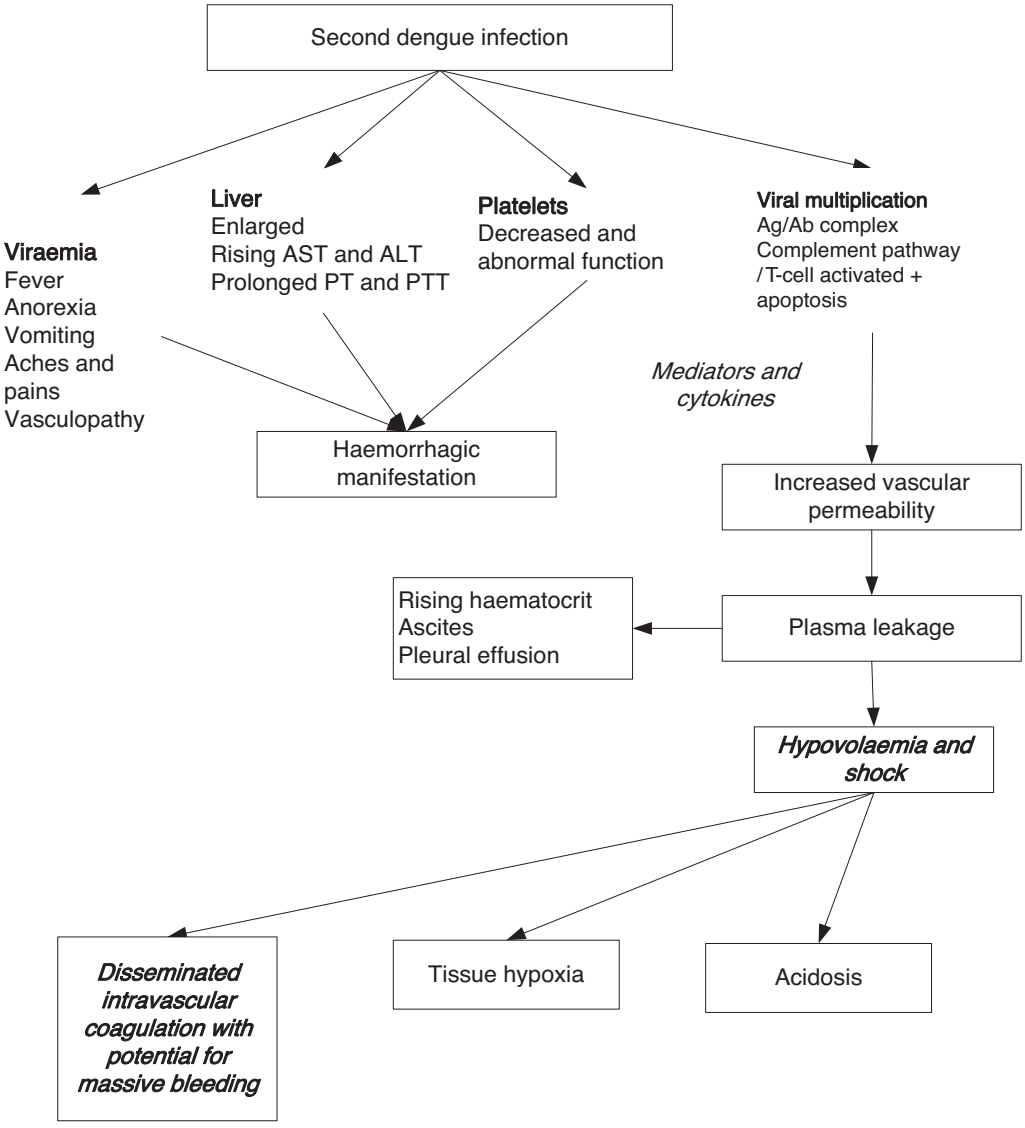

FIGURE 6.2.B.1 Pathophysiology of severe dengue or dengue haemorrhagic fever. AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; PTT, partial thromboplastin time.

TABLE 6.2.B.2 Clinical course of severe dengue or DHF

Phase	Symptoms	Signs	Laboratory test
1. Febrile phase duration 3–5 days (days 1–5)	High continuous fever (39–40°C), headache, anorexia, nausea, vomiting, myalgia, arthralgia, epigastric discomfort, right upper quadrant pain, fine rubelliform maculopapular rash, mucosal bleeding	Facial flushing, injected conjunctivae Tourniquet test positive (*see* Figure 6.2.B.2), tenderness at right upper quadrant, hepatomegaly, lymphadenopathy, dry lips and mucosa	Not significant
2. Haemorrhagic shock or toxic phase duration 1–2 days (days 4–6)	Fever declines, abdominal pain especially in the right upper quadrant, bleeding in skin and mucosa (nose, gums, gastrointestinal tract) About 30% of cases will develop shock (irritability, restlessness, severe abdominal pain, sweating) Shock is less common when IV fluids have been given early	Right upper quadrant tenderness, hepatomegaly, tourniquet test positive, bleeding of mucosa, signs of dehydration (dry lips and mucosa, dark yellowish urine) Cold clammy skin (prolonged capillary refill time > 2 seconds) Thready pulse, tachycardia, narrow pulse pressure (≤ 20 mmHg, e.g. 90/70, 100/80)	Blood count: rising haematocrit, decreased platelet count (< 100 × 10^9/litre), leucopenia Abnormal liver function test (albumin, liver enzyme: AST, ALT), renal function, calcium, electrolyte, blood gas in severe dengue with intractable and prolonged shock
3. Convalescence phase Duration 2–3 days	No fever or low-grade biphasic fever Increased appetite Diuresis	Convalescence rash on extremities with itching Widespread petechial rash with scattered round pale areas Sinus bradycardia	Stable haematocrit (or slowly increasing is a good clinical sign due to diuresis in some cases) Rising platelet count

Dengue or dengue fever (non-severe dengue) has only phases 1 and 3.

- Antibodies against dengue virus bind to complement pathway, releasing mediators that lead to vascular leakage as well.

Figure 6.2.B.1 shows a proposed pathophysiological pathway for severe dengue.

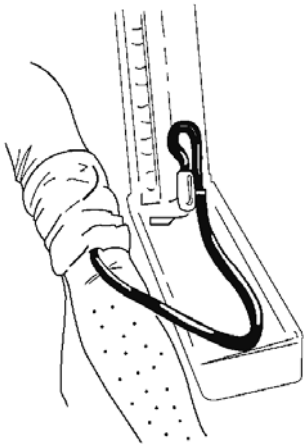

FIGURE 6.2.B.2 Tourniquet test showing petechiae.

Tourniquet test:

1 Apply an appropriate blood pressure cuff (it should be two-thirds of upper arm length)
2 Inflate to the level of mean arterial pressure (systolic plus diastolic blood pressure, divided by 2) for 5 minutes.
3 Positive test: petechiae > 10/square inch after removing the cuff for 2 minutes or longer.

Management of dengue and severe dengue (dengue haemorrhagic fever, DHF)

The aim of management of dengue and severe dengue is supportive, aiming to maintain adequate intravascular volume to prevent shock and to use blood and blood products to combat severe bleeding.

Management of severe dengue with shock and respiratory distress

Initial management of shock

1 Give high-flow oxygen with a mask with reservoir or nasal cannulae.
2 Give a bolus of Ringer-lactate or Hartmann's or 0.9% saline solution (20 mL/kg).
3 If the child shows improvement, give 10 mL/kg of Ringer-lactate or Hartmann's solution or 0.9% saline with 5% dextrose over 1 hour (add 50 mL of 50% dextrose to each 500-mL bag).
4 Reduce IV fluids (Ringer-lactate or Hartmann's solution or 0.9% saline plus 5% dextrose) to 7 mL/kg/hour for 6 hours if vital signs improve.
5 Check vital signs every 15 minutes until stable, then every hour for 4 hours, then every 2–4 hours.
6 Check haematocrit every 4 hours.
7 If vital signs are stable, haematocrit declines to 36–40% and no warning signs appear, then reduce IV fluid to 5 mL/kg/hour for 6 hours followed by maintenance fluids (2–3 mL/kg/hour).
8 Stop IV fluid when the child drinks more than half of the required intake or there is a diuresis.

TABLE 6.2.B.3 Management of dengue and severe dengue without shock

Day of illness	Assessment	Management
Days 1–3 (febrile phase)	**Monitor** temperature, blood pressure and pulse rate at least every 4–6 hours **Do** tourniquet test **Look for** signs of dehydration (dry lips and mucosae, low urine output) **Look for** warning signs (*see* Table 6.2.B.1)	1 Tepid sponge, paracetamol (do not give salicylate or other non-steroidal anti-inflammatory drugs, as they may cause bleeding, acidosis, hepatotoxicity and Reye's syndrome) 2 Give ORS/fruit juice/water frequently and in small amounts 3 If the child is vomiting, try domperidone 0.2 mg/kg 6- to 8-hourly 4 Admit if the child has signs of dehydration, gastrointestinal bleeding or cannot drink 5 Give IV fluid: 5% dextrose in Ringer-lactate or Hartmann's or 0.9% saline 1–3 mL/kg/hour depending on oral intake and haematocrit
Days 4–6 (toxic phase)	**Monitor** vital signs every 2–4 hours **Do:** • tourniquet test if previously negative • complete blood count (CBC) • serial haematocrit every 4 hours • palpate liver • record intake and output **Look for** warning signs (*see* Table 6.2.B.1)	1 Admit if the child has signs of dehydration or warning signs 2 Give IV fluid: 5% dextrose in Ringer-lactate or Hartmann's or 0.9% saline = maintenance + 3–5% deficit depends on haematocrit (maintain latter at 36–43 vol%) 3 If haematocrit is rising above 44% (or above 5% of previous value) increase rate of IV fluid to 6–7 mL/kg/hour (or 7% deficit) to prevent shock 4 If haematocrit is still high (> 45%), change IV fluid to low dose of colloid, e.g. Dextran 40 (maintenance + 3% deficit) or 2–4 mL/kg/hour (maximum dose of 30/kg/day) 5 Decrease IV fluid when vital signs are stable, haematocrit declines and urine is clear 6 Stop IV fluid when the child can drink more than half of normal or there is a diuresis

Haematocrit of normal child is usually 35–36%, so if a child has haematocrit > 42% this means that it has risen to 20% or more above normal level.

Shock that does not improve with the first 20 mL/kg bolus of Ringer-lactate or Hartmann's or 0.9% saline solution

1 Continue high-flow oxygen.
2 Give a bolus of Dextran 40 (especially if the haematocrit is very high (> 50%) or the child has a puffy face or distended abdomen), 10 mL/kg over 15–30 minutes.
3 If the haematocrit is < 42% or has decreased by more than 5% consider careful transfusion of packed red cells, 5–10 mL/kg over 30 minutes to 1 hour.
4 If the child improves, revert to Ringer-lactate or Hartmann's solution or 0.9% saline plus 5% dextrose, 5–7 mL/kg/hour for 6 hours and follow management in steps (7) and (8) above, 5 mL/kg/hour for 6 hours.
5 Check vital signs every 15 minutes until the child is stable, then every hour.
6 Check haematocrit every 4 hours and aim to maintain it at 40–45%.
7 Measure fluid intake and output every 4–8 hours.

Shock that does not improve with Dextran 40 bolus

1 Consider giving 4.2% sodium bicarbonate, 1–2 mL/kg IV slowly over 10 minutes.
2 Continue giving Dextran 40 at 7 mL/kg/hour.
3 Consider using an inotropic drug, such as dopamine or dobutamine 5–15 micrograms/kg/minute, if the child is still shocked or not improving.
4 Consider transfusion with packed red cells if the child is shocked with haematocrit < 42% or haematocrit declines by more than 5% of previous value.

Intractable shock with respiratory distress

1 Continue high-flow oxygen.
2 If calculated total intake is maximum (≥ 7 mL/kg/hour), haematocrit is > 40%, and shock has been present for > 24 hours, try furosemide 200–500 microgram/kg IV or 5–10 mg per dose for most children > 1 year of age.
3 If total intake is maximum (≥ 7 mL/kg/hour), haematocrit is > 40% and duration since first shock is < 24 hours **consider giving sodium bicarbonate, give inotropic drugs and consider positive pressure ventilation with PEEP** (if available).
4 Drain pleural effusion if it is interfering with ventilation (and if high pressure settings are needed on the ventilator); diagnose from chest X-ray or ultrasound.
5 Monitor electrolytes, calcium, albumin, renal function, blood gas and blood clotting according to clinical severity.

Blood and blood components should be given only in cases of suspected or severe bleeding or intractable shock.

Fluid management

Plasma expanders

Colloid solutions to expand the intravascular volume:

- Dextran 40 (osmolarity = 600 mOsmol/litre), maximum 30 mL/kg/day
- 6% hydroxyethyl starch (osmolarity = 308 mOsmol/litre)
- 4.5% albumin in severe hypoalbuminaemia with moderate to massive effusion/ascites and respiratory distress.

Blood products to combat bleeding:

- fresh frozen plasma (FFP), 10 mL/kg/dose
- packed red cells (PRC), 5–10 mL/kg/dose
- platelet transfusion, 0.2 units/kg/dose.

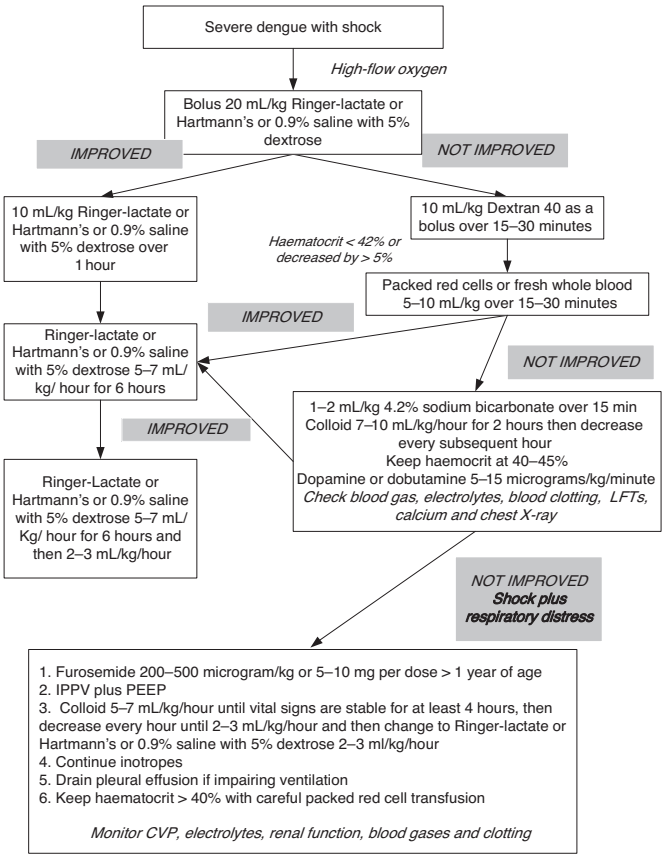

FIGURE 6.2.B.3 Management of severe dengue with shock. LFTs, liver function tests; IPPV, intermittent positive pressure ventilation; PEEP, positive end-expiratory pressure; CVP, central venous pressure.

Crystalloids

Normal maintenance fluids are 5% dextrose in Ringer-lactate or Hartmann's or 0.9% saline solution, about 2–3 mL/kg/hour or:

Up to 10 kg	= 100 mL/kg/day
From 11–20 kg	= 100 mL/kg/day × 10 kg for the first 10 kg, PLUS 50 mL/kg/day × body weight in kg above 10 kg
> 20 kg	= 1500 mL PLUS 20 mL/kg/day × body weight in kg > 20 kg

Example: body weight of 14 kg = 1000 mL + (4 × 50) = 1200 mL.

Example body weight of 30 kg = 1500 mL + (10 × 20) = 1700 mL.

In an obese child, use ideal body weight to calculate IV fluids. For example, for an obese 7-year-old girl with body weight 40 kg, IV fluids should be calculated from her age multiplied by 2 plus 8 (7 × 2 + 8 = 22 kg).

In practice, based on the above we can calculate IV fluids easily and rapidly as follows:

- 5 mL/kg/hour is equal to a 5% deficit if body weight < 40 kg
- 4 mL/kg/hour is equal to a 5% deficit if body weight > 40 kg

The maximum fluid that should be given in 24 hours (maximum fluid = resuscitation [20 mL/kg] + 10% deficit + maintenance) is 7 mL/kg/hour.

Inotropic drugs

- Dopamine will increase renal blood flow: dose is 5–15 micrograms/kg/minute.
- Dobutamine is usually used in patients with poor peripheral circulation: dose is 5–15 micrograms/kg/minute.

Severe dengue with organ involvement

Vital organs are not primarily involved in severe dengue, but are affected secondarily to plasma leakage, shock, haemorrhage and hypoxia. Notably, hepatic dysfunction and renal failure may occur especially in cases with prolonged shock.

Central nervous system involvement may be manifested by convulsions, spasticity and/or change in consciousness. Some cases have reported dengue virus in cerebrospinal fluid as in encephalitis.

Prevention and control

There is no vaccine to protect against dengue. Development of a vaccine against dengue infection has been challenging, although there has been recent progress.

At present, the only method for controlling or preventing the transmission of dengue virus is to combat vector mosquitoes by preventing them from accessing egg-laying habitats. This is achieved by environmental management and modification, with community participation and active monitoring.

6.2.C Acute hepatitis

BOX 6.2.C.1 Minimum standards
- Liver function tests.
- International normalised ratio (INR) or prothrombin time.
- Blood glucose measurement.
- Vitamin K.
- Immunisation against hepatitis B: population vaccination.

Introduction

- Acute hepatitis results in liver dysfunction of duration less than 6 months.
- Transaminases (AST and ALT) are abnormal, but patients are not necessarily jaundiced.
- Acute hepatitis may be cholestatic, and may be complicated by acute liver failure as described in Section 5.7.A.
- Hepatitis A is common and usually self-limiting, but other important diseases may occur at the same time or appear similar and be overlooked (*see* Table 6.2.C.1).

TABLE 6.2.C.1 Causes of acute hepatitis-like presentation

Aetiological group	Examples	Possible cholestasis
Viral	Hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus, delta superinfection, cytomegalovirus, Epstein–Barr virus, herpes simplex, parvovirus, measles, mumps, varicella, rubella, adenovirus, ECHO, coxsackie, flaviviruses (e.g. yellow fever, dengue, Lassa, Ebola, Rift Valley fever).	Hepatitis A virus, hepatitis B virus, hepatitis E virus
Bacterial/fungal	*Salmonella*, *Leptospira*, any septicaemia	Not usually
Protozoal + parasitic	*See* Section 6.3.A.d and 6.3.C	Not usually
Drugs and toxins	*See* Section 7.4	Drug cholestasis
Shock	Cardiac arrest, post surgery, heat stroke, radiation	Occurs 7–10 days after injury
Immune	Autoimmune, lupus, Kawasaki disease	Autoimmune, lupus, Kawasaki disease
Infiltrative	Leukaemias, haemophagocytic syndromes, Hodgkin's disease	Leukaemias, Hodgkin's disease
Metabolic	Urea cycle disorders Wilson's disease	Usually not Yes

Management of acute hepatitis

- Exclude hepatitis A with HAV IgM and attempt diagnosis with tests (if available).
- Monitor hepatic synthetic function for liver failure using prothrombin time or INR, having given IV vitamin K.
- Monitor for complications, including hypoglycaemia, encephalopathy, bone-marrow aplasia, secondary sepsis and pancreatitis (*see* Section 5.7.A).
- Treat complications when possible.
- Give vitamin K, 300 micrograms/kg.
- Give anti-emetics if there is severe nausea and vomiting.
- Give intravenous fluids **only if oral or nasogastric rehydration is not possible**.
- *See* Section 5.7.A for the management of acute liver failure if this develops.
- If available, immunise all family contacts for HAV and HBB (HAV A, two doses 2 weeks apart; HAV B, three doses, the first being given immediately, the second 1 month later, and the third 3–6 months later).

Hepatitis A

- Hepatitis A (HAV) is a picornavirus spread by the faecal–oral route.
- The incubation period from infection to raised transaminases is 10–20 days.
- Before jaundice is seen there may be anorexia, nausea, vomiting, fever and liver tenderness.
- Jaundice is related to age, with more than 90% of children under 2 years being asymptomatic, and only 76% of teenagers jaundiced.
- A minority of cholestatic cases have a relapsing course, and 0.1–0.2% develop acute liver failure. The prognosis for almost all is excellent with symptomatic treatment.
- Chronic liver disease does not develop, but occasional patients have a transient nodular regenerative phase with evidence of portal hypertension lasting up to 1 year. Aplastic anaemia is a rare complication.
- HAV vaccine is highly efficacious and without side effects.

Hepatitis B

Acute hepatitis B (see also section on chronic hepatitis)

- This is spread by blood and body fluid products, vertical transmission from mother to baby, and sexual contact. The risk of all such spread is much greater than for HIV infection.
- The incubation period is 60–90 days, but rarely up to 7 months.
- The risk of acute liver failure is less than 1%, and the risk of chronic liver disease depends on the patient's age: it is approximately 90% at birth, 25% in childhood and less than 10% in adults.
- Hepatitis B vaccine is usually given by three injections over 6 months, but an accelerated course can be given

over 21 days, and post-exposure vaccination is usually given in combination with immunoglobulin in a different site. All healthcare workers should be immunised against HBV and their immunity status checked.

Hepatitis C

- The mechanisms of spread are the same as for hepatitis B, but vertical spread is rare (around 4%).
- The incubation period is 2–26 weeks, followed by acute hepatitis that is almost always asymptomatic.
- Chronic hepatitis ensues in 30–90% of cases.
- Symptomatic liver disease is almost never seen in childhood.
- Treatment with a combination of pegylated interferon and ribavirin is becoming progressively more successful (if available).

Hepatitis E

- Spread is by the faecal–oral route and is endemic in Southern Europe, the Middle East and Asia.
- It is rare in children, and the highest rate in adolescents is 3%.
- A relapsing course is seen.
- The prognosis is usually good, but mortality is recognised in pregnant women.

Epstein–Barr virus (EBV)

- EBV infection is accompanied by hepatosplenomegaly and hepatitis.
- The prognosis is usually good, but rare cases are complicated by lymphoproliferative disease or haemophagocytic syndrome in immune-deficient individuals.

Cytomegalovirus (CMV)

- Spread is the same as for EBV and hepatitis, but symptoms are usually only seen in the newborn and immunocompromised.

Parvovirus B19

- This infection can be accompanied by acute liver failure and aplastic anaemia.

6.2.D Human immunodeficiency virus (HIV) infection

BOX 6.2.D.1 Minimum standards

- Preventive campaigns.
- Antenatal HIV screening.
- Antenatal and postnatal antiretroviral (ARV) drugs.
- Paediatric HIV testing.
- Antiretroviral drugs (triple drug regimes for all), including those to prevent vertical transmission guaranteed.
- Health system strengthening to provide a capacity to treat all with ARV and give supportive treatment.
- Correction of nutritional deficiencies.
- Antibacterial drugs, including anti-TB and antifungal drugs.
- Analgesia and palliative care.
- Counselling and family support.

Introduction

The human immunodeficiency virus (HIV) epidemic has spread to all corners of the world, affecting millions of infants, children and adults. It is the most common cause of acquired immune deficiency in children. The timely and early diagnosis of neonates, infants and children with HIV is vital. However, the healthcare system of resource-limited countries has its own strengths and limitations. Pitfalls in accurate testing, poor access to health, and high financial costs are a few of the many factors that hamper efforts to limit the spread of diseases such as HIV. In addition, the management of HIV is complex and intricate. Many factors, including proper assessment and indication, counselling, availability and choice of antiretroviral drugs, toxicity, monitoring, financial burden, and social and psychosocial support have to be addressed for HIV care to be successful. Education, evaluation, building expertise, establishing HIV referral centres with diagnostic testing (including virological testing), ensuring availability of antiretroviral drugs, monitoring and follow-up are some of the key elements necessary for programmes to have adequate impact.

Epidemiology

- There are two major strains of the human immunodeficiency virus: HIV1 and HIV2. HIV1 is the more pathogenic, and is responsible for the global epidemic. HIV2 is largely confined to West Africa. This subsection reflects current management of HIV1, but the principles apply to both strains.
- Infection with HIV leads to progressive destruction of the cellular immune system, ultimately resulting in an acquired immune deficiency syndrome (AIDS) in the vast majority of infected individuals.
- HIV/AIDS is now one of the leading causes of death in children.
- Mother-to-child transmission results in approximately 1000 children becoming infected with HIV each day worldwide. There were 2.5 million children under 15 years old living with HIV in 2009.
- Around 97% of the world's new HIV infections occur in people living in low- and middle-income countries. About 92% of children living with HIV are from sub-Saharan Africa.
- The number of new infections fell from a peak in the late 1990s, but has now plateaued at a high incidence of 2.6 million new infections per year, just below the maximum level reached previously.
- Deaths from AIDS have decreased by 19% between 2004 and 2009 with increasing access to antiretroviral therapy.
- Around 95% of the world's HIV-infected children have been from resource-limited countries. About 90% have been from sub-Saharan Africa, but the prevalence elsewhere is rising, particularly in India, South-East Asia, and countries of the former Soviet Union.

- More than 90% of children acquire HIV perinatally (vertically) from their mothers. The rest are infected through transfusion of infected blood products or via unsterilised needles (extent unknown but probably small), or via sexual transmission among adolescents, or in younger children through child sexual abuse.
- In non-breastfed infants, vertical transmission occurs mainly around the time of delivery, with transmission rates in resource-limited countries ranging from 17% to 24%. Breastfeeding roughly doubles the risk of transmission. In breastfed cohorts from resource-limited countries the rates of transmission are 25–45%.
- Management ideally begins before birth, with counselling and voluntary testing of HIV-infected women during pregnancy, and institution of measures to reduce transmission. In almost all countries, antiretroviral therapy for mothers and infants, elective (pre-labour) Caesarean section and avoidance of breastfeeding have reduced transmission rates to less than 2%.
- Without prenatal counselling and screening, as is frequently the case in resource-limited countries, management begins only when the child becomes symptomatic, with subsequent identification of the HIV infection in the mother.
- Treatment may not be successful if presentation is at an advanced stage of immunosuppression.
- In all societies, even those with a high prevalence, HIV is a potentially stigmatising condition, and the mother or both parents may be reluctant to undergo testing. Confidentiality is essential.
- Counselling must be confidential, requires time and should be undertaken by trained staff.
- Even if a child born to an infected mother is uninfected, he or she will inevitably be affected. Between 14.4 and 18.8 million children were estimated to have lost one or both parents to AIDS in 2010 (UNAIDS data). These children may be abandoned by relatives, ostracised by the community, poorly educated and highly vulnerable. Many support themselves and surviving siblings by commercial sex work, and may acquire HIV infection as a result.

Natural history data

- Before the advent of **highly active antiretroviral therapy (HAART)**, infant mortality doubled and mortality in children aged 1–5 years increased from 8 to 20 per 1000 in Harare between 1990 and 1996.
- However, even in resource-limited countries, some children may be symptom-free into the second decade of life. There is no upper age limit at which it is appropriate to test for HIV if the mother does not have a negative test after the child's birth.
- Data from large long-term prospective perinatally recruited cohort studies are limited in resource-limited countries.
- Growth failure, generalised lymphadenopathy, hepatosplenomegaly, persistent diarrhoea, pulmonary infections, chronic cough and recurrent fevers are the most frequent clinical manifestations.
- The most common causes of death are pneumonia, diarrhoea and malnutrition. Post-mortem studies from the Cote d'Ivoire and clinical studies in Malawi and South Africa showed that *Pneumocystis jiroveci* pneumonia (PCP) is a frequent cause of death in children under 15 months of age.
- Malignancy is a relatively rare AIDS-defining illness in children, compared with HIV-infected adults. However, substantial increases in Kaposi's sarcoma in children have been reported from East and Central Africa. Co-infection with the human herpes virus (HHV8) is a crucial aetiological factor. Kaposi's sarcoma typically presents with large non-tender firm mobile lymph nodes in the head and neck region, and there may be skin lesions and pulmonary disorders. Median survival in one series was only 3 months.

Diagnostic issues

Confirming a diagnosis of HIV infection in young children can be difficult in resource-limited settings.

Early infant diagnosis of HIV: exposed infants should be tested at 6 weeks or as soon as possible thereafter. Infant blood samples are sent as dried blood spots to a laboratory that has the required equipment for HIV PCR testing. This laboratory may be close by, but could also be far from the site. The results then need to be sent back to sites and returned to caregivers in a timely manner. Finally, infants who have tested positive must be started on ART.

In areas of high HIV prevalence, WHO *Integrated Management of the Child* recommends that, when

TABLE 6.2.D.1 Signs and symptoms for use in endemic areas with limited access to diagnostic laboratories

Signs or illness specific to HIV infection	Signs or illness uncommon in HIV-negative children	Signs common in both HIV-positive and ill non-HIV-infected children
Pneumocystis pneumonia	Molluscum contagiosum with multiple lesions	Persistent diarrhoea (> 14 days)
Oesophageal candidiasis	Oral thrush (especially after the neonatal period) without antibiotic treatment and lasting > 1 month or recurrent	Failure to thrive
Herpes zoster	Generalised pruritic dermatitis	Persistent cough > 1 month
Lymphoid interstitial pneumonia	Recurrent severe infections (three or more per year)	Generalised lymphadenopathy
Kaposi's sarcoma	Persistent and/or recurrent fever lasting > 1 week	Hepatosplenomegaly
Chronic parotid enlargement	Neurological dysfunction (progressive neurological impairment, delayed development, intellectual impairment, hypertonia)	Chronic otitis media
Recto-vaginal fistula (rare)	Failure to thrive in a fully breastfed infant < 6 months of age	Moderate or severe malnutrition

assessing sick children aged 2 months to 5 years, healthcare workers ask about a history of pneumonia, persistent diarrhoea, ear discharge or very low weight, and look for oral thrush, parotid enlargement and generalised persistent lymphadenopathy. If there are two or more of the above, HIV infection should be suspected and an HIV antibody test performed.

Clinical diagnosis

- The symptoms and signs are often non-specific. The most recent modified WHO clinical case definition for paediatric AIDS is a useful tool for epidemiological surveillance, but lacks sensitivity and has a low positive predictive value (PPV). It is therefore not useful for confirming a diagnosis of HIV infection in an individual child.
- The presence of oral candidiasis does not distinguish HIV-infected from HIV-uninfected children. However, failure of oral candidiasis to respond to treatment or rapid relapse is a highly specific sign of HIV infection. After the neonatal period, the presence of oral thrush without antibiotic treatment, or lasting over 30 days despite treatment, or recurring, or extending beyond the tongue, is highly suggestive of HIV infection. Also typical is extension to the back of the throat, which indicates oesophageal candidiasis.
- Chronic parotitis, the presence of unilateral or bilateral parotid swelling (just in front of the ear) for 14 or more days, with or without associated pain or fever or shingles, is highly suggestive of HIV infection.
- Shingles is unusual in healthy children. Herpes zoster ophthalmicus (i.e. shingles around one eye) is said to have greater than 95% PPV for HIV infection in African children.
- Geographical variation in patterns of disease must be recognised. *Penicillium marneffei* infection, an opportunistic fungal disease that presents with nodular skin lesions, is an AIDS-defining illness that has been reported in South-East Asia. Giant molluscum contagiosum has been a presenting sign in children in Eastern Europe.
- None of these clinical features is a sensitive marker of HIV infection in childhood populations, in that a minority of HIV-infected children manifest them.

There are many clinical signs or conditions that are quite specific to HIV infection, which should be strongly suspected if these conditions are present (*see* Table 6.2.D.1). Some of these features are listed below.

1 Signs or conditions that are very specific to HIV-infected children:
   - Pneumocystis pneumonia (PCP).
   - Oesophageal candidiasis.
   - Lymphoid interstitial pneumonia (LIP).
   - Kaposi's sarcoma.
2 Signs that may indicate possible HIV infection:
   - **Recurrent infection:** three or more severe episodes of a bacterial infection (e.g. pneumonia, meningitis, sepsis, cellulitis) in the past 12 months.
   - **Oral thrush:** after the neonatal period, the presence of oral thrush in the absence of antibiotic treatment, or lasting over 30 days despite treatment, or recurring, or extending beyond the tongue.
   - **Chronic parotitis:** the presence of unilateral or bilateral parotid swelling for 14 or more days.
   - **Generalised lymphadenopathy:** the presence of enlarged lymph nodes in two or more non-inguinal regions without any apparent underlying cause.
   - **Hepatomegaly** with no apparent cause.
   - **Persistent and/or recurrent fever.**
   - **Neurological dysfunction:** progressive neurological impairment, microcephaly, developmental delay, hypertonia, encephalopathy.
   - **Herpes zoster.**
   - **HIV dermatitis:** typical skin rashes include erythematous papular rashes, extensive fungal infections of the skin, scalp and nails, and extensive molluscum contagiosum.
   - **Chronic suppurative lung disease.**
3 Signs that are common in HIV-infected and non-HIV-infected children:
   - Chronic otitis media.
   - Persistent diarrhoea.
   - Moderate or severe malnutrition.

Counselling and testing

If there are reasons to suspect HIV infection, and the child's HIV status is not known, the family should be offered diagnostic testing for HIV.

Counselling used to be more complex when there was no treatment available. There is now no question that it is in the child's best interest to be tested so that treatment can be given to prolong life if they are HIV-positive. The lessons of obtaining informed consent still apply, just as with any other important investigation. If the mother has not already been tested, a positive result in a child is most likely to mean that the mother is infected, too. However, if the mother is not present when the child presents, the onus of responsibility of the paediatrician is to the child, and testing should not be delayed.

The additional consideration with testing for HIV is the stigma associated with the diagnosis. When HIV meant inevitable death, there was enormous fear of the diagnosis. The potentially better prognosis has been hard to accept when so many present too late. Stigma is also associated with the fact that it is a sexually transmitted disease. This raises issues of where the infection was acquired and contact tracing. The fear of domestic violence and social ostracisation sometimes creates reluctance to allow children to be tested.

The process of counselling starts with always ensuring that the test is done with consent. The person giving consent should be the carer at the time when the test is indicated. If the child is of an age at which they can be responsible for taking their own medicines, they can give their own consent for testing. There are no surrogate tests for HIV, such as lymphocyte counts; the appropriate test according to what is available should always be done. If there is delay in getting a result it may be necessary to start appropriate treatment – for example, for suspected PCP pneumonia with IV co-trimoxazole.

If there is refusal to allow testing, the test cannot be carried out. If the test is positive, the family need to have confidence in the healthcare professionals to ensure adherence to treatment. Counselling requires time, and must be done by trained staff. If staff at the first referral level have not been trained, assistance should be sought from other sources, such as local community AIDS support organisations. A time limit should be set to prevent repeated

procrastination and the risk of death from opportunistic infection.

HIV counselling should take account of the child as part of a family. This should include the psychological implications of HIV infection for the child, mother, father and other family members. Counselling should stress that, although cure is currently not possible, there is much that can be done to improve the quality and duration of the child's life. Antiretroviral treatment (ART) is available and greatly improves survival and the quality of life of the child and the parents. Counselling should make it clear that the hospital staff want to help, and that the mother should not be frightened of going to a health centre or hospital early in an illness, even if this is only to ask questions.

HIV is talked about much more openly now than was the case at the start of the epidemic, and testing is seen as an expected part of routine healthcare. The request for testing should not be built up as a major event, but included as part of the diagnostic work-up along with malaria, TB and other investigations.

As mentioned above, counselling requires time, and must be done by trained staff.

Indications for HIV counselling

HIV counselling is indicated in the following situations.

Child with unknown HIV status presenting with clinical signs of HIV infection and/or risk factors (e.g. a mother or sibling with HIV/AIDS)

- Make time for the counselling session.
- Take advice from local people experienced in offering testing, so that any advice given is consistent with what the mother will receive from professional counsellors at a later stage.
- Where available, arrange an HIV test, according to national guidelines, to confirm the clinical diagnosis, alert the mother to HIV-related problems, and discuss prevention of future mother-to-child transmission.

Note the following:

1 If HIV testing is not available, discuss the presumptive diagnosis of HIV infection in the light of the existing signs and symptoms and risk factors.
2 In countries with generalised HIV epidemics, routine healthcare provider-initiated testing and counselling (PITC) is recommended for all children seen in paediatric health services (World Health Organization, 2007).

Child known to be HIV-infected but responding poorly to treatment, or needing further investigations

Discuss the following:

- the parents' understanding of HIV infection
- management of current problems
- the role of ART and adherence to regular drug administration
- the need to refer to a higher level, if necessary
- support from community-based groups (if available).

Child known to be HIV-infected who has responded well to treatment and is to be discharged (or referred to a community-based care programme)

Discuss the following:

- the reason for referral to a community-based care programme, if appropriate
- follow-up care
- risk factors for future illness
- immunisation and HIV
- adherence and ART treatment support.

Laboratory diagnosis

The definitive diagnosis of HIV requires laboratory confirmatory testing. The HIV antibody test is commonly used as a screening test. However, in the neonatal and infantile period, the antibody test is not recommended. This is because the maternal HIV antibodies readily cross the placenta and persist in the neonate for up to 18 months. Also, all screening tests should be confirmed by a second test. The following are some of the tests used for laboratory diagnosis of HIV in children:

- Antibody tests:
  - HIV IgG antibody tests.
  - Rapid Test.
- Virological tests:
  - HIV DNA polymerase chain reaction (PCR).
  - HIV RNA PCR.
  - HIV culture.
- P24 antigen assay:
  - Direct.
  - Acid hydrolysis.

DNA-based assays are the most reliable for diagnosis, and are recommended for diagnosis in infants. However, the cost and availability of tests may be an issue in resource-limited countries. The simplest laboratory test is an HIV antibody test, usually done by enzyme-linked immunosorbent assay (ELISA). However, even this may not be affordable or available in many settings.

The WHO recommends the use of a presumptive clinical diagnosis of severe HIV disease in the **absence** of virologic testing **if**:

- an infant's HIV exposure is confirmed by antibody testing **and** if either:
  - clinical stage 3 or 4 or AIDS-indicator condition(s) are present **or**
  - the child has two or more of the following: oral thrush, severe pneumonia, severe sepsis.

A **presumptive** diagnosis of AIDS can also be made in an antibody-positive infant **if** CD4 percentages are below 20% **or** other factors are present, including recent HIV-related maternal death or advanced HIV disease in the mother.

Infants acquire maternal HIV IgG transplacentally, and this can be detected by ELISA up to 18 months of age. Thus antibody tests cannot reliably distinguish infected from uninfected children until they are 18 months old. Additional diagnostic challenges arise if the child is still breastfeeding or has been breastfed. Although HIV infection cannot be ruled out until 18 months for some children, many children will have lost HIV antibodies between 9 and 18 months of age. The importance of this is that a rapid antibody test can be done if the mother is unwilling or unavailable to be tested herself. If the antibody test is negative and the child has not been breastfed in the last 6 weeks, there is then no need for further testing unless there is ongoing exposure (e.g. through breastfeeding). If the antibody is positive, this does not mean that the child is infected, but if other signs of immune deficiency are present it may warrant empirical treatment according to WHO guidelines if PCR testing is not available.

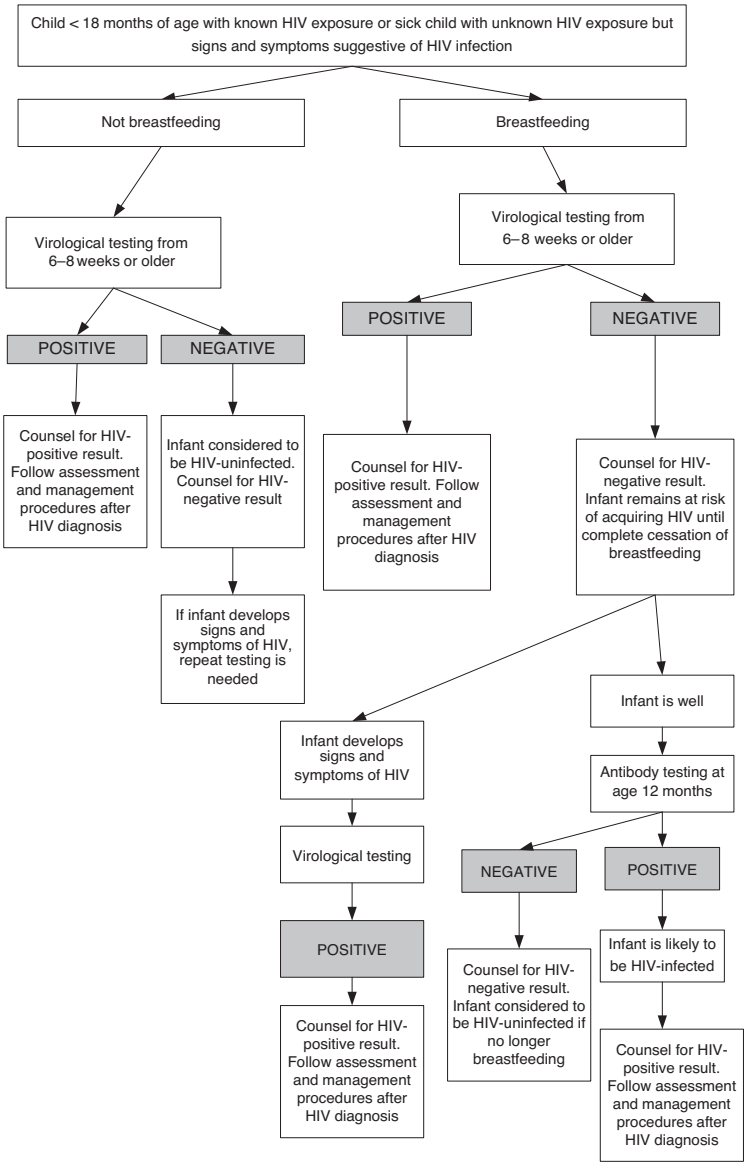

FIGURE 6.2.D.1 Algorithm for diagnosing HIV infection in infants and children less than 18 months of age.

Many children born to HIV-infected mothers may die before this age, and a diagnosis of HIV infection may be presumptive, dependent on signs and symptoms. Thus, based on age, the clinical, serological and virological tests and status of breastfeeding will determine the diagnosis of a child undergoing evaluation (*see* Table 6.2.D.2).

TABLE 6.2.D.2 Proposed methods for diagnosing HIV in children (born to mothers identified as HIV-positive or with unknown HIV status) in resource-limited settings* (*see* Figure 6.2.D.1)

	Age of child		
Diagnostic method	**< 12 months**	**12–18 months**	**> 18 months**
Clinical staging	Yes	Yes	Yes
Serological (antibody)	May be helpful†	Yes‡	Yes
Virological	Yes	Yes, if serology is positive	No, serology is definitive

*If the child is breastfeeding, a negative diagnostic test, either serological or virological, would have to be repeated 6 weeks after cessation of all breastfeeding.

† A positive antibody test in a child under 12 months of age defines the exposure status of the child and may be helpful when the mother's HIV status is unknown.

‡ By the age of 12 months, HIV antibody-positive testing can be considered indicative of probable HIV infection, and should be confirmed by a second antibody test after 18 months.

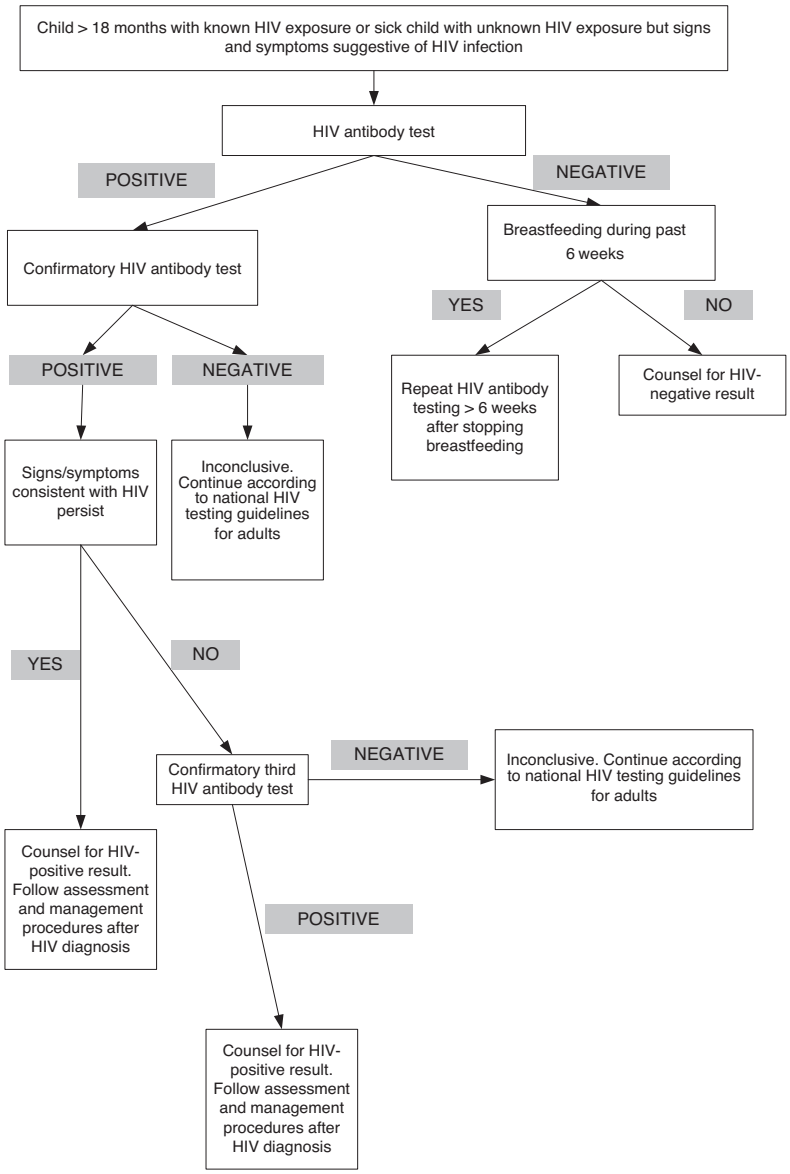

FIGURE 6.2.D.2 Algorithm for diagnosing HIV infection in infants and children aged 18 months or older.

Algorithms for diagnosis are shown in Figures 6.2.D.1 and 6.2.D.2.

Notes to Figure 6.2.D.1.

1 If HIV exposure is not certain, consider testing the mother first before doing a virological test on the child. If the mother tests negative for HIV, explore other risk factors for HIV transmission.
2 In infants and children under 18 months of age considered to be HIV-uninfected who develop signs or symptoms suggestive of HIV, virological testing should be performed.
3 If virological testing is not available, antibody testing can be performed. By the age of 12 months most uninfected children will have lost maternal antibody, and positive antibody testing at this time usually indicates HIV infection in the child (96% specificity). In infants younger than 12 months where antibody testing is still positive, a presumptive clinical diagnosis of severe HIV disease may need to be made, as it is not possible to reliably establish HIV infection with antibody testing before the age of 12 months (i.e. specificity at age 9–12 months is 74–96%). In this situation, confirmation of the presumptive clinical diagnosis of HIV infection by virological testing should be sought as soon as possible.
4 Antibody testing can be performed at the age of 12 months (see above).
5 Where the infant is being considered to be HIV-infected based upon a positive antibody test performed at 12 months of age or older, the result should be confirmed by virological testing (in children less than 18 months of age) or by antibody testing (once they are over 18 months of age).

Notes to Figure 6.2.D.2.

1 A definitive diagnosis of HIV infection in children aged ≥ 18 months can be made with antibody testing. HIV testing procedures for children aged ≥ 18 months follow the national HIV testing guidelines for adults. Virological testing can be used to diagnose HIV infection at any age.
2 One positive HIV antibody test (rapid test or ELISA) should be confirmed by a second HIV antibody test

(rapid test or ELISA) using an assay that relies on a different antigen or has different operating characteristics. In low-HIV-prevalence settings, a third confirmatory test may be required.

3 Children who are breastfed have an ongoing risk of acquiring HIV infection. Therefore HIV infection can be excluded only after stopping breastfeeding for more than 6 weeks.

HIV antibody test (ELISA or rapid tests)

Rapid tests are widely available and are safe, effective, sensitive and reliable for diagnosing HIV infection in children above the age of 18 months. For those under 18 months, HIV antibody tests are a sensitive reliable way to exclude HIV infection in non-breastfeeding children. For those children under 18 months, confirm all positive HIV antibody tests by virological tests as soon as possible (see below). Where this is not possible, repeat antibody testing at 18 months.

Rapid HIV tests can be used to exclude HIV infection in a child presenting with malnutrition or other serious clinical events in areas with high HIV prevalence.

To confirm the diagnosis, it is necessary to use assays that detect the virus itself or viral components. Such tests include **antigen detection tests, viral culture, amplification techniques and HIV-specific IgA tests**.

Virological testing

Virological testing for HIV-specific RNA or DNA is the most reliable method of diagnosing HIV infection in children under 18 months of age. This requires sending a blood sample to a specialised laboratory that can perform this test, and these are becoming increasingly available in large centres in many countries. It is relatively inexpensive, easy to standardise, and can be done using dried blood spots. In infants and children undergoing virological testing, the following assays (and respective specimen types) are potentially available:

- HIV DNA on whole blood specimens or dried blood spots (DBS)
- HIV RNA on plasma or DBS
- ultrasensitive p24 antigen (Up24 Ag) on plasma or DBS.

The new ultrasensitive p24 assay is as accurate as PCR virology, significantly less expensive, and less resource demanding when used to diagnose HIV. It is particularly valuable in infants under 12 months old.

A test at birth will only detect *in-utero* infection, whereas most infection occurs at delivery. Infected infants can suffer life-threatening infections in the first weeks of life. Where there is a high risk of infection (e.g. a mother who seroconverts in pregnancy, has a low CD4 count or other genital lesions and has had no antiretrovirals), testing should be done at 2 weeks of age. Where the risk is low (e.g. a mother who has been on HAART throughout pregnancy), the test can be delayed until 6 weeks of age. At the first DTP immunisation of all infants, the maternal HIV status should be checked from records or rapid testing. If it is positive or unavailable, the child should be tested. All HIV-exposed infants should have HIV virological testing at 4–6 weeks of age or at the earliest opportunity thereafter.

If the child has had zidovudine (ZDV) prophylaxis during and after delivery, virological testing is not recommended until 4–8 weeks after delivery, as ZDV interferes with the reliability of the test.

One virological test that is positive at 4–8 weeks is sufficient to diagnose infection in a young infant. If the young infant is still breastfeeding, and the DNA virological test is negative, it needs to be repeated 6 weeks after the complete cessation of breastfeeding to confirm that the child is not HIV infected.

Infants with signs or symptoms suggestive of HIV infection must undergo HIV serological testing and, if this is positive, virological testing. In breastfeeding infants or children it is strongly recommended that breastfeeding is not discontinued in order to perform any kind of diagnostic HIV test. In sick infants in whom HIV infection is being considered as an underlying cause of symptoms and signs, and virological testing is not available, HIV serological testing and the use of a clinical algorithm for presumptive clinical diagnosis of HIV infection are strongly recommended.

In infants with an initial positive virological test result, it is strongly recommended that ART be started without delay and, at the same time, a second specimen be collected to confirm the initial positive virological test result. **Do not delay ART. In infected infants, immediate initiation of ART saves lives, and commencement of ART should not be delayed while waiting for the results of the confirmatory test. Results from the CHER trial suggest initiation of ART before 12 weeks of age results in a 75% reduction in early mortality.**

(Cotton MF, Violari A, Otwombe K, *et al.* (2013) Early time-limited antiretroviral therapy versus deferred therapy in South African infants infected with HIV: results from children with HIV early antiretroviral (CHER) randomised trial. *Lancet* 382: 1555–63.)

Test results from virological testing in infants should be returned to the clinic and the child and their mother or carer as soon as possible, but at the very latest within 4 weeks of specimen collection. Positive test results should be fast-tracked to the mother–baby pair as soon as possible to enable prompt initiation of ART.

All infants with unknown or uncertain HIV exposure who are being seen in healthcare facilities at or around the time of birth or at the first postnatal visit (usually 4–6 weeks), or at another child health visit, should have their HIV exposure status ascertained.

Clinically well, HIV-exposed infants should undergo HIV serological testing at around 9 months of age (or at the time of the last immunisation visit). Those who have positive serological assays at 9 months should have a virological test to identify whether they need ART.

Recently the WHO Technical Reference Group for Paediatric HIV/ART and Care made the following key recommendations with regard to when and how to test for HIV in children:

1 Infants known to have been exposed to HIV should have a virological test (HIV nucleic acid test) at 4–6 weeks of age, or at the earliest opportunity for infants seen after 4–6 weeks.
2 Urgent HIV testing is recommended for any infant presenting to healthcare facilities with signs, symptoms or medical conditions that could indicate HIV.
3 All infants should have their HIV exposure status established at their first contact with the healthcare system, ideally before 6 weeks of age.
4 Infants under 6 weeks of age, of unknown HIV exposure status and in settings where local or national antenatal HIV seroprevalence is greater than 1%, should be offered maternal or infant HIV antibody testing and counselling in order to establish their exposure status.

Other laboratory tests

- **A low CD4 count or CD4:CD8** ratio suggests HIV infection, but requires specialised equipment. **A low total lymphocyte count** is a much less expensive though less specific surrogate marker of HIV infection and immunosuppression.
- HIV infection can also cause anaemia or thrombocytopaenia. It is appropriate to test for HIV in children who present with low platelet counts.
- Lack of thymic shadow on chest X-ray is a feature of advanced disease, but is clearly not specific, as the thymus tends to shrink in volume in response to a variety of acute infections in childhood.

Assessment of HIV-infected and HIV-exposed children

Any child with an illness compatible with HIV infection should be properly evaluated irrespective of HIV exposure. This includes neonates, infants and children with perinatal exposure, and those with specific signs and symptoms suggestive of HIV infection, chronic or unexplained illness, or known exposure during childhood. Figure 6.2.D.3 shows a useful algorithm that can be used by paediatricians and other clinical care providers for the initial evaluation and management of children with known exposure to HIV, or sick children with symptoms suggestive of HIV infection but unknown history of exposure.

Notes to Figure 6.2.D.3.

1 An expert in the management of children with HIV should be consulted wherever this is feasible.
2 If HIV is suspected, compassionate counselling before HIV testing should be arranged.
3 Maternal advanced HIV disease and low CD4 are risk factors for HIV transmission.
4 Successful treatment with ART in mothers reduces the risk of transmission.
5 PMTCT using ZDV monotherapy alone, ZDV plus NVP single dose, and NVP single dose alone is associated

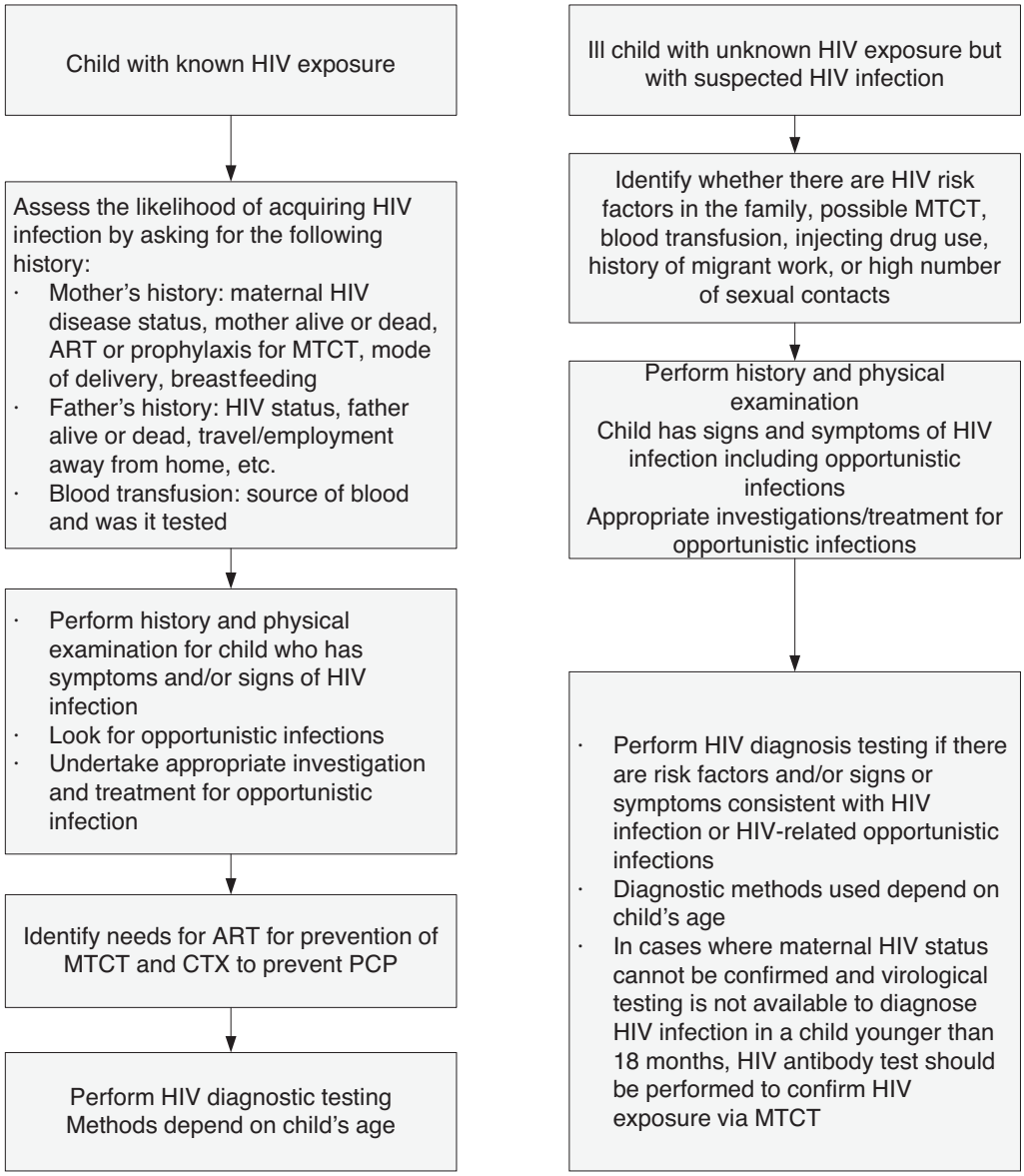

FIGURE 6.2.D.3 Initial assessment of a child with known HIV exposure or a sick child with unknown HIV exposure but with suspected HIV infection. MTCT, mother-to-child transmission; ART, antiretroviral therapy; PCP, pneumocystis pneumonia.

with transmission rates of approximately 5–10%, 3–5% and 10–20%, respectively.

6 An infant remains at risk of acquiring HIV for as long as he or she is breastfed.

Perinatally acquired HIV infection

HIV1 transmission occurs more frequently than that of HIV2. It occurs in late pregnancy, during delivery and through breastfeeding, and transmission is more likely if any of the following factors are present:

- advanced maternal HIV disease
- premature labour
- prolonged rupture of membranes
- contact with maternal blood
- in the first twin
- maternal genital infection.

Prevention of mother-to-child transmission (PMTCT) of HIV and infant feeding in the context of HIV

HIV transmission may occur during pregnancy, labour and delivery, or through breastfeeding. The best way to prevent transmission is to prevent sexually acquired HIV infection, especially in pregnant women, and to prevent unintended pregnancies in HIV-positive women. If an HIV-infected woman becomes pregnant, she should be provided with services including antiretroviral drugs, safe obstetric practices, and infant feeding counselling and support (*see* Section 2.8.C).

The key recommendations of the 2010 WHO guidance on ARV drugs for treatment of pregnant women and prevention of HIV in infants are as follows:

Women who are immunocompromised

As early as possible, provide ART for all HIV-positive pregnant women both to benefit the health of the mother and to prevent HIV transmission to her child during pregnancy and breastfeeding.

Start lifelong ART for all pregnant women with severe or advanced clinical disease (stage 3 or 4), or with a CD4 count of ≤ 350 cells/mm^3, regardless of symptoms. HIV-positive pregnant women in need of treatment for their own health (i.e. as soon as the eligibility criteria are met) should start ART irrespective of gestational age, and should continue with it throughout pregnancy, delivery, during breastfeeding and thereafter.

The recommended first-line regimens for pregnant women are as follows:

- AZT + 3TC + NVP **or**
- AZT + 3TC + EFV **or**
- TDF + 3TC (or FTC) + NVP **or**
- TDF + 3TC (or FTC) + EFV.

The infant is given NVP or AZT starting as soon as possible after birth (aim for less than 6 hours postpartum) and continued for 4–6 weeks.

Women who are not immunocompromised

Antiretroviral (ARV) prophylaxis is indicated for HIV-positive pregnant women with relatively strong immune systems who do not need ART for their own health. This would reduce the risk of HIV transmission from mother to child. There are two options, both of which should start early in pregnancy, at 14 weeks or as soon as possible thereafter. The two options provide a significant reduction in MTCT with equal efficacy in this group of women who are not eligible for ART.

Option A: Twice daily AZT for the mother during pregnancy; if the mother has less than 4 weeks of AZT, give single-dose nevirapine during labour, and AZT and lamivudine during labour and for 7 days postpartum. Give the infant prophylaxis with either AZT or NVP for 6 weeks after birth if he or she is not breastfeeding. If the infant is breastfeeding, daily NVP infant prophylaxis should be continued for 1 week after the end of the breastfeeding period.

or

Option B: a three-drug prophylactic regimen for the mother, taken during pregnancy and throughout the breastfeeding period, as well as infant prophylaxis for 6 weeks after birth, whether or not the infant is breastfeeding.

Option B+: all pregnant and breastfeeding women infected with HIV should initiate ART as lifelong treatment.

Breastfeeding

The global availability of ART means that there is enough evidence for the WHO to recommend breastfeeding for mothers with HIV.

Even with ART there is still a small risk of HIV transmission, particularly if there is any interruption to treatment, either in supply or absorption (due to diarrhoea or vomiting). HIV can be transmitted through breast milk at any point during lactation, so the rate of infection in breastfed infants increases with duration of breastfeeding.

In many countries, public health services where there is poor access to clean drinking water and alternatives to breastfeeding have not been able to adequately support and provide safe replacement feeding. HIV-positive mothers have faced the dilemma of whether to give their babies all the benefits of breastfeeding but expose them to the risk of HIV infection, or avoid all breastfeeding and increase the risk of their baby's death from diarrhoea and malnutrition.

The effectiveness of ART in reducing transmission through breastfeeding has resulted in two major changes in 2012 from previous guidelines:

1 National health authorities should decide whether health services will principally counsel and support HIV-positive mothers to either:
   - breastfeed and receive ARV interventions **or**
   - avoid all breastfeeding, as the strategy that is most likely to give infants the greatest chance of HIV-free survival.
2 In settings where national authorities recommend that HIV-positive mothers should breastfeed, and provide ARVs to prevent transmission, mothers should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and should continue breastfeeding for the first 12 months of life.

Mothers who are known to be HIV infected and who decide to stop breastfeeding at any time should stop gradually over 1 month. Stopping breastfeeding abruptly is not advisable (World Health Organization, 2010).

These new guidelines have great potential to improve the mother's own health and to reduce the mother-to-child HIV transmission risk to 5% or lower in a breastfeeding population in the absence of any interventions and with continued breastfeeding. With ART the WHO is aiming

for complete prevention of mother-to-child transmission worldwide by 2015.

Where a decision has been made to continue breastfeeding because the child is already infected, infant feeding options should be discussed for future pregnancies. This should be carried out by a trained and experienced counsellor.

If a child is known to be HIV-infected and is being breastfed, encourage the mother to continue breastfeeding if living in a resource-limited country, as there is usually a high risk of gastroenteritis in such regions.

If the mother is known to be HIV-positive and the child's HIV status is unknown, the mother should be counselled about the benefits of breastfeeding as well as the risk of HIV transmission through breastfeeding. If replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of further breastfeeding is recommended. Otherwise, exclusive breastfeeding should be practised if the child is less than 6 months of age, and breastfeeding should be discontinued as soon as these conditions are in place.

Infants born to HIV-positive mothers who have escaped perinatal infection have a lower risk of acquiring HIV if they are not breastfed. However, their risk of death may be increased if they are not breastfed in situations where there is no regular access to nutritionally adequate, safely prepared breast milk substitutes, and there is a high risk of gastroenteritis.

Counselling should be provided by a trained and experienced counsellor. Take advice from local people experienced in counselling so that any advice given is consistent with what the mother will receive from professional counsellors at a later stage.

If the mother decides to use breast milk substitutes, counsel her about their correct use and demonstrate their safe preparation.

Management of the child with a suspected or proven HIV infection

- The aim of treatment should be to maintain the best possible quality of life for the child for as long as possible, without bankrupting the family. This disease affects the whole family, and the child must be treated in the context of the needs of all of the family.
- Currently there are far more questions than evidence-based answers; published data on many management issues in the context of resource-limited countries are not available.
- Much can be achieved with compassionate supportive care, by applying existing guidelines (such as Integrated Management of Childhood Illness algorithms) with an awareness of the need for early diagnosis and intervention in the HIV-infected child.
- Diagnosis of infections such as tuberculosis, lower respiratory infections, bacteraemia (particularly with non-typhoid salmonellae, staphylococci or streptococci) and opportunistic infections can be difficult, and often relies on empirical trials of therapy.

A low threshold for antibiotic use is appropriate, but may exacerbate diarrhoea and candidiasis, and may only be effective if given IV or IM, in the presence of diarrhoea and malabsorption.

Most infections in HIV-positive children are caused by the same pathogens as in HIV-negative children, although they may be more frequent, more severe and occur repeatedly. There is recent evidence that *Staphylococcus aureus* may be more invasive in children with HIV.

Clinical staging of HIV infection

In a child with diagnosed or highly suspected HIV infection, a clinical staging system helps to identify the degree of damage to the immune system and to plan treatment and care options. The stages determine the likely prognosis of HIV, and are a guide as to when to start, stop or substitute ARV therapy in HIV-infected children.

The clinical stages identify a progressive sequence from least to most severe, such that the higher the clinical stage the poorer the prognosis. For classification purposes, once a stage 3 clinical condition has occurred, the child's prognosis will probably remain that of stage 3, and will not improve to that of stage 2, even with resolution of the original condition, or the appearance of a new stage 2 clinical event. ART with good adherence dramatically improves the prognosis.

The clinical staging events can also be used to identify the response to ARV treatment if there is no easy or affordable access to viral load or CD4 testing.

TABLE 6.2.D.3 WHO paediatric clinical staging system for use in children under 13 years with confirmed laboratory evidence of HIV infection (HIV antibody where age is > 18 months, DNA or RNA virological testing where age is < 18 months)

Stage 1	• Asymptomatic • Persistent generalised lymphadenopathy (PGL)
Stage 2	• Unexplained persistent hepatosplenomegaly • Papular pruritic eruptions • Fungal nail infections • Lineal gingival erythema (LGE) • Extensive wart virus infection • Extensive molluscum infection (> 5% of body area) • Recurrent oral ulcerations (two or more episodes in 6 months) • Parotid enlargement • Herpes zoster • Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, two or more episodes in any 6-month period)
Stage 3	• Unexplained moderate malnutrition not responding to standard therapy • Unexplained persistent diarrhoea (for > 14 days) • Unexplained persistent fever (intermittent or constant, for > 1 month) • Oral candidiasis (outside the neonatal period) • Oral hairy leukoplakia • Pulmonary tuberculosis[1] • Severe recurrent presumed bacterial pneumonia (two or more episodes in 6 months) • Acute necrotising ulcerative gingivitis or periodontitis • Lymphoid interstitial pneumonia (LIP) • Unexplained anaemia (< 8 grams/dL), neutropenia (< 500/mm^3) or thrombocytopenia (< 30 000/mm^3) for > 1 month

(*continued*)

Stage 4	• Unexplained severe wasting or severe malnutrition not responding to standard therapy • Pneumocystis pneumonia • Recurrent severe presumed bacterial infections (two or more episodes within 1 year, e.g. empyema, pyomyositis, bone or joint infection, or meningitis, but excluding pneumonia) • Chronic orolabial or cutaneous herpes simplex infection (for > 1 month) • Disseminated or extrapulmonary tuberculosis • Kaposi's sarcoma • Oesophageal candidiasis • Symptomatic HIV seropositive infant < 18 months of age with two or more of the following: oral thrush, with or without severe pneumonia, with or without failure to thrive, with or without severe sepsis[2] • CMV retinitis • CNS toxoplasmosis • Any disseminated endemic mycosis, including cryptococcal meningitis (e.g. extrapulmonary cryptococcosis, histoplasmosis, coccidiomycosis, penicilliosis) • Cryptosporidiosis or isosporiasis (with diarrhoea for > 1 month) • Cytomegalovirus infection (onset at age > 1 month in an organ other than liver, spleen or lymph nodes) • Disseminated mycobacterial disease other than tuberculous • Candida of trachea, bronchi or lungs • Acquired HIV-related recto-vesical fistula • Cerebral or B-cell non-Hodgkin's lymphoma • Progressive multifocal leukoencephalopathy (PML) • HIV encephalopathy • HIV-related cardiomyopathy • HIV-related nephropathy

[1] TB may occur at any CD4 count, and CD4% should be considered where available.

[2] Presumptive diagnosis of stage 4 disease in seropositive children under 18 months of age requires confirmation with HIV virological tests, or with HIV antibody test if over 18 months of age.

Antiretroviral therapy (ART)

Antiretroviral (ARV) drugs are becoming more widely available, and have revolutionised the care of children with HIV/AIDS. ARV drugs are not a cure for HIV, but they have dramatically reduced mortality and morbidity, and improved the quality and length of life. The WHO recommends that in resource-limited settings, HIV-infected adults and children should start ARV therapy based upon clinical or immunological criteria, and using simplified standardised treatment guidelines.

Resistance to single or dual agents is quick to emerge, so **single-drug regimens are contraindicated**. Indeed **at least three drugs are the recommended minimum standard for all settings**. Although new ARV drugs are coming on to the market, frequently these are not available for use in children, due to lack of suitable formulations or dosage data, or their high costs.

As children with HIV are often part of a household that includes an adult with HIV, ideally access to treatment and ARV drugs needs to be ensured for other family members, and where possible similar drug regimens should be used. Fixed-dose combinations are increasingly available, and are preferred as they promote and support treatment adherence, as well as reducing the cost of treatment. Existing tablets often cannot be divided into lower dosages for children (under 10 kg), so syrups or solutions and suspensions are needed.

The underlying principles of ART and the choice of first-line ART in children are largely the same as for adults. However, it is also important to consider the following:

- availability of a suitable formulation that can be taken in appropriate doses
- simplicity of the dosage schedule
- taste/palatability and thus compliance in young children
- the ART regimen that the parent(s) or carers are or will be taking.

Suitable formulations for children are not available for some ARVs (particularly the protease inhibitor class of drugs).

Antiretroviral drugs

Antiretroviral drugs fall into three main classes, namely nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) (*see* Table 6.2.D.4).

Triple therapy is the standard of care.

The WHO currently recommends that first-line regimens should be based upon two nucleoside analogue reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside drug (NNRTI). The use of triple NRTI as first-line therapy is currently considered a secondary alternative because of recent research findings in adults. Protease inhibitors are usually recommended as part of second-line regimens in most resource-limited settings.

Efavirenz (EFV) is the NNRTI of choice in children who are on rifampicin, if treatment needs to start before antituberculous therapy is completed.

For drug dosages and regimens, *see* Appendix 4.

Calculation of drug dosages

Drug doses are given per kg for some drugs and per m^2 surface area of the child for others. A table giving the equivalent weights of various surface area values is provided in Section 9 of this textbook, to aid dosage calculation. In general, children metabolise PI and NNRTI drugs faster than adults, and require higher than adult equivalent doses to achieve appropriate drug levels. Drug doses have to be increased as the child grows, otherwise there is a risk of under-dosage and development of resistance.

Formulations

Liquid formulations may not be readily available, are more expensive, and may have a reduced shelf-life. As the child gets older, the amount of syrup that needs to be taken becomes quite considerable. Therefore, in patients over 10 kg in weight, it is preferable to give parts of scored tablets or combination preparations (*see* Appendix 4).

TABLE 6.2.D.4 Classes of antiretroviral drugs recommended for use in children in resource-limited settings

Nucleoside analogue reverse transcriptase inhibitors (NRTIs)		
Zidovudine	ZDV/AZT	180–240 mg/m^2 twice daily
Lamivudine	3TC	4 mg/kg twice daily up to a maximum of 150 mg twice daily
Stavudine	d4T	1 mg/kg twice daily up to 30 mg twice daily
Didanosine	ddI	90–120 mg/m^2/dose twice daily
Abacavir	ABC	8 mg/kg/dose given twice daily up to 300 mg twice daily
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Nevirapine	NVP	160–200 mg/m^2 up to a maximum of 200 mg twice daily
Efavirenz	EFV	15 mg/kg/day up to 600 mg once daily
Etravirine	ETV	200 mg twice daily for adolescents
Protease inhibitors (PIs)		
Lopinavir/ ritonavir	LPV/r	230–350 mg/m^2 twice daily
Darunavir	DRV	10–20 mg/kg twice daily
Atazanavir	ATV	7 mg/kg once daily
Ritonavir	RTV	Given as a 'booster' with another PI
Integrase inhibitors		
Raltegravir	RAL	400 mg twice daily for adolescents

First-line ART for children under 3 years of age

An LPV/r-based regimen should be used as first-line ART for all children infected with HIV who are under 3 years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with an NVP-based regimen.

Where viral load monitoring is available, consideration can be given to substituting LPV/r with an NNRTI after virological suppression is sustained.

For infants and children under 3 years of age who are infected with HIV, ABC + 3TC + AZT is recommended as an option for children who develop TB while on an ART regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted.

For infants and children under 3 years of age who are infected with HIV, the NRTI backbone for an ART regimen should be ABC + 3TC or AZT + 3TC (this is a strong recommendation but with low-quality evidence).

First-line ART for children aged 3 years or older (including adolescents)

For children aged 3 years or older (including adolescents) who are infected with HIV, EFV is the preferred NNRTI for first-line treatment, and NVP is the alternative.

For children aged 3–9 years (and adolescents weighing less than 35 kg) who are infected with HIV, the NRTI backbone for an ART regimen should be one of the following, in order of preference:

- ABC + 3TC
- AZT or TDF + 3TC (or FTC).

For adolescents who are infected with HIV (10–19 years old, weighing 35 kg or more), the NRTI backbone for an ART regimen should align with that of adults and be one of the following, in order of preference:

- TDF + 3TC (or FTC)
- AZT + 3TC
- ABC + 3TC.

When to start ART

About 20% of HIV-infected infants in developing countries progress to AIDS or death by 12 months of age (with a substantial contribution from PCP infections in infants under 6 months of age who are not receiving co-trimoxazole treatment).

ART should be initiated in all children infected with HIV below 5 years of age, regardless of WHO clinical stage or CD4 count, that is:

- Infants diagnosed in the first year of life.
- Children infected with HIV when aged 1–4 years.

ART should be initiated in all children infected with HIV aged 5 years or older with a CD4 cell count of less than 500 cells/mm^3, regardless of WHO clinical stage, that is:

- CD4 count less than 350 cells/mm^3.
- CD4 count between 350 and 500 cells/mm^3.

ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 count.

ART should be initiated in any child younger than 18 months who has been given a presumptive clinical diagnosis of HIV infection.

Infants and children with specific conditions

- For children or adolescents with severe anaemia (< 7.5 g/dL) or severe neutropenia (< 0.5/mm^3), avoid AZT.
- For adolescents over 12 years of age with hepatitis B, the preferred regimen is tenofovir (TDF) + emtricitabine (FTC) or 3TC + NNRTI.

Side effects of antiretroviral therapy and monitoring

The response to antiretroviral treatment and the side effects of treatment both need to be monitored. Where CD4 cell count or viral load monitoring is available, this should be done every 3 to 6 months and can provide information on the success or failure of the response to treatment, and therefore guide changes to treatment. Where this is not possible, clinical parameters, including clinical staging events, need to be used (*see* Table 6.1.D.3).

Monitoring the response after ARV initiation

- After ARV initiation or a change in ARVs see the child at 2 and 4 weeks after the start or change.
- All children should be seen if there are any problems that concern the caregiver, or inter-current illness.

Long-term follow-up

- A clinician should see the child at least every 3 months.
- A non-clinician (ideally the provider of ARV medication, such as a pharmacist, who would assess adherence and provide adherence counselling) should see the child monthly.
- The child should be seen more frequently, preferably by a clinician, if clinically unstable.

Monitoring the response (see Appendix 1)

At entry into care and at initiation of ART, and then at regular intervals and as required by symptoms, monitor the following:

- weight and height (monthly)
- neurodevelopment (monthly)
- adherence (monthly)
- CD4 (%) if available (then every 3 to 6 months)
- viral load if available (every 3 to 6 months)
- baseline haemoglobin or haematocrit (if on ZDV/AZT), full chemistry (renal function, liver enzymes, especially ALT for liver toxicity) and lipids (if available)
- symptom-related determination: haemoglobin or haematocrit or full blood count, ALT.

General long-term side effects of antiretroviral therapy include lipodystrophy. The specific side effects of individual antiretroviral drugs are summarised in Appendix 5.

When to change treatment

Drugs need to be substituted for others when there is:

- treatment-limiting toxicity, such as:
  - Stevens–Johnson syndrome (SJS)
  - severe liver toxicity
  - severe haematological findings
- drug interaction (e.g. tuberculosis treatment with rifampicin interfering with NVP or PI)
- potential lack of adherence by the patient if they cannot tolerate the regimen.

TABLE 6.2.D.8 Clinical and CD4 definition of ARV treatment failure in children (after 6 months or more of ARV)

Clinical criteria	CD4 criteria
Lack of or decline in growth among children with an initial growth response to ARV	Return of CD4% if aged < 6 years (% or count if aged ≥ 6 years) to pre-therapy baseline or below, without other cause
Loss of neurodevelopmental milestones or onset of encephalopathy	≥ 50% fall from peak CD4% if aged < 6 years (% or count if aged ≥ 6 years), without other aetiology
New or recurrent WHO clinical Stage 4 conditions	

First-line regimen treatment failure; when to switch regimens

1 A switch to a second-line regimen is recommended when:
   - clinical failure is recognised **and/or**
   - immunological failure is recognised **and/or**
   - virological failure is recognised.
2 Clinical failure is defined as the appearance or reappearance of WHO clinical stage 3 or stage 4 events after at least 24 weeks on ART in a treatment-adherent child. It is important to exclude TB as a cause of clinical failure, especially when there is poor growth.
3 Immunological failure is defined as developing or returning to the following age-related immunological thresholds after at least 24 weeks on ART, in a treatment-adherent child:
   - CD4 count of < 200 cells/mm^3 or CD4+% < 10% for a child between 2 and 4 years of age
   - CD4 count of < 100 cells/mm^3 for a child aged 5 years or older.
4 Virological failure is defined as a persistent viral load above 5000 RNA copies/mL, after at least 24 weeks on ART, in a treatment-adherent child.

Principles

Virological failure is due to resistance mutations acquired either at the time of infection or as a result of poor adherence. Even a resistance test before starting treatment (not widely available) will not always show archived mutations (not in the majority of the virus tested). Acquired resistance is more likely if there is initial improvement (ideally documented virologically). A history of missed doses is usually not given readily, but it is essential that support to ensure 100% adherence is put in place before second-line treatment is started.

In the absence of routine CD4 or viral load assays, judgements should be made about treatment failure based on:

- clinical progression
- CD4 decline as defined in Table 6.2.D.8.

Generally, patients should have received 6 months or more of ARV therapy, and adherence problems must be ruled out where possible before considering treatment failure and switching ARV regimens.

If an apparent deterioration is due to the immune reconstitution inflammatory syndrome (IRIS), this is not a reason for switching therapy. IRIS usually starts within weeks or the first few months after starting ART in children who have very low CD4 counts (< 15%). The most common initiator is TB which has been latent, but the symptoms of other opportunistic infections can develop as the immune recovery enables a response. Treatment is of the infection, and ART should be continued.

Immune reconstitution inflammatory syndrome (IRIS)

It is important to differentiate IRIS clinically from treatment failure, because the symptoms may be similar. IRIS can be confused with several other clinical events that are also observed in children with advanced HIV disease, such as opportunistic infections, ARV-related toxicity, or HIV disease clinical progression.

What is IRIS?

IRIS is an exaggerated immune response to antigens or organisms. The related organisms could be mycobacteria (e.g. *Mycobacterium tuberculosis*, non-tuberculosis mycobacteria), viruses (e.g. herpes zoster, herpes simplex) or fungi (e.g. *Cryptococcus neoformans*).

Who is at risk of developing IRIS?

It usually occurs in a child with low baseline CD4 or WHO clinical stage 3 or 4 before initiation of ART. The incidence rate of IRIS could be as high as 15–25%.

When does IRIS develop?

It usually occurs during the first 6 months after initiation of ART, although it commonly manifests during the first month. During the initial period of ART, antiretroviral drugs cause a rapid decline in HIV viral load and a rapid rise in CD4, so a brisk immune response to antigen is developed.

What are the common manifestations of IRIS?

There are two types of IRIS:

- **'Worsening type':** clinical worsening of a previously treated opportunistic infection. For example:
  - worsening of respiratory symptoms and/or chest X-ray finding in a child with previously treated pulmonary tuberculosis
  - severe headache in a child with previously treated cryptococcal meningitis.
- **'Unmasking type':** unmasking of a previously subclinical infection with exaggerated inflammatory response. For example:
  - suppurative lymphadenitis from *Mycobacterium* infection
  - development of an abscess at the BCG vaccination site.

How should IRIS be managed?

- ARVs should be continued.
- For the 'unmasking type', the appropriate anti-infective agents are needed.
- In most cases, the symptoms of IRIS resolve after a few weeks. However, some reactions can be severe or life-threatening, requiring a short course of steroid treatment (e.g. IRIS from pulmonary tuberculosis with acute respiratory distress syndrome (ARDS), IRIS from *M. avium* complex infection with high-grade fever and severe abdominal pain, IRIS from cryptococcal meningitis with a severe increase in intracranial pressure).

Second-line treatment regimens in the event of treatment failure

After failure of a first-line NNRTI-based regimen, a boosted PI plus two NRTIs are recommended for second-line ART. LPV/r is the preferred boosted PI.

After failure of a first-line LPV/r-based regimen, children younger than 3 years should remain on their first-line regimen, and measures to improve adherence should be undertaken.

After failure of a first-line LPV/r-based regimen, children aged 3 years or older should be switched to a second-line regimen containing an NNRTI plus two NRTIs. EFV is the preferred NNRTI.

After failure of a first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is AZT + 3TC.

After failure of a first-line regimen containing AZT or d4T + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC).

Third-line ART

Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors and second-generation NNRTIs and PIs.

Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen.

Strategies that balance the benefits and risks for children need to be explored when second-line treatment fails.

- For older children and adolescents who have more therapeutic options available to them, constructing third-line ARV regimens with novel drugs used to treat adults, such as ETV, DRV and RAL, may be possible.
- Children on a second-line regimen that is failing with no new ARV drug options should continue with a tolerated regimen. If ART is stopped, opportunistic infections still need to be prevented, symptoms relieved and pain managed.

Nutritional care and failure to thrive (*see* Appendix 3)

Nutrition is a long-term concern in all HIV-infected children. Stunting frequently develops within the first 12 months, although most children maintain normal weight-for-height ratios. Close monitoring of growth, and early protein/calorie, vitamin A and other micronutrient supplementation need to be evaluated.

- Regular vitamin A as per WHO guidelines.
- Supplementary feeding if possible (aim for 150 kcal/kg/day).
- Exclude or treat *Candida*.
- Exclude or treat enteric infection.
- Consider zinc deficiency (*see* Section 5.10.A).
- Consider fever.
- Consider depression.
- Consider pain.

Clinical management

1 HIV-infected children should be assessed routinely for nutritional status, including weight and height, at scheduled visits, particularly after the initiation of ART.
2 HIV-infected children on or off ART who are symptomatic, who have conditions requiring increased energy (e.g. TB, chronic lung disease, chronic oral infections, malignancies) or who have weight loss or evidence of poor growth, should be provided with 25–30% additional energy.
3 HIV-infected children who are severely malnourished should be managed as per the guidelines for uninfected children and provided with 50–100% additional energy.
4 HIV-infected children should receive one recommended daily allowance of micronutrients daily. If this cannot be ensured through the diet, or there is evidence of deficiency, supplementation should be given.
5 HIV-infected infants and children should receive high-dose vitamin A supplementation every 6 months between 6 and 59 months of age, as per the guidelines for uninfected children (*see* Section 5.10.A).
6 HIV-infected children who have diarrhoea should receive zinc supplementation as part of management, as per the guidelines for uninfected children.

7 For infants and young children who are known to be HIV infected, mothers are strongly encouraged to exclusively breastfeed for 6 months and to continue breastfeeding as per recommendations for the general population (i.e. up to 2 years of age and beyond).

Respiratory disorders in children with HIV infection

Symptoms include cough, shortness of breath, fever, sweats and cyanosis.

The aetiology of acute respiratory infections is similar to that of community-acquired infections in immunocompetent children (*Mycobacterium tuberculosis*, *Pneumococcus*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Mycoplasma pneumonia*) (*see* Section 5.3.A and Section 6.1.N). However, children with HIV may require more prolonged courses of treatment.

Studies on the aetiology of pneumonia among HIV-infected children in resource-limited countries have identified *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* and *Klebsiella* species as the major bacterial pathogens in HIV-infected children. HIV-negative children are affected by the same pathogens, although at lower rates. The post-mortem studies showed similar results, except that *H. influenzae* was slightly less prominent. *M. tuberculosis* was prevalent regardless of HIV status, reflecting its significance in resource-limited countries. From the limited data available, **RSV** and **parainfluenza** appear to be the most prevalent viral causes of pneumonia.

In cases of failed treatment, consider using a second-line antibiotic.

Treatment of recurrent infections is the same, regardless of the number of recurrences.

Specific HIV-related causes of infection and illness

Pneumocystis jiroveci (formerly carinii) pneumonia (PCP)

- PCP should be suspected and anti-pneumocystis therapy considered in any HIV-positive infant with severe pneumonia.
- Severe generalised pneumonia usually includes ventilation/perfusion mismatch and severe hypoxaemia.
- High fever is uncommon compared with bacterial pneumonia.

PCP is most likely to develop in a child whose HIV infection occurred in the previous 12 months (the peak time is 4–6 months), or over 12 months if they have a low CD4 count and are not on co-trimoxazole prophylaxis. There is an absent or low-grade fever, non-productive cough and difficulty breathing. Signs include severe respiratory distress (tachypnoea, chest indrawing), which is disproportionate to findings on auscultation (usually normal breath sounds or only a few crackles). If an oxygen saturation monitor is available, check at rest and, if normal, again after exercise. The latter may show hypoxia or, if there is a severe infection, cyanosis.

There may be a history of a poor response to 48 hours of first-line antibiotics, and elevated levels of lactate dehydrogenase.

PCP is often the first clinical indicator of HIV infection, and is a WHO clinical stage 4 criterion.

Clinical and radiological signs are not diagnostic. However, a clear chest or diffuse chest signs on auscultation are typical with PCP infection, as is the presence of diffuse infiltrates and areas of hyperinflation rather than focal signs on a chest X ray.

Induced sputum and nasopharyngeal aspiration are useful for obtaining sputum for examination. Nasopharyngeal aspirate has a low sensitivity with conventional staining techniques, and requires **PCR**. Induced sputum techniques greatly increase the diagnostic yield. Beware the risk of infection being transmitted to operators, especially of multiple drug-resistant tuberculosis, for example. **Bronchoalveolar lavage** may provide a diagnosis if adequate resources are available.

Treatment of PCP

Severe disease (severe respiratory distress, severe hypoxia): treat with co-trimoxazole 60–90 mg/kg IV 12-hourly for a minimum of 7 days, followed by oral drugs in the same doses for another 2 weeks (IV if there is severe nausea). In addition, give high-dose dexamethasone for the first 5 days (150 micrograms/kg/dose 6-hourly for 4 days) or prednisolone 0.5 mg/kg 12-hourly for 5 days, then 0.25 mg/kg 12-hourly for 5 days, then 0.25 mg/kg daily for 5 days. The response usually occurs after more than 5–7 days of appropriate high-dose therapy.

Less severe disease: treat with oral co-trimoxazole 30 mg/kg 6-hourly for 21 days (trimethoprim (TMP) 5 mg/kg; sulfamethoxazole (SMX) 25 mg/kg).

If the child has a severe drug reaction, change to pentamidine (4 mg/kg once a day by IV infusion) for 3 weeks, or trimethoprim 5 mg/kg/dose orally 6-hourly and dapsone 100 mg/kg once a day for 21 days.

Continue co-trimoxazole prophylaxis (see below) on recovery, and ensure that ART is being given.

Co-trimoxazole prophylaxis

Co-trimoxazole prophylaxis has been shown to be very effective in HIV-infected infants and children in reducing mortality and the likelihood of PCP as a cause of severe pneumonia. PCP is now unusual in countries where prophylaxis is routine.

Co-trimoxazole also protects against common bacterial infections, toxoplasmosis and malaria.

Who should be given co-trimoxazole?

- All HIV-exposed children (children born to HIV-infected mothers) from 4–6 weeks of age, whether or not they are part of a prevention of mother-to-child transmission (PMTCT) programme.
- Any child under 5 years old identified as HIV-infected, regardless of CD4 count.
- Any child over 5 years old with a CD4 count of less than 25%.
- Any child with a history of PCP.

See Appendix 2 for management.

For how long should co-trimoxazole be given?

- HIV-exposed children: for the first year, or until HIV infection has been definitively ruled out and the mother is no longer breastfeeding.

- HIV-infected children:
  - Indefinitely where ARV treatment is not yet available.
  - Where ARV treatment is being given, co-trimoxazole may only be stopped once clinical or immunological indicators confirm restoration of the immune system for 6 months or more (also see below). On the basis of current evidence it is not yet clear whether co-trimoxazole continues to provide protection after immune restoration is achieved.
  - If there is a history of PCP pneumonia, continue indefinitely.

Under what circumstances should co-trimoxazole be discontinued?

- If severe cutaneous reactions such as Stevens–Johnson syndrome occur with co-trimoxazole or other sulpha drugs, or if there is renal and/or hepatic insufficiency or severe haematological toxicity (severe anaemia or pancytopenia). It is contraindicated in children with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- **In an HIV-exposed child**, only after HIV infection has confidently been excluded:
  - For a non-breastfeeding child under 18 months of age, this is by negative DNA or RNA virological HIV testing.
  - For a breastfed HIV-exposed child under 18 months of age, negative virological testing is only reliable if performed 6 weeks after cessation of breastfeeding.
  - For a breastfed HIV-exposed child over 18 months of age, negative HIV antibody testing 6 weeks after stopping breastfeeding.
- **In an HIV-infected child:**
  - If the child is on ARV therapy, co-trimoxazole can be stopped only when evidence of immune restoration has been obtained. Continuing co-trimoxazole may continue to provide benefit even after the child has clinically improved.
  - If ARV therapy is not available, co-trimoxazole should not be discontinued.

What doses of co-trimoxazole should be used?

- Recommended dosages of 6–8 mg/kg TMP once daily should be used.
  - For children under 6 months of age, give 2.5 mL of suspension (40/200 mg in 5 mL) or 1 paediatric tablet (or ¼ adult tablet, 20 mg TMP/100 mg SMX: tablets can be crushed).
  - For children aged 6 months to 5 years, give 5 mL of suspension or 2 paediatric tablets (or ½ adult tablet).
  - For children aged 6–14 years, give 10 mL of suspension or 1 adult tablet.
  - For children over 14 years, give 2 adult tablets.
- Use weight-band dosages rather than body-surface-area doses.
- If the child is allergic to co-trimoxazole, dapsone is the best alternative. Give dapsone after 4 weeks of age in an oral dose of 2 mg/kg/24 hours once daily.
- If the patient is G6PD-positive, consider giving pentamidine or atovaquone.

What follow-up is required?

Co-trimoxazole prophylaxis should be a routine part of the care of HIV-infected children, and must be assessed for tolerance and adherence at all regular clinic visits or follow-up visits by healthcare workers and/or other members of the multidisciplinary care team. It is suggested that initial clinic follow-up in children takes place monthly, and then every 3 months if co-trimoxazole is well tolerated.

Lymphocytic interstitial pneumonitis (LIP)

LIP is a non-infectious pulmonary disorder caused by white cell infiltration into alveolae. It is most common in children over 2 years old, and is a clinical stage criterion which is an indication for starting ART.

LIP is common in children (it occurs in at least 40% of children with perinatal HIV), but rare in adults (it occurs in about 3% of adults with HIV). Various studies in Africa have documented a 30–40% prevalence of LIP in HIV-infected children, and up to 60% prevalence in those with chronic lung disease. LIP is often mistaken for pulmonary TB (miliary) because of the chronic cough and the miliary-like pattern on chest X-ray.

Pathogenesis: Possible explanations for LIP include a co-infection of the lungs by HIV and Epstein–Barr virus (EBV), leading to immune stimulation with lymphoid infiltration and chronic inflammation.

The child is often asymptomatic in the early stages, but may later have a mild persistent cough, with or without difficulty in breathing, bilateral parotid swelling, persistent generalised lymphadenopathy, poor growth, hepatomegaly and other signs of heart failure (tender hepatomegaly, bilateral pitting pedal oedema, loud second heart sound and finger clubbing). Chest auscultation may be normal, or there may be widespread crackles. It may produce severe ventilatory perfusion mismatch with hypoxaemia, but may be asymptomatic.

There is an increased risk of lower respiratory tract infection, including bronchiectasis. It is also associated with parotid, adenoid and tonsillar enlargement (and may produce sleep-related upper airway obstruction; *see* Section 5.1.D).

LIP may be mistaken for miliary TB, but the child is systematically too well.

Suspect LIP if the chest X-ray shows a bilateral reticulonodular interstitial pattern that is prominent in the lower lobes, nodules less than 5 mm in diameter, a single patchy alveolar opacity, hyperinflation or isolated bullae. It must be distinguished from pulmonary tuberculosis and bilateral

FIGURE 6.2.D.4 Chest X ray showing lymphocytic interstitial pneumonia (LIP): typical is hilar lymphadenopathy and lacelike infiltrates.

hilar adenopathy (*see* Figure 6.2.D.4). Chest X-ray diffuse infiltrations and hilar lymphadenopathy persisting for more than 2 months despite antibiotic treatment are also a clue.

X-ray appearances are often more severe than the clinical features.

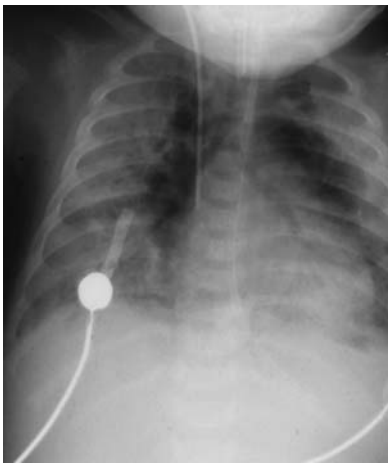

FIGURE 6.2.D.5 Pneumocystis jiroveci pneumonia (PCP): typical is a ground glass appearance.

Treatment of LIP

- Give oxygen therapy during episodes of hypoxia.
- Give a trial of antibiotic treatment for bacterial pneumonia before starting treatment with prednisolone.
- Start treatment with steroids only if there are chest X-ray findings suggesting lymphocytic interstitial pneumonitis, plus any of the following signs:
  - fast or difficult breathing
  - cyanosis
  - pulse oximetry reading of oxygen saturation < 90% (normal value is > 93%).
- Bronchodilators (e.g. salbutamol) are of benefit where wheezing is a problem. For moderate symptoms give oral prednisone, 1–2 mg/kg daily for 3 days, and for more severe symptoms for up to 4 weeks. Then slowly decrease the dose over 2–4 weeks depending on the treatment response. If there is no response by 4 months, slowly taper the dose to stop over a further 2 months.
- Only start steroid treatment if it is possible to complete the full treatment course (which may take several months depending on the resolution of signs of hypoxia), as partial treatment is not effective and could be harmful. Beware of reactivation of TB.

Tuberculosis (*see also* Section 6.1.N)

In a child with suspected or proven HIV infection, it is important always to consider the co-diagnosis of tuberculosis, a diagnosis which is often difficult. Early in HIV infection, when immunity is not impaired, the signs of tuberculosis are similar to those in a child without HIV infection. Pulmonary tuberculosis is still the commonest form of tuberculosis, even in HIV-infected children. As HIV infection progresses and immunity declines, dissemination of tuberculosis becomes more common. Tuberculous meningitis, miliary tuberculosis and widespread tuberculous lymphadenopathy occur.

All children with HIV should be screened for TB.

Avoid, if practicable, children with HIV being in contact with a TB-infected person.

Isoniazid preventive therapy (IPT)

1 All HIV-infected infants and children who are exposed to TB through household contacts, but show no evidence of active disease, should begin isoniazid preventive therapy (IPT).
2 Children who have either poor weight gain, fever, cough or a contact with TB should be evaluated for active TB. If TB is excluded, give IPT.
3 Children living with HIV (over 12 months of age, and including those previously treated for TB), who are not likely to have active TB, and who are not known to be exposed to TB, should receive 6 months of IPT as part of a comprehensive package of HIV care.
4 Infants living with HIV, who have been exposed to TB but are evaluated as not having active TB, should receive IPT as part of a comprehensive package of HIV care.
5 The recommended dose of isoniazid (INH) for preventive therapy in HIV co-infection is 10 mg/kg daily for 6 months (maximum 300 mg/day).
6 See the child monthly and give a 1-month supply of isoniazid at each visit.

Investigations

A tuberculin skin test (TST, Mantoux) is unreliable in HIV and should not be used. Since a definitive diagnosis of TB in children is difficult, there could be clinical features that are very suggestive of TB, leading to a high index of suspicion. In such cases a negative TST should not prevent you from starting anti-TB treatment. Furthermore, several people develop TB infection when they come into contact with the TB pathogens, but they do not go on to develop signs and symptoms of TB disease, because their immune systems control the infection. When the immune systems break down, such individuals develop signs and symptoms suggestive of TB disease. A TST can be positive in either state, and without signs and symptoms would be suggestive of TB infection and not TB disease.

Chest X-ray: this may be normal, or it may show non-specific infiltrates, hilar or paratracheal lymphadenopathy, persistent opacities after an antibiotic trial, or a miliary pattern.

Microscopy (alcohol and acid-fast bacilli, AAFB), Ziehl–Neelsen (ZN) stain) **and culture:** this is the most important investigation. Sputum which may need to be induced by saline nebuliser (in an isolation room with staff wearing a fine-particle (FP3) mask), and gastric aspirate (if the child is coughing, take this in the early morning before they have had anything to eat or drink). Collect at least three specimens.

Treatment of infants and children diagnosed with TB and HIV

Treat TB in HIV-infected children with the same anti-TB drug regimen as for non-HIV-infected children with TB.

Thiacetazone is associated with a high risk of severe, and sometimes fatal, skin reactions in HIV-infected children, and must not be given. These reactions can start with itching, but progress to severe reactions.

Recommended ART regimens for children who need TB treatment

Recommended regimens for children and adolescents initiating ART while on TB treatment

Younger than 3 years

Two NRTIs + NVP, ensuring that the dose is 200 mg/m^2
or
Triple NRTI (AZT + 3TC + ABC).

3 years or older
Two NRTIs + EFV
or
Triple NRTI (AZT + 3TC + ABC).

Recommended regimens for children and infants initiating TB treatment while receiving ART
Child on standard NNRTI-based regimen (two NRTIs + EFV or NVP)

Younger than 3 years
Continue NVP, ensuring that the dose is 200 mg/m^2
or
Triple NRTI (AZT + 3TC + ABC).

3 years or older
If the child is receiving EFV, continue the same regimen.
If the child is receiving NVP, substitute with EFV
or
Triple NRTI (AZT + 3TC + ABC).

- TB should be treated with standard regimes, the emphasis being on achieving high adherence rates. The development of multi-drug-resistant TB is a very real threat if compliance is poor. Directly observed therapy (DOT) may be the best approach.
- Any child with active TB disease and HIV infection should begin TB treatment immediately, and start ART as soon as tolerated in the first 8 weeks of TB therapy, irrespective of CD4 count and clinical stage.
- For all HIV-infected children, anti-TB therapy should be started immediately upon the diagnosis of TB, and ART should continue.

Bronchiectasis

Suspect bronchiectasis if there is a persistent cough productive of copious sputum (in vomit in young children) or haemoptysis associated with fever, anorexia and failure to thrive. There may be clubbing and localised coarse crackles on auscultation. Obtain a chest X-ray and sputum for Gram stain and culture as well as AAFB; differential diagnoses include TB and LIP. Treatment consists of physiotherapy with postural drainage, bronchodilators and antibiotics. Intravenous amoxicillin (50 mg/kg 6-hourly) and gentamicin (7.5 mg/kg daily) may be required for 2 weeks.

Cytomegalovirus (CMV)

CMV can present with pneumonia with fever, dry cough, respiratory distress and hypoxia. CMV also causes oesophagitis and gastroenteritis presenting with nausea, difficulty swallowing, diarrhoea and vomiting. CMV retinitis is often asymptomatic or may cause blurred vision, strabismus and ultimately blindness. The fundi show white perivascular infiltrates and haemorrhages, reduced acuity and field defects.

A chest X-ray may show diffuse interstitial infiltrates. Oesophageal endoscopy may show linear, localised or punctate ulcers. Biopsies show typical inclusion cells.

Treatment is with ganciclovir 6 mg/kg 12-hourly for 14 days.

Other lung infections

Other opportunistic lung infections that may occur include *Pseudomonas aeruginosa*, *Chlamydia*, *Mycoplasma*, *Cryptococcus neoformans*, *Aspergillus*, cytomegalovirus, *Histoplasma*, *Coccidioides*, *Legionella* and *Nocardia.*

Gastrointestinal disorders

Oral and oesophageal problems

Oral candidiasis

This is the most common form of fungal infection and the most common orofacial manifestation encountered in HIV-infected children. It progresses to involve the oesophagus in 20% of cases, and denotes significantly impaired T-cell function.

It presents as white plaques on mucosa that are difficult to remove, loss of taste, pain on swallowing, reluctance to eat, increased salivation and crying during feeds.

Treatment for oral candida

- Nystatin 100 000 IU/mL oral suspension, 1–2 mL four to six times a day for 7 days **or**
- Local gentian violet 0.5% aqueous solution twice daily for 7 days (dissolve one teaspoonful (5 mL) of crystals in 1 litre of water, filter off the residue, and use within 7 days) **or**
- Clotrimazole 1%, miconazole 2% gel, or amphotericin B suspension/lozenges three times daily **or**
- Fluconazole 3–6 mg/kg on the first day, then 3 mg/kg (maximum 100 mg) daily for 1–2 weeks. If there is rare resistance to fluconazole, give ketoconazole oral tablets, 3.3–6.6 mg daily.

Oesophageal candidiasis

Oesophageal candidiasis is a stage 4 clinical feature indicating profound immune impairment (advanced HIV disease). The only clinical symptom may be reluctance to feed. It presents as difficulty or pain while vomiting or swallowing, reluctance to take food, excessive salivation, or crying during feeding. The condition may occur with or without evidence of oral candida. If oral candida is not found, give a trial of treatment with fluconazole (3–6 mg/kg once a day). Exclude other causes of painful swallowing (e.g. cytomegalovirus, herpes simplex, lymphoma and, rarely, Kaposi's sarcoma), if necessary by referral to a larger hospital where appropriate testing is possible.

Treatment for oesophageal candidiasis

- Give oral fluconazole, 3–6 mg/kg once a day for 7 days, except if the child has active liver disease.
- Give amphotericin B, 0.5–1 mg/kg/dose once a day) by IV infusion for 10–14 days to children with liver disease and in cases where there is a lack of response to oral therapy, inability to tolerate oral medications, or the risk of disseminated candidiasis (e.g. in a child with leukopenia).

Viral oesophagitis

Herpes simplex virus (HSV)

Herpes simplex virus (HSV) infection may either be primary (herpetic gingivostomatitis) or secondary (herpes labialis). The prevalence of oral HSV infection ranges from 10% to 35% in adults and children with HIV infection. The presence

of HSV infection for more than 1 month constitutes an AIDS-defining condition.

Clinical appearance

HSV infection appears as a crop of vesicles, usually localised on the keratinised mucosa (hard palate, gingiva) and/or the vermillion borders of the lips and perioral skin. The vesicles rupture and form irregular painful ulcers. They may interfere with mastication and swallowing, resulting in decreased oral intake and dehydration.

Systemic therapy with antiviral agents is recommended. The treatment is more effective if it is instituted in the prodromal stage of infection. Treat with aciclovir 20–40 mg/kg orally or IV four times daily for 7 days (maximum single dose is 800 mg).

Cytomegalovirus (CMV) infection: treat with ganciclovir IV 5 mg/kg every 12 hours for 14–21 days.

Reflux oesophagitis may also be present. Treat with antacids and/or an H_2-antagonist, such as ranitidine 2 mg/kg twice daily (*see* Section 5.12.E).

Idiopathic aphthous ulcers: if possible these need to be differentiated from HSV **by viral culture**. Pay attention to oral hygiene. Thalidomide is useful if they are severe.

Severe periodontal and gingival disease (cancrum oris)

Periodontal (gum) disease is common among HIV-infected patients. It is characterised by bleeding gums, bad breath, pain or discomfort, mobile teeth, and sometimes sores. Its reported prevalence ranges widely, from 0% to 50%. If left untreated, HIV-associated periodontal disease may progress to life-threatening infections, such as Ludwig's angina and noma (cancrum oris).

Noma is a gangrenous condition that primarily affects children. It is a multifactorial disease. The most important risk factors are poverty, chronic malnutrition, poor oral hygiene and severe immunosuppression. Although it is considered to be a preventable disease, noma has a case-fatality rate of 70–90% if left untreated.

- Treat with benzylpenicillin 50 mg/kg 4-hourly or amoxicillin 40–60 mg/kg IV 8-hourly. Change to oral antibiotics once the child is able to swallow (usually after 24–48 hours).
- Provide materials for and education on dental hygiene.

Rarely, **malignancy** (Kaposi's sarcoma or non-Hodgkin's lymphoma) or oral hairy leukoplakia (white lacy markings on the sides of the tongue associated with Epstein–Barr virus infection; no treatment required) occur. Visceral Kaposi's sarcoma may present with persistent diarrhoea, intestinal obstruction and abdominal pain.

Persistent diarrhoea (see Section 5.12.B)

Case management should start with management of dehydration with oral rehydration solution. Dysentery (loose stools with blood) should be managed in the same way as for non-HIV-infected children (e.g. for *Shigella* infection). Concur with the local prevalence of treatable infections. Giardiasis, cryptosporidiosis, microsporidiosis, *Shigella*, *Salmonella*, *Campylobacter*, enteropathogenic *E. coli* and *Yersinia* may each contribute to gastrointestinal dysfunction. HIV itself may cause an enteropathy, and in highly immunosuppressed children, atypical mycobacterial infection and protozoa such as *Blastocystis hominis* may cause diarrhoea. Even with sophisticated microbiology, no pathogen may be found, and malabsorption due to lactase deficiency and other brush-border defects should be considered. All antiretroviral drugs (except AZT) can cause diarrhoea, particularly ritonavir.

Chronic or recurrent diarrhoea

Normal endemic pathogens may be responsible, such as rotavirus, *Giardia lamblia*, *Campylobacter jejuni* (*see* Section 5.12.A and Section 5.12.B), salmonellae (typhoid and non-typhoid), *E. coli*, *Shigella*, *Entamoeba histolytica* and *Strongyloides stercoralis.*

Investigations

- Fresh stool microscopy and culture: *Giardia*, *Entamoeba*.
- Ova and cysts: helminths.
- ZN stain: cryptosporidia, cyclospora.
- pH and reducing substances: lactose intolerance.
- CD4 count < 50: CMV, mycobacterium avium intracellulare
- CD4 count < 100: cryptosporidium, microsporidiosis.

Look for signs of vitamin deficiencies:

- Vitamin A: night blindness, dry eyes, Bitot's spots (on conjunctivae).
- Vitamin D: rickets (wide wrist, double malleoli, bow legs, rachitic rosary, Harrison's sulcus).
- Vitamin E: dry rough skin.
- Vitamin K: ecchymosis, purpura.

Opportunistic infections such as those listed below may be responsible:

- Bacterial: atypical mycobacterial infections, such as *Mycobacterium avium* complex (MAC) (see below).
- Protozoa and parasites: cryptosporidia, microsporidia, *Isospora belli*. Treat with azithromycin 10 mg/kg once daily.
- Viral: cytomegalovirus, herpes simplex virus.
- Fungal: histoplasmosis, coccidiomycosis, *Candida*. If severe, treat with fluconazole 3 mg/kg once daily.

Diarrhoea may be secondary to antibiotics, either by direct effects or through *Clostridium difficile*. Stop antibiotics as soon as possible. Give live yoghurt with or without oral vancomycin.

If lactose intolerance is present, give lactose-free feeds.

Treat dysentery with ciprofloxacin 15 mg/kg 12-hourly for 3 days, or ceftriaxone 50 mg/kg once a day for 2–5 days, plus metronidazole 7.5 mg/kg 8-hourly for 7 days.

Nutritional management includes calorie replacement, which may need to be nasogastric, but always encourage eating. Ensure that additional food is not just recommended but actually given. Vitamin A, multivitamins and zinc (10–20 mg once a day for 10–14 days) supplementation may be of benefit (*see* Section 5.10.A).

Prevention: Use hygienic practices during food preparation, always use clean water, avoid bird and animal faeces, avoid swimming in fresh water, and avoid reptiles (salmonellae).

Abdominal pain

This is most frequently related to infections, but occasionally is caused by tumours (non-Hodgkin's lymphoma and Kaposi's sarcoma).

Malabsorption

HIV can be directly associated with an enteropathy. Lactase deficiency and other brush-border defects can also be responsible. Consider trial of a lactose-free diet.

Central nervous system disorders

A myriad of HIV-related CNS diseases have been described. Primary CNS infection by HIV is quite common, as it is a neurotropic virus. Various abnormalities of the central nervous system (CNS) and peripheral nervous system (PNS) are associated with HIV and AIDS. These abnormalities may be attributable to the following causes: HIV infection, complications related to immunosuppression, neurotoxic effects of antiretroviral treatments, and other systemic complications of HIV that affect brain function.

Neurological disorders in people with HIV infection include peripheral neuropathies (nerve disorders that affect the limbs or feet and hands), myelopathy (disorders of the spinal cord), focal cerebral mass lesions (brain tumours such as CNS lymphoma), CNS complications of opportunistic infections, vascular (blood vessel) abnormalities, seizures and encephalopathies. Developmental delays and regression are also important CNS-related problems in HIV-infected children.

The neurological manifestations of HIV infection include the following:

- progressive or static encephalopathy
- seizures
- strokes
- HIV myopathy
- HIV myelopathy
- peripheral neuropathy
- psychiatric manifestations
- sleep problems.

The effect of HIV on the brain ranges from severe effects, found in more than 50% of patients dying of AIDS at post-mortem, to the much more common and milder effects on the developing brain in children, which result in mild learning difficulties. It is particularly important to recognise this so that appropriate support can be given (e.g. reminding the patient to take ART).

TABLE 6.2.D.10 Comparison of features of major CNS mass lesions in HIV

Clinical			*Neuroimaging (if available)*		
Disease	*Timing*	*Fever*	*Number of lesions*	*Type of lesions*	*Location of lesions*
Cerebral toxoplasmosis	Acute onset of symptom	Common	Multiple	Enhancing spherical rings; mass effect	Basal ganglia
Primary CNS lymphoma	Insidious onset of symptom	Usually absent	One or few	Irregular shape, weakly enhancing, mass effect	Periventricular, peri-ependymal, corpus callosum
Tuberculoma	Insidious onset of symptom	Common	One or few	Discrete lesions, significant surrounding oedema, mass effect	Supratentorial in adults, infratentorial in children (at the base of the brain near the cerebellum)
Cryptococcoma cryptococcal meningitis	Acute onset of symptom	Common	Variable	Mass lesions, dilated perivascular spaces, oedema	Basal ganglia

Care of HIV-infected children with CNS involvement requires a thorough evaluation and stepwise therapy according to the underlying aetiology. A multidisciplinary approach is usually needed for appropriate care.

Specific neurological problems

HIV encephalopathy

- Rapid onset or chronic and relapsing forms.
- Hypertonic (spastic) diplegia and expressive language delay.
- Acquired microcephaly with developmental regression (loss of skills).
- White-matter disease predominates. It does not cause seizures, and therefore seizures need to be fully investigated for another pathology.

Encephalitis

Toxoplasma gondii

- Prevention: avoid cats and cat faeces:
  - avoid raw uncooked or partially cooked food
  - can be acquired congenitally.
- Diagnosis: CT/MRI of the brain, and serology (if available).
- Treat with co-trimoxazole 60 mg/kg orally (IV if there is severe nausea) 12-hourly for 2 weeks.
- Then give lifelong prophylaxis: sulfadiazine 85–120 mg/kg/day in two doses, pyrimethamine 1 mg/kg/day (maximum 25 mg) and folinic acid 5 mg every 3 days.

JC virus (papovavirus)

The JC virus is associated with progressive multifocal leukoencephalopathy, a disease characterised by altered mental status, limb weakness, or both. Patients may also exhibit personality changes with frequent emotional outbursts. There is no treatment for this illness, but strong antiretroviral medications (if available) can sometimes improve the symptoms.

Fungal lesion

This is rare.

Diffuse CMV encephalitis

Treat with ganciclovir 5 mg/kg orally or IV 12-hourly for 14–21 days.

Malaria

See Section 6.3.A.d.

Meningitis

Bacterial meningitis

This has the usual spectrum of pathogens, such as

TABLE 6.2.D.11 Neurological manifestations of paediatric HIV infection

Abnormality	Clinical findings	*Diagnostic studies (if available)*
Focal cerebral mass lesions	Headache, nausea/vomiting, motor deficits (usually asymmetrical), discoordination, visual changes, altered mental status	CT/MRI: enhancing lesions Lumbar puncture: CSF may reveal abnormal cytology or Epstein–Barr virus via PCR Brain biopsy: sometimes needed to confirm diagnoses
Myelopathy	Gait disturbances, lower-extremity weakness/spasticity incontinence, sensory abnormalities, abnormal lower-extremity reflexes	CT/MRI on mass lesions seen; nerve-root thickening may be present CSF: polymorphonuclear pleocytosis
Myopathy	Muscle weakness, muscle soreness, weight loss	EMG: irritative myopathy Muscle biopsy: inflammation, degeneration
Opportunistic infections	Headache, nausea/vomiting, fever, seizures, altered mental status, malaise	CT/MRI: multiple enhancing lesions (toxoplasmosis), periventricular and meningeal abnormalities (CMV)
Peripheral neuropathy	*Distal symmetrical neuropathy* • Distal numbness/pain • Paraesthesias • Stocking/glove sensory loss • Decreased ankle reflexes	*Distal symmetrical neuropathy* EMG: distal axonopathy
	Inflammatory demyelinating polyneuropathy • Progressive weakness • Paraesthesias • Areflexia • Mild sensory loss	*Inflammatory demyelinating polyneuropathy* EMG: demyelination
	Progressive polyradiculopathy • Lower-extremity weakness • Paraesthesias • Urinary incontinence and retention • Diminished reflexes	*Progressive polyradiculopathy* EMG: polyradiculopathy Serum: increased creatine kinase
Progressive encephalopathy	Fine and gross motor deficits (usually symmetrical), abnormal tone, neurodevelopmental delay, microcephaly, altered mental status	CT/MRI: brain atrophy, white-matter abnormalities
Seizures	Focal or generalised seizures, post-ictal stare (fatigue and confusion following seizure)	EEG: abnormal patterns CT/MRI and CSF studies: mass lesions may be seen via imaging, and CSF may be positive for pathogens and abnormal cells if aetiology is infectious or neoplastic Lumbar puncture: may reveal infection
Strokes (cerebrovascular accidents)	Rapid onset of focal neurological signs, seizures, altered mental status	CT/MRI: extent of bleeding seen (in ischaemic strokes, CT may not show changes during the first 2–1 hours): contributing factors such as CNS neoplasms may be identified Lumbar puncture: with subarachnoid haemorrhages, blood will be present in the CSF

Pneumococcus, *Haemophilus influenzae*, *Meningococcus* and *Mycobacterium TB.* (*see* Section 5.16.B).

Viral meningitis
See Section 5.16.C.

Cryptococcosis and other fungi
- Prevention: avoid bird faeces.
- Clinical features: chronic onset, headache (common), fever, meningism (usually but not always present), and there may be a change in mental state.
- Diagnosis: based on staining of CSF sample with Indian ink.
- Treatment:
  - Fluconazole 6–12 mg/kg orally or, if there is severe nausea, IV once daily for 14 days. There is a high relapse rate, therefore give prophylactic fluconazole 3–6 mg/kg/day **or** amphotericin IV 0.5–1.5 mg/kg/day for 14 days followed by oral fluconazole for 8 weeks.

Syphilis
Treat with benzylpenicillin IV 50 mg/kg every 6 hours for 48 hours, then oral penicillin 25 mg/kg 6-hourly for 3 weeks (20% of cases may have a systemic febrile response to penicillin).

Tuberculosis
See Section 6.1.N.

Cerebral abscess
Acute bacterial or tuberculosis.

TABLE 6.2.D.12 Care guidelines for children with neurological manifestations of paediatric HIV infection

Abnormality	Care guidelines
Focal cerebral mass lesions	• Assess for signs of increased intracranial pressure, fever, focal neurological signs and behavioural changes • Administer chemotherapy or antibiotics as needed • Provide support to family and education regarding specific medications needed by patients
Myelopathy	• Assess for pain, muscle weakness, lower-extremity weakness, incontinence and spasticity • Administer HAART to reverse immune suppression • Administer muscle relaxants as needed • Provide physical therapy for weakened muscles and to maintain range of motion • Teach exercises to the family so that they can help the patient at home
Myopathy	• Assess for pain, muscle weakness and range of motion • Consider discontinuing medications that may be contributing to the condition • Administer corticosteroids and pain medications as needed • Provide physical therapy for weakened muscles and to maintain range of motion • Teach exercises to the family so that they can help the patient at home
Opportunistic infections	• Assess for signs of increased intracranial pressure, fever, focal neurological signs and behavioural changes • Administer appropriate medication based on the suspected or confirmed pathogen: – toxoplasmosis: pyrimethamine, sulfadiazine, clindamycin – cryptococcosis: fluconazole, flucytosine, amphotericin B – herpes simplex: aciclovir – cytomegalovirus: ganciclovir, foscarnet
Peripheral neuropathy	• Assess for numbness, paraesthesias, pain and weakness • Administer analgesics, tricyclic antidepressants, anticonvulsants and steroids as needed • Provide support to the family and education regarding progression of symptoms
Progressive encephalopathy	• Assess for progressive motor dysfunction, and failure to reach or loss of age-appropriate milestones • Administer antiretroviral medications and muscle relaxants as needed • Assist with ambulation and activities of daily living • Provide information to the family regarding progression of symptoms
Seizures	• Assess for seizure activity • Protect the patient from injury during seizure activity • Monitor respiratory status: suction airway and administer oxygen as needed • Administer anticonvulsant medications as needed • Provide support to the family during seizures • Educate the patient and the family about long-term use of anticonvulsant medications and seizure precautions (e.g. patients with seizures should never swim alone or climb to high places from which they could fall during a seizure)
Strokes	• Intensive care, including neurosurgical intervention, is often needed immediately after a stroke occurs • Look for contributing factors, such as low platelet levels, which may be correctable • Assess for seizures • Assist with ambulation and activities of daily living • Provide physical therapy as needed • Provide support and education to the family regarding the long-term prognosis

Skin disorders

Cutaneous lesions are often the first manifestation of HIV noted by patients and healthcare professionals. These can be due to infectious or non-infectious causes. Viral, bacterial and fungal infections have been very frequently reported in HIV-infected children. These usually tend to be more severe and resistant to therapy. Common skin diseases may present with unusual skin lesions such as Norwegian scabies and disseminated, confluent and large lesions of molluscum contagiosum (*see* Table 6.2.D.13).

Seroconversion rash

Maculopapular erythematous rash (very rarely observed in infants).

Viral infections

Varicella

- Chickenpox: can be very severe (affecting the lungs and brain) or even fatal.
- Herpes zoster: can involve single or multiple dermatomes and may affect the eyes.

Treat with:

1 IV aciclovir (poorly absorbed by the oral route):
   - Age < 3 months: 10 mg/kg 8-hourly.
   - Age > 3 months: 20 mg/kg 8-hourly.
2 Valacyclovir is the prodrug of aciclovir, and achieves better blood levels orally and is an alternative to IV aciclovir (if available).
3 VZIG within 96 hours of contact (if available).

HSV 1 and 2

Infection appears as a crop of localised vesicles. It may affect the lips, mouth and anogenital areas (rare in children unless sexually abused). The vesicles rupture and form irregular painful ulcers. They may interfere with mastication and swallowing, resulting in decreased oral intake and dehydration.

TABLE 6.2.D.13 Common infectious and non-infectious skin lesions in paediatric HIV

Infectious disorders and lesions	Non-infectious disorders and lesions
Viral infections • Herpes simplex, herpes zoster • Molluscum contagiosum • CMV • Warts Fungal infections • Candida • Tinea onychomycosis Bacterial infections • Impetigo • Scabies	Seborrhoeic dermatitis, atopic dermatitis, general dermatitis Nutritional deficiency Eczema Psoriasis Drug eruptions Vasculitis Alopecia

- May be recurrent and severe.
- Treat with oral aciclovir, 20 mg/kg four times daily for 5–7 days (maximum single dose 800 mg).

Molluscum contagiosum

Umbilicated papular lesions. Treat with ARVs (no other measures are effective). If neglected, giant lesions can result which require surgical excision.

Measles

- Prevent by immunisation (see below and Section 6.2.E).
- May not have a rash.
- Giant-cell pneumonitis may occur.
- Treat with Vitamin A and human immunoglobulin (if available).

Viral warts

These can be persistent and severe. Topical treatment is ineffective (*see* molluscum contagiosum above), and ARVs are the only effective treatment.

Bacterial infections

Impetigo and furunculitis due to *Staphylococcus aureus* are common. Treat with (flu)cloxacillin, 12.5–25 mg/kg four times daily orally, or a first-generation cephalosporin such as cephradine.

Fungal infection

Fungal infection is common and involves the feet, hands and groin. Treat with topical imidazole (e.g. miconazole 2% twice daily until healed) or terbinafine cream. If severe, widespread or for nail infections, use itraconazole or terbinafine. Treatment will be needed for 4–6 weeks.

Antifungal drugs commonly used in paediatric patients include the following:

- **Itraconazole:** children aged 1–12 years: course ('pulse') of 5 mg/kg (maximum 200 mg) daily for 7 days, with subsequent courses repeated after 21-day intervals; fingernails need two courses, and toenails need three courses. For children aged 12–18 years: either 200 mg once daily for 3 months or course ('pulse') of 200 mg twice daily for 7 days, with subsequent courses repeated after 21-day intervals; fingernails need two courses, and toenails need three courses.
- **Terbinafine:** children aged over 1 year: body weight 10–20 kg, 62.5 mg once daily; body weight 20–40 kg, 125 mg once daily; body weight over 40 kg, 250 mg once daily, for 6 weeks to 3 months.
- **Fluconazole:** 6 mg/kg weekly.
- **Griseofulvin:** 20–25 mg/kg/day (microsize formulation) **or** 10–15 mg/kg/day (ultramicrosize formulation) for 6–12 weeks.

Seborrhoeic dermatitis and pityriasis versicolor

Seborrhoeic dermatitis occurs in up to 85% of adults and children with HIV infection. It may be an early sign of HIV. It is caused by the yeast *Malassezia furfur.*

It is characterised by thick yellow hypopigmented scaly macules occurring on the scalp but also on the face or in the diaper (nappy) area. Older children may also have involvement of the nasolabial folds, the skin behind the ears, and the eyebrows.

Treatment consists of selenium-based or ketoconazole shampoo, topical coal tar or antifungal creams, aqueous cream, UVB light therapy or salicylic acid. To decrease inflammation, 1% hydrocortisone cream can be applied to the affected area (except for the face) three times per day. Parents should be instructed to use 1% hydrocortisone cream sparingly in the diaper area.

If the condition is severe, give oral fluconazole 3 mg/kg once daily.

Non-specific pruritic papular rash

This is a common and severe problem in children with HIV infection. In a previously untested child it should be an indication for HIV testing. In a child who is known to have HIV, the CD4 count should be checked and ARV started if appropriate.

Treatment

- Bathe in a skin antiseptic wash (e.g. dilute chlorhexidine solution).
- Antihistamines: give chlorpheniramine:
  - Age < 1 year: 1 mg twice daily.
  - Age 1–5 years: 1–2 mg three times daily.
  - Age 6–12 years: 2–4 mg three times daily.
  - Age > 12 years: 4 mg three times daily.
- Aqueous cream and calamine lotion may be of benefit.

Drug side effects

Drug eruptions can occur in patients who are receiving treatment for HIV infection. These can be severe (e.g. erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis).

Drug side effects are most common with co-trimoxazole, sulfadiazine, anti-tuberculous drugs (e.g. thiacetazone, which is contraindicated in HIV infection), penicillin, cephalosporins and dapsone.

Drug eruptions usually appear as pink to erythematous papules that run together and create a blotchy appearance, but may include elevated patches (hives), mucous membrane ulceration, scaling and light sensitivity.

NRTIs (nevirapine and efavirenz) have been associated with pruritic maculopapular eruptions. Most eruptions are mild, and the medication can be continued with eventual spontaneous resolution of the eruption.

To promote comfort, the patient can be given oral antihistamine such as diphenhydramine hydrochloride 1 mg/kg

every 6 hours. In more severe cases, the eruptions resolve when the medication is discontinued.

Most drug eruptions are mild and resolve after the causative medication is discontinued.

Infestations

Sarcoptes scabiei (*see* Section 5.18) may present as in children without HIV infection. It is characterised by pruritic papular lesions that most commonly occur in the webs of the fingers and toes, the folds of the wrist, the antecubital area and the axilla. Infants may also have lesions on the palms and soles of the feet. Scrapings observed under a microscope may reveal the mite, eggs or faeces.

Treatment consists of an application of topical benzyl benzoate lotion, 25%, which is left on the skin to dry and repeated the next day. HIV-infected patients with advanced disease can experience a variant of scabies called Norwegian scabies. This type of scabies is characterised by generalised scaling and enlarged crusted plaques. After a patient is treated for scabies, the family should be advised to wash all clothing and bedclothes in hot water and iron them to kill any mites that may be living in the cloth.

Malignancy

Consider Kaposi's sarcoma in children presenting with nodular skin lesions, diffuse lymphadenopathy and lesions on the palate and conjunctiva with peri-orbital bruising. The diagnosis is usually clinical, but can be confirmed by a needle biopsy of skin lesions or a lymph node biopsy. Suspect Kaposi's sarcoma also in children with persistent diarrhoea, weight loss, intestinal obstruction, abdominal pain or a large pleural effusion. Consider referral to a larger hospital for management.

Eye involvement (*see* Section 5.15)

- Malignancy (e.g. non-Hodgkin's lymphoma, Kaposi's sarcoma).
- HIV retinopathy: this is a microangiopathy with soft exudates. It is asymptomatic and does not require treatment. It needs to be differentiated from tuberculosis.
- Cytomegalovirus retinitis: this is the most common cause of visual loss in HIV. Treat with ganciclovir 5 mg/kg IV or orally 12-hourly for 14–21 days.
- Herpes zoster: this may produce corneal ulceration and retinal necrosis.
- Toxoplasmosis: this usually causes CNS disease and reactivation disease, and may cause visual problems or blindness. Treatment includes pyrimethamine, 1–2 mg/kg/day orally for 2 days, then 1 mg/kg/day orally for 2 months, then 1 mg/kg/day orally for 3 days a week (maximum 50 mg). Secondary prophylaxis may also be given to prevent reactivation.

Prophylaxis for any opportunistic infections consists of the following:

- **Primary prophylaxis:** giving medication to prevent infection that has not yet occurred.
- **Secondary prophylaxis:** giving medication to prevent recurrence of an infection after an episode.

Prophylaxis can often be stopped after sustained immune reconstitution secondary to ART, but not in all cases.

Mycobacterium avium complex (MAC)

- This produces a systemic infection with fever, chronic diarrhoea, abdominal pain, chronic malabsorption, generalised lymphadenopathy and obstructive jaundice (from lymph node enlargement around the porta hepatis).
- Treat with clarithromycin 7.5 mg/kg twice daily IV or orally **or** azithromycin 10 mg/kg once daily **and** ciprofloxacin and rifabutin.
- Consider prophylaxis with the above drugs if **CD4 cell counts are persistently < 50/mm^3 despite antiretroviral therapy, as the risk of MAC is high.** The opportunistic infection guidelines recommend that all HIV-infected individuals with CD4 counts of < 50 cells/mm^3 should have primary prophylaxis against disseminated MAC initiated. Prior to initiating prophylaxis, patients should be evaluated for active MAC infection by clinical assessment.

Fever of unknown origin

- HIV infection itself can cause fever.
- In an endemic area, always treat for malaria (ideally after a blood film). Malaria has not usually been reported to be more severe in HIV-infected children in terms of parasite density or response to treatment. The main interaction between the two diseases has been the acquisition of HIV by children through blood transfusion for malaria-associated anaemia.
- Have a low threshold for diagnosing septicaemia and meningitis and giving powerful empirical antibiotics if severe sepsis is suspected.
- Consider tuberculosis and non-Hodgkin's lymphoma.

Immunisation

Early immunisations can help HIV-infected children who are more likely to acquire diseases that are preventable by immunisation because of their compromised immune system. Appropriate immunisations vary according to geographical location.

Routine immunisations appear to be generally safe for children with HIV infection without fever. Although immune responses may be suboptimal in some HIV-infected children, because of the severe nature of infections and associated mortality, routine immunisation of all children with HIV exposure or confirmed HIV infection is recommended with few exceptions.

Immunisations should generally follow the Expanded Programme on Immunisation (EPI) scheme. The current EPI schedule includes DTP, OPV, hepatitis B, *Haemophilus influenzae* type B vaccine (Hib) and measles vaccine. The difference in HIV-infected children is an extra dose of measles vaccine to be given at the age of 6 months. **BCG and yellow fever vaccines should not be given to HIV-symptomatic children.**

In HIV-endemic areas, BCG is routinely administered postnatally. This should be given even to infants of mothers known to be HIV-infected, as the damage to the immune system generally occurs after the onset of viraemia (i.e. after the first 6 weeks of life). There is no evidence of frequent dissemination occurring after neonatal administration of BCG, although BCG-osis is not an easy diagnosis to establish, and there may be unrecognised cases.

Because most HIV-positive children have an effective immune response in the first year of life, EPI should be

started as early as possible after the recommended age of vaccination.

There are theoretical risks associated with giving live oral polio vaccine, particularly to other immunocompromised members of the household. However, cases of vaccine-associated paralytic illness are rare, and oral poliomyelitis vaccine (OPV) continues to be recommended.

Live attenuated measles vaccine is recommended by the WHO for children in resource-limited countries, where the risks from wild-type measles virus are high. Responses to the vaccine tend to be lower in HIV-infected children with more advanced disease. The WHO recommends giving an extra dose of measles vaccine at 6 months, as well as the standard dose at 9 months, to HIV-infected children. It is important to be aware of measles in the differential diagnosis of any child with fever or pneumonia and HIV, as a typical morbilliform rash and standard symptoms may not be present.

Other non-EPI vaccines are encouraged and recommended, especially in children whose immune systems have recovered. These more expensive but strongly recommended vaccines include MMR, pneumococcal conjugate vaccine, hepatitis A, typhoid and varicella vaccines. Diseases caused by these organisms have a greater propensity to cause severe life-threatening infections in HIV-infected children.

Terminal care of children dying from HIV infection

See also Section 1.16.

Despite the increased availability and effectiveness of ARVs, death is still a possible outcome of HIV/AIDS. Each year, millions of children lose one or both parents to AIDS. Although relatives often go to heroic lengths to provide orphans with food, shelter and housing, often the children's psychosocial needs are overlooked, and these young people are not given full recognition or support after their loss. This is usually due to the belief that children are too young to understand what is happening or are better off not dwelling on their loss. Consequently, they are not properly supported in their time of mourning.

Local groups for the support of families with HIV infection are essential, and ideally should be funded by local government.

Give end-of-life (terminal) care if:

- the child has had a progressively worsening illness
- everything possible has been done to treat the presenting illness.

Keep up to date on how to contact local community-based home care programmes and HIV/AIDS counselling groups. Find out whether the carers are receiving support from these groups. If not, discuss the family's attitude towards these groups and the possibility of linking the family with them.

Pain control for children with HIV

See Section 1.15.

Need for referral

Often the facilities or expertise that are needed will not be available at the health centre or hospital to which a child with suspected or confirmed HIV has come for treatment. If the child is not suffering from a life-threatening condition that requires urgent treatment, and referral can be arranged, it is advisable to refer the child to a paediatric infectious disease specialist or HIV treatment centre for the following:

- HIV testing with pre- and post-test counselling
- further investigations to confirm the diagnosis
- evaluation of immunological status and the need to initiate ART
- management of complicated HIV-related conditions and infections
- evaluation of possible treatment failure
- second-line treatment if there has been little or no response to treatment
- HIV medication-related toxicities
- HIV-related expert counselling.

Summary

- The major practical focus should be on prevention of childhood HIV infection. This means implementing effective strategies for reduction of mother-to-infant transmission, such as prenatal screening of mothers and administration of ARV drugs for mother and baby.
- Unfortunately, establishing the infrastructure that is required to implement effective interventions is lagging far behind the scientific advances in this field. Surmounting the sense of hopelessness among health-care professionals who are dealing with overwhelming numbers of patients without resources is a critical issue. This may come in part from research that identifies practical interventions which improve the quality of life for HIV-infected children and their families.
- Limiting the use of blood transfusions and ensuring that the blood supply is safe, and preventing sexual transmission among adolescents, are vital public health issues.
- Positive education is required to encourage testing in the knowledge that there is now accessible safe treatment to keep children alive so that they can have a full healthy life.
- The key to successful treatment is 100% adherence. Do not start outpatient treatment until the child's carer and ideally all the family have expressed a commitment to treatment. Choose ART regimes which are simple, and ensure that there is no problem with swallowing.
- Predict growth for dosing so that the child is never under-dosed.
- Frequent review is necessary to re-emphasise the importance of adherence and education of young people.
- It is essential that resource-limited countries are permitted by multinational drug companies to develop low-cost and effective forms of HAART, without being limited by international patent regulations.
- Without question, health system strengthening is essential if the advent of ARVs for all is to be adequately managed.

This is a very optimistic time in the field of paediatric HIV, with the potential to aim for eradication of mother-to-child transmission, and to provide successful treatment.

Appendix 1

TABLE 6.2.D.14 Monitoring children on ART

Item	Before or at ART initiation	Month (M) 1	M 2	M 3	M4	M5	M 6	Every 2–3 months	Symptom-directed
Clinical evaluation: history and physical examination (including neurodevelopment)	X	X	X	X	X	X	X	X	X
Weight and height	X	X	X	X	X	X	X	X	
Calculation of ART dose[1]	X	X	X	X	X	X	X	X	
Concomitant medications[2]	X	X	X	X	X	X	X	X	
Check ART adherence[3]		X	X	X	X	X	X	X	
Haemoglobin and white blood cell count[4]	X								X
Full chemistry[5]									X
CD4% or count[6]	X							X*	X
HIV viral load measurement[7]									X

* If signs of clinical progression of disease are seen, the CD4 count should be done earlier.

- The child should be seen again within 1 week of starting ART to resolve any problems.
- If the child has missed a visit, attempts should be made to call or visit the child's home.
- In addition to these suggested appointments, caregivers should be encouraged to bring the child in if he or she is sick, especially during the first few months of ART when the child may experience ART side effects and intolerance.

[1] Children may show rapid weight and height gain after ART, in addition to expected normal growth. Therefore the ART dose should be recalculated at every visit. Under-dosing of ART can lead to the development of resistance.

[2] Concomitant drugs should be asked for at every visit to ensure that the child is on appropriate CTX dosing (if indicated) and is not taking drugs that have potential interactions with ART.

[3] ART adherence can be assessed by asking questions about missed doses and the times when the child takes ART. Performing a pill count is time consuming, but may give a more accurate indication of adherence, if done correctly.

[4] Haemoglobin (Hb) and white blood cell count (WBC) monitoring may be considered in children on ZDV at 1, 2 and 3 months.

[5] Full chemistry includes but is not restricted to liver enzymes, renal function, glucose, lipids, amylase, lipase and serum electrolytes. Monitoring depends on symptoms and regimens. Regular liver enzyme monitoring during the first 3 months of treatment may be considered for certain children using nevirapine-based regimens, in particular for adolescent girls with a CD4 count of > 250 cells/mm^3, and for infants and children who are co-infected with hepatitis B or hepatitis C virus, or other hepatic disease.

[6] TLC is not suitable for monitoring of therapy; therefore it cannot be a substitute for CD4. If CD4 is not available, clinical monitoring alone is used.

[7] At present, viral load measurement is not recommended for decision making about the initiation or regular monitoring of ART in resource-limited settings. Tests for assessment of HIV RNA viral load can also be used to diagnose HIV infection, and to assess discordant clinical and CD4 findings in children in whom ART is suspected of failing.

Appendix 2

Treatment of PCP infection

TABLE 6.2.D.15 Starting co-trimoxazole (CTX) prophylaxis for *Pneumocystis jiroveci* pneumonia (PCP)

HIV-exposed infants and children	Confirmed HIV-infected infants and children		
	Under 1 year	1–5 years	6 years or older
CTX prophylaxis is universally indicated, starting at 4–6 weeks after birth, and maintained until cessation of risk of HIV transmission and exclusion of HIV infection	CTX prophylaxis is indicated regardless of CD4 percentage or clinical status	WHO stages 2, 3 and 4 regardless of CD4 percentage **or** Any WHO stage and CD4 < 25%	Any WHO clinical stage and CD4 < 350 cells/mm^3 **or** WHO stage 3 or 4 and any CD4 level

Patient information: It needs to be explained to patients that although CTX does not cure HIV, regular dosing is essential for protection of children from infections that are more common or more likely to occur in HIV infection. CTX does not replace the need for antiretroviral therapy.

TABLE 6.2.D.16 Dosing for PCP: once-daily CTX dosing

Weight	Suspension: 40 mg TMP + 200 mg SMX/5 mL	Tablets (SS): 80 mg TMP/400 mg SMX	Tablets (DS): 160 mg TMP/800 mg SMX
1–4 kg	2.5 mL	–	–
5–8 kg	5 mL	½ tablet	–
9–16 kg	10 mL	1 tablet	½ tab
17–50 kg	20 mL	2 tablets	1 tablet
> 50 kg	20 mL	2 tablets	1 tablet

Appendix 3

Summary of nutritional recommendations and support for HIV-infected children

- Regular growth monitoring.
- Safe infant feeding advice (the emphasis is on an **exclusive** infant feeding option). Substitute feeds if they are acceptable, affordable, feasible, sustainable and safe, otherwise exclusive breastfeeding, and early weaning. Avoid all mixed feeding.
- Dietary counselling for asymptomatic children to increase energy intake by 10% compared with HIV-uninfected children.
- Dietary counselling for symptomatic children to increase energy intake by 20–30% compared with HIV-uninfected children.
- Counselling on the importance of a balanced diet, including affordable choices from all food groups (micronutrient requirement of 1 RDA for age).
- Counselling on high-energy affordable food options for children with growth failure.
- Counselling on the use of clean water and hygienic food preparation.
- Vitamin A supplementation to prevent vitamin A deficiency in children aged 6 to 59 months with dosing schedule as follows:
  - Children aged 6–11 months: 100 000 IU (30 mg) once every 6 months.
  - Children aged 12–59 months: 200 000 IU (60 mg) once every 6 months.
- Zinc supplementation during diarrhoeal episodes: 10 mg once daily for 10 days in children older than 6 months if weight is ≤ 10 kg, and 20 mg if weight is > 10 kg.
- Assessment and management for underlying HIV-associated illnesses.
- Assessment for need to initiate ART.
- Referral to outreach service providers for food assistance, if needed.

Appendix 4

TABLE 6.2.D.17 Formulations and dosages of ART drugs for children

Name of drug	Formulation	Age	Age (weight), dose and dose frequency	Other comments
Nucleoside analogue reverse transcriptase inhibitors (NRTIs)				
Zidovudine (ZDV) AZT	Syrup: 10 mg/mL Capsules: 100 mg, 250 mg Tablet: 300 mg	All ages	< 4 weeks: 4 mg/kg/dose twice daily 4 weeks to 13 years: 180–240 mg/m^2/dose twice daily Maximum dose: ≥ 13 years: 300 mg/dose twice daily	Large volume of syrup is not well tolerated in older children, Syrup needs to be stored in glass jars and is light sensitive Can give with food Doses of 600 mg/m^2/dose per day required for HIV encephalopathy Capsule can be opened and its contents dispersed, or tablet crushed and its contents mixed with a small amount of water or food and immediately taken (solution is stable at room temperature) Do not use with d4T (antagonistic antiretroviral effect)
Lamivudine (3TC)	Oral solution: 10 mg/mL Tablet: 150 mg	All ages	< 30 days: 2 mg/kg/dose twice daily ≥ 30 days or < 60 kg: 4 mg/kg/dose twice daily Maximum dose: > 60 kg: 150 mg/dose twice daily	Well tolerated Can give with food Store solution at room temperature (use within 1 month of opening) Tablet can be crushed and its contents mixed with a small amount of water or food and immediately taken
Fixed-dose combination of ZDV plus 3TC	No liquid formulation available Tablet: 300 mg ZDV plus 150 mg 3TC	Adolescents and adults	Maximum dose: > 13 years old or weight > 60 kg: 1 tablet per dose twice daily (should not be given if weight is < 30 kg)	Ideally, tablet should not be split Tablet can be crushed and its contents mixed with a small amount of water or food and immediately taken At weights of < 30 kg, ZDV and 3TC cannot be dosed accurately in tablet form
Stavudine (d4T)	Oral solution: 1 mg/mL Capsules: 15 mg, 20 mg, 30 mg, 40 mg	All ages	< 30 kg: 1 mg/kg/dose twice daily 30–60 kg: 30 mg/dose twice daily Maximum dose: > 60 kg: 40 mg/dose twice daily	Large volume of solution Keep solution refrigerated; it is stable for 30 days, but must be shaken well. It needs to be stored in glass bottles Capsules can be opened and their contents mixed with a small amount of food or water (stable in solution for 24 hours if kept refrigerated) Do not use with ZDV (antagonistic antiretroviral effect)
Didanosine (ddI, dideoxyinosine)	Oral suspension paediatric powder/water: 10 mg/mL (In many countries needs to be made up with additional antacid) Chewable tablets: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg Enteric-coated beadlets in capsules: 125 mg, 200 mg, 250 mg, 400 mg	All ages	< 3 months: 50 mg/m^2/dose twice daily 3 months to < 13 years: 90–120 mg/m^2/dose twice daily or 240 mg/m^2/dose once daily Maximum dose: ≥ 13 years or > 60 kg: 200 mg/dose twice daily or 400 mg once daily	Keep suspension refrigerated; it is stable for 30 days, but must be shaken well Administer on an empty stomach, at least 30 minutes before or 2 hours after eating If tablets are dispersed in water, at least 2 appropriate-strength tablets should be dissolved for adequate buffering Enteric-coated beadlets in capsules can be opened and sprinkled on a small amount of food

(*continued*)

Name of drug	Formulation	Age	Age (weight), dose and dose frequency	Other comments
Abacavir (ABC)	Oral solution: 20 mg/mL Tablet: 300 mg	Over 3 months	< 16 years or < 37.5 kg: 8 mg/kg/dose twice daily Maximum dose: > 16 years or ≥ 37.5 kg: 300 mg/dose twice daily	Can give with food Tablet can be crushed and its contents mixed with a small amount of water or food and immediately ingested **Warn parents about hypersensitivity reaction** ABC should be stopped permanently if a hypersensitivity reaction occurs
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)				
Nevirapine (NVP)	Oral suspension: 10 mg/mL Tablet: 200 mg	All ages	15–30 days: 5 mg/kg/dose once daily for 2 weeks, then 120 mg/m^2/dose twice daily for 2 weeks, then 200 mg/m^2/dose twice daily > 30 days to 13 years: 120 mg/m^2/dose once daily for 2 weeks, then 120–200 mg/m^2/dose twice daily Maximum dose: > 13 yrs: 200 mg/dose once daily for first 2 weeks, then 200 mg/dose twice daily	If rifampicin co-administration, avoid use Store suspension at room temperature, but it must be shaken well Can give with food Tablets are scored and can be divided into two equal halves to give a 100 mg dose; can be crushed and combined with a small amount of water or food and immediately administered Warn parents about rash Do not dose escalate if rash occurs (if mild or moderate rash, hold drug; when rash has cleared, restart dosing from beginning of dose escalation; if severe rash, discontinue drug)
Efavirenz (EFV)	Syrup: 30 mg/mL (note that syrup requires higher doses than capsules; see dosing chart) Capsules: 50 mg, 100 mg, 200 mg	Only for children over 3 years of age or who weigh > 10 kg	Capsule (liquid) dose: 10–15 kg: 200 mg (270 mg = 9 mL) once daily 15–19 kg: 250 mg (300 mg = 10 mL) once daily 20–24 kg: 300 mg (360 mg = 12 mL) once daily 25–32 kg: 350 mg (450 mg = 15 mL) once daily 33–39 kg: 400 mg (510 mg = 17 mL) once daily Maximum dose: ≥ 40 kg: 600 mg once daily	Capsules may be opened and added to food, but have a very peppery taste; however, can mix with sweet foods or jam to disguise taste Can give with food (but avoid giving after high-fat meals which increase absorption by 50%) Best given at bedtime, especially in the first 2 weeks, to reduce CNS side effects
Etravirine	100 mg, 200 mg dispersible tablets	Child over 6 years	16–20 kg, 100 mg twice a day, 21–25 kg, 125 mg twice a day 26–30 kg, 150 mg twice a day > 30 kg, 200 mg twice a day	AUC decreased by 50% if taken on an empty stomach
Protease inhibitors (PIs)				
Nelfinavir (NFV)	Powder for oral suspension (mix with liquid): 200 mg per level teaspoon (50 mg per 1.25 mL scoop): 5 mL Tablet: 250 mg (tablets can be halved; can be crushed and added to food or dissolved in water)	All ages However, extensive pharmacokinetic variability in infants, with requirement for very high doses in infants under 1 year	< 1 year: 50 mg/kg/dose three times daily or 75 mg/kg/dose twice daily ≥ 1 year to < 13 years: 55–65 mg/kg/dose twice daily Maximum dose: ≥ 13 years: 1250 mg/dose twice daily	Powder is sweet, faintly bitter, but gritty and hard to dissolve; must be reconstituted immediately prior to administration in water, milk, formula, pudding, etc.; do not use acidic food or juice (which increase the bitter taste); solution is stable for 6 hours Because of difficulties with use of powder, the use of crushed tablets is preferred (even for infants) if the appropriate dose can be given

(*continued*)

Name of drug	Formulation	Age	Age (weight), dose and dose frequency	Other comments
Nelfinavir (NFV) (*cont.*)				Powder and tablets can be stored at room temperature Take with food Drug interactions (less than with ritonavir-containing protease inhibitors)
Lopinavir/ ritonavir (LPV/r)	Oral solution: 80 mg/ mL lopinavir plus 20 mg/mL ritonavir Note that oral solution contains 42% alcohol Capsules: 133.3 mg lopinavir plus 33.3 mg ritonavir	6 months or older	> 6 months to 13 years: 225 mg/m^2 LPV and 57.5 mg/ m^2 ritonavir twice daily, or weight-based dosing as follows: 7–15 kg: 12 mg/kg LPV and 3 mg/kg ritonavir twice daily 16–40 kg: 10 mg/kg lopinavir and 5 mg/kg ritonavir twice daily Maximum dose: > 40 kg: 400 mg LPV and 100 mg ritonavir (3 capsules or 5 mL) twice daily	Preferably oral solution and capsules should be refrigerated; however, they can be stored at room temperature up to 25°C (77°F) for 2 months; at temperatures > 25°C (77°F) the drug degrades more rapidly Liquid formulation has low volume but bitter taste Capsules are large Capsules should **not** be crushed or opened, but must be swallowed whole Should be taken with food
Saquinavir/r	Soft gel capsule: 200 mg Hard gel capsule: 200 mg, 500 mg	> 25 kg	Approved dosing in adults: SQV 1000 mg and RTV 100 mg twice daily There are no data for children For children who weigh > 25 kg, the approved adult dosing can be used If possible, monitoring of SQV level is recommended	Capsules are large Capsules should **not** be crushed or opened, but must be swallowed whole Should be taken with food
Darunavir plus Ritonavir (RTV)	75 mg (white), 150 mg (white), 400 mg (light orange), 600 mg (orange)		**PI experienced, 3–6 years:** 10–11 kg: 200 mg twice a day + RTV 32 mg twice a day 11–12 kg: 220 mg twice daily + RTV 32 mg twice a day 12–13 kg: 240 mg twice a day + RTV 40 mg twice a day 13–14 kg: 260 mg twice a day + RTV 40 mg twice a day 14–15 kg: 280 mg twice a day + RTV 48 mg twice a day **6 years:** 15–30 kg: 375 mg twice a day + RTV 50 mg twice a day 31–40 kg: 450 mg twice a day + RTV 60 mg twice a day. > 40 kg: 600 mg twice a day + RTV 100 mg twice a day	DRV and RTV levels reduce in combination
Integrase inhibitor				
Raltegravir	400 mg tablets (pink)	> 6 years	> 25 kg: 400 mg twice a day	With or without food Avoid indigestion remedies

Appendix 5

TABLE 6.2.D.18 Side effects of ARVs

Drug		Side effects	Comments
Nucleoside analogue reverse transcriptase inhibitors (NRTIs)			
Lamivudine	3TC	Headache, nausea, abdominal pain, diarrhoea, fatigue, pancreatitis	Well tolerated, can be crushed
Stavudine	d4T	Headache, abdominal pain, neuropathy, pancreatitis, lactic acidosis, hepatitis, lipodystrophy	Large volume of suspension, capsules can be opened
Zidovudine	AZT	Headache, anaemia, neutropenia, nausea, hepatitis, neuropathy, nail pigmentation	Do not use with d4T (antagonistic ARV effect)
Abacavir	ABC	Hypersensitivity reaction, with fever, mucositis and rash; this is rare, but if it occurs stop the drug	Tablets can be crushed
Didanosine	ddI	Peripheral neuropathy, diarrhoea, nausea, abdominal pain, lipodystrophy. Lactic acidosis and pancreatitis (especially with d4T)	On empty stomach, give with antacid
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Efavirenz	EFV	Vivid dreams, sleepiness, rash, mood changes, hypercholesterolaemia	Take at night, avoid taking with fatty food
Nevirapine	NVP	Rash (Stevens–Johnson syndrome), liver toxicity (check liver function tests at 2, 4 and 8 weeks)	When given with rifampicin, increase NVP dose by 30% or avoid use
Protease inhibitors (PIs)			
Lopinavir/ritonavir*	LPV/r NFV SQV	Diarrhoea, nausea, vomiting, headache Diarrhoea, vomiting, rash Diarrhoea, abdominal discomfort	Liquid: bitter taste. Take with food Take within 2 hours of food
Darunavir	DRV	Rash, nausea, diarrhoea, headache	
Atazanavir	ATV	Rash, nausea, jaundice, headache	Avoid antacids
Ritonavir*	RTV	Rash, nausea, diarrhoea, peri-oral paraesthesia, flushing, hepatitis	Liquid: bitter taste
Integrase inhibitor			
Raltegravir		Nausea, dizziness, insomnia, rash, pancreatitis, elevated ALT, AST, GGT	Avoid indigestion remedies

*Requires cold storage and cold chain for transport.

TABLE 6.2.D.19 Number of tablets of child-friendly solid formulations for twice daily dosage (morning and evening)

Drug	Strength of paediatric tablet (mg)	Children aged ≥ 6 weeks										Strength of adult tablet (mg)	Number of tablets by weight-band	
		Number of tablets by weight-band morning and evening												
		3–5.9 kg		*6–9.9 kg*		*10–13.9 kg*		*14–19.9 kg*		*20–24.9 kg*			*25–34.9 kg*	
		am	*pm*	*am*	*pm*	*am*	*pm*	*am*	*pm*	*am*	*pm*		*am*	*pm*
Single drugs														
AZT	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
ABC	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
NVP	50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200	1	1
Ddl	25	2[a]	2[a]	3	2	3	3	4	3	4	4	25	5	5
Combinations														
AZT/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150	1	1
AZT/3TC/NVP	60/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150/200	1	1
ABC/AZT/3TC	60/60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/300/150	1	1
ABC/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	[b]		
d4T/3TC	6/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	30/150	1	1
d4T/3TC/NVP	6/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	30/150/200	1	1
LPWr[c]	100/25	NR	NR	NR	NR	2	1	2	2	2	2	100/25	3	3

[a] This dose of Ddl is only approximate for children aged 3 months or older and weighing between 6 kg and 6.9 kg.

[b] See ABC/3TC FDC dosing table.

[c] Higher doses of LPWr may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, fos-amprenavir (FPV) and rifampicin.

TABLE 6.2.D.20 Number of tablets or capsules of child-friendly solid formulations for once-daily dosage

Drug	Strength of tablet or capsule (mg)	Number of tablets or capsules by weight-band once daily					Strength of tablet/ capsule (mg)	Number of tablets or capsules by weight-band once daily
		3–5.9 kg	*6–9.9 kg*	*10–13.9 kg*	*14–19.9 kg*	*20–24.9 kg*		*25–34.9 kg*
		Once daily	*Once daily*	*Once daily*	*Once daily*	*Once daily*		*Once daily*
Single drugs								
EFV[a]	200 mg	NR	NR	1	1.5	1.5	200	2
Ddl[b]	125 mg or 200 mg EC	NR	NR	1 (125 mg)	1 (200 mg)	2 (125 mg)	125 mg EC	2

[a] EFV is not recommended for children under 3 years and weighing less than 10 kg.

[b] Ddl EC is not recommended for children weighing less than 10 kg.

NR, not recommended; EC, enteric coated.

Further reading

World Health Organization (2010) *Antiretroviral Therapy for HIV Infection in Infants and Children: towards universal access*. http://whqlibdoc.who.int/publications/2010/9789241599801_eng.pdf

6.2.E Measles

BOX 6.2.E.1 Minimum standards
- Immunisation.
- Vitamin A.
- Oral rehydration solution and nutritional provision.
- Antibiotics for secondary infection.
- Oxygen.
- Nebulised adrenaline and corticosteroids for croup.
- Eye pads.
- Public health measures.

Introduction

Measles is an acute viral disease characterised by fever, cough, coryza, conjunctivitis, an erythematous maculopapular rash, and typical oral lesions (Koplik's spots). It is caused by an RNA virus, a member of the genus *Morbillivirus* in the Paramyxoviridae family. Humans are the only natural hosts. It is transmitted by direct contact with infectious droplets or, less commonly, by airborne spread. It has a high incidence in winter. Measles is one of the most highly communicable of all infectious diseases.

Measles occurs worldwide, and is a significant cause of morbidity and mortality worldwide. It is the fifth most common cause of death in children under 5 years of age. There has been a 78% reduction in measles mortality worldwide in recent years, largely as a result of immunisation, from 733 000 deaths in 2000 to 164 000 in 2008, and a reduction in the total number of cases from 39.9 to 20 million.

Epidemiology

- Measles is transmitted by droplet spread of virus in nasopharyngeal secretions. It is most infectious before the appearance of rash, and for at least 7 days after the onset of the first symptoms. The incubation period is 10–12 days. Quarantine can be lifted 2 days after the fever subsides.
- Epidemic cycles of infection in urban areas may occur every 2 years. In isolated communities, all age groups are affected. In resource-limited countries, the population peak incidence is at 1–2 years, with a mortality of 1–5%, although during epidemics it may rise to 30%. Mortality is low in the well nourished. Children who acquire infection in overcrowded conditions tend to have more severe disease, probably due to a larger infecting dose of the virus.
- Pneumonia and upper airway obstruction account for about 75% of measles deaths. Measles is more severe in HIV-infected children.
- In resource-limited countries, measles commonly occurs in previously vaccinated children. This is partly explained by a persistent maternal antibody at 9 months of age when vaccine is usually given, and also a relatively poor efficacy of the vaccine and waning immunity.
- It rarely occurs in infants under 3 months of age because of maternal immunity transferred *in utero*.

Clinical features

Prodromal period (3–5 days): acute coryza-like illness with high-grade fever, cough and conjunctivitis. Febrile seizures may occur. Koplik's spots (tiny bluish-white specks on a red base on the buccal mucosa of the cheeks, resembling grains of salt) appear by days 2–4.

A maculopapular rash commences on day 4 on the face and neck, behind the ears and along the hairline, and spreads to become generalised and reaches the feet after 3 more days). Fades after 5–6 days in order of appearance, developing a brownish colour and often becoming scaly. If severe, there may be petechiae and ecchymoses. The rash is due to infiltration of lymphocytes into areas of virus replication in skin.

Persistence of fever beyond day 3 of the rash is usually due to complications (see below).

Diagnosis

This is mostly clinical (diagnosis is based on the specific pattern of rash, history of contact with a measles patient, and Koplik's spots). Serology, viral culture or PCR may be used to confirm it.

Laboratory findings

Leukopenia and thrombocytopenia may be observed during measles infection. Chest radiography may demonstrate interstitial pneumonitis.

Complications

Recovery following acute measles may be delayed for weeks or months due to failure to thrive, recurrent infections, persistent pneumonia and diarrhoea.

Pneumonia (*see* Section 5.3.A)

- Bacterial pneumonia usually occurs during convalescence and after several days of an afebrile period. It is the most frequent cause of death with an incidence of 10–25% of hospitalised cases in developing countries.
- Viral pneumonia occurs during the acute phase of measles, and may progress to giant-cell pneumonia in the immunosuppressed (e.g. leukaemia, HIV).
- Mediastinal emphysema occurs in 1 in 300 measles cases, and may lead to subcutaneous emphysema.

Diarrhoea

Incidence 20–40%. May become persistent and frequently precipitates malnutrition (*see* Section 5.12.A).

Tracheobronchitis

This presents as croup. Laryngeal tissue sometimes becomes necrotic, which may lead to laryngeal obstruction (*see* Section 5.1.A).

Otitis media

This is common, especially in infants. Mastoiditis may develop. It is an important cause of chronic otitis media and hearing impairment (*see* Section 5.1.C).

Stomatitis

There is mucosal inflammation and ulceration with bleeding gums and secondary *Candida albicans* and herpes simplex infections. Stomatitis causes difficulty in eating and worsens malnutrition. Cancrum oris (noma) may develop.

Xerophthalmia
Vitamin A deficiency may combine with measles to precipitate xerophthalmia and blindness (*see* Section 5.10.A).

Malnutrition
Malnutrition secondary to measles results from anorexia and poor nutrition following infection. Mortality is high (> 15%) (*see* Section 5.10.B).

Tuberculosis
Tuberculosis, including tuberculous meningitis, may first be noticed in the post-measles period (*see* Section 6.1.N).

Encephalitis
- **Acute allergic encephalitis:** this is a demyelinating disorder and the most common CNS complication of measles. Onset is often in the second week as exanthema is clearing. It occurs in one or two per 1000 cases of measles, and can be fatal. Virus is not found in the brain.
- **Acute measles inclusion-body encephalitis:** this results from direct invasion of brain cells by virus (which may be isolated from CSF). There is a more rapid onset if there is immunosuppression or malignancy.
- **Subacute sclerosing panencephalitis (SSPE):** there is a long latent period (several years) between infection and the onset of symptoms. Commonly, measles occurred at an early age. SSPE is characterised by lethargy, psychological changes, myoclonic jerks and mental deterioration, eventually leading to death. Virus has been isolated from brain biopsy specimens.
- Atypical measles may have prolonged fever and present with pneumonia or rarely encephalitis. Rash may or may not appear. Prolonged fever for 2–3 weeks with diarrhoea may simulate enteric fever.

Differential diagnosis
- Other exanthema and drug reactions.
- Koplik's spots are the most helpful diagnostic feature in the prodromal period.

Case assessment and classification
Cases may be classified into:
- uncomplicated measles
- severe measles requiring treatment or urgent referral.

TABLE 6.2.E.1 Clinical features of severe disease

Symptom	Complication
Cough, tachypnoea or indrawing	Pneumonia
Stridor when quiet	Croup, necrotising tracheitis
Severe diarrhoea	Dehydration
Recent severe weight loss	Malnutrition
Corneal damage or Bitot spots	Blindness
Ear discharge	Otitis media, deafness
Lethargy, convulsions	Encephalitis
Inability to drink or eat	Dehydration, malnutrition
Blood in the stools	Dysentery, haemorrhagic measles
Severe stomatitis	Cancrum oris

Danger signs
These include the following:
- breathing difficulty
- cyanosis
- bleeding
- corneal/mouth ulcers
- coma/lethargy
- seizures
- inability to eat or drink.

Management
Mild measles
- Give small frequent feeds. Infants should continue breastfeeding. Extra energy should be provided by adding vegetable oil or sugar to cereals (1 teaspoon of each). Follow-up nutritional support is needed.
- Give paracetamol for temperature > 39ºC. Saline drops for blocked nose.
- Maintain oral hygiene by rinsing the mouth several times daily. Apply 1% gentian violet to mouth sores. Treat oral thrush with nystatin drops.
- If mouth ulcers are secondarily infected, give an antibiotic (penicillin or metronidazole orally for 5 days).
- If the mouth is too sore to feed or drink, a nasogastric tube may be required.
- Maintain ocular hygiene for purulent conjunctivitis, with daily washings with sterile 0.9% saline or boiled water (using cotton-wool swabs) and the application of tetracycline eye ointment three times daily. **Never use topical steroids.** Consider using protective eye pads.
- **Vitamin A treatment** of children with measles in developing countries has been associated with decreased morbidity and mortality rates. The dose is 100 000 IU as a capsule (in children under 1 year old) or 200 000 IU (in those over 1 year old). **Give a second capsule the next day.**
- Give oral rehydration solution (ORS) for diarrhoea.
- Give an oral antibiotic (co-trimoxazole, amoxicillin, ampicillin) if there is a clear indication of lower respiratory tract infection (*see* Section 5.3.A).
- Admit the child to hospital if they show signs or symptoms of severe measles.

Severe measles
Admit the child to hospital and isolate them. Airborne transmission precautions are indicated for 4 days after the onset of rash in otherwise healthy children, and for the duration of illness in immunocompromised patients.

In addition to the care for mild measles described above:
- Give parenteral antibiotics for pneumonia or septicaemia (e.g. benzylpenicillin or ceftriaxone/cefotaxime if available). Give (flu)cloxacillin plus gentamicin or cefuroxime (if available) if *Staphylococcus aureus* is suspected. If stridor associated with fever is present use ceftriaxone/cefotaxime (if available) or chloramphenicol. Rapidly spreading pulmonary tuberculosis may be difficult to distinguish from a progressive pyogenic pneumonia.
- Give oxygen as required to keep $SpO_2 \geq 94\%$.
- Croup: nebulised adrenaline, 1 mL adrenaline (1 in 1000) mixed with 1 mL of saline every 2 hours, **careful observation** (*see* Section 5.1.A, which also describes the use of oral steroids or nebulised budesonide, either of which can be life-saving in this situation).
- Diarrhoea: give oral rehydration and appropriate

antibiotic if the child passes bloody stools. Persistent diarrhoea requires nutritional support.
- Otitis media: give antibiotics and maintain regular aural hygiene. Screen for hearing impairment during follow-up.
- Xerophthalmia: use protective eye pads, and give vitamin A capsules (see above).
- Malnutrition: treat according to management guidelines (*see* Section 5.10.B).
- Encephalopathy: follow the management guidelines for coma and convulsions (*see* Section 5.16.A and Section 5.16.E).

Prevention and follow-up
- Give 'normal immunoglobulin' (if available) for susceptible immunocompromised contacts of measles cases or those under 1 year old. It is given intramuscularly to prevent or modify measles in a susceptible child within 6 days of exposure. The usual recommended dose is 0.25 mL/kg given intramuscularly; immunocompromised children (e.g. those with HIV) should receive 0.5 mL/kg intramuscularly (the maximum dose is 15 mL).
- Improve vaccination coverage (*see* Section 1.17).
- Give a follow-up vitamin A dose (after 2 weeks) if the child is malnourished or has an eye disorder.
- Measles control by immunisation is one of the most important public health interventions in reducing child mortality. If a child with measles is admitted, immunise all other unimmunised children under 6 months of age in the hospital, with a follow-up second dose in all aged 6–9 months as soon after 9 months as possible. A second dose is given at 12–15 months of age.

6.2.F Mumps

BOX 6.2.F.1 Minimum standards
Measles, mumps, rubella (MMR) vaccination two-dose schedule.

Introduction
Mumps is a systemic disease characterised by swelling of one or more of the salivary glands, usually the parotid glands. It is caused by a virus of the paramyxovirus family (which also includes measles and parainfluenza). The virus is spread by airborne droplets through the respiratory tract, mouth and possibly the conjunctivae and urine, and is present in saliva, CSF, blood and urine. Other viruses and bacteria (cytomegalovirus, parainfluenza virus types 1 and 3, influenza A virus, coxsackieviruses and other enteroviruses, human immunodeficiency virus (HIV), *Staphylococcus aureus* and non-tuberculous *Mycobacterium*) may also cause parotitis.

Clinical presentation
- The incubation period is 14–24 days. Onset is with painful swelling of parotid glands, fever, general malaise, and occasionally headache. Parotid swelling may be unilateral at first, followed a couple of days later by swelling of the opposite parotid gland, with pain on opening the dry mouth.
- Mild meningoencephalitis is common and usually neither serious nor recognised clinically. There may be nausea and vomiting, and abdominal pain.
- Orchitis presents with fever and tender oedematous swelling of the testis. In 10–20% of cases the second testicle may be affected. However, infertility is rare.
- Differential diagnosis of parotitis includes cervical adenitis, pyogenic parotitis, recurrent parotitis, tumours of the parotid and tooth infections.
- Mumps orchitis can mimic hernias, tumours, haematomas, epididymo-orchitis and testicular torsion.

Complications
Complications include oophoritis, mastitis, pancreatitis, nephritis, myocarditis, thyroiditis, labyrinthine disturbance, painful swelling of the lacrimal glands, optic neuritis, uveokeratitis, rapid loss of vision, arthritis, jaundice, pneumonia and thrombocytopenia. Transient or permanent unilateral nerve deafness has been reported. Infection during pregnancy very rarely causes disease of the fetus (e.g. aqueductal stenosis, hydrocephalus).

Management
Symptomatic treatment includes analgesics, fluids, and scrotal support for orchitis. Antibiotics are usually not warranted for the uncomplicated disease, but each complication should be treated on its own merits with antibiotics (in the case of pneumonia or wherever a secondary bacterial infection is suspected), or with appropriate local treatment and monitoring. The value of corticosteroids for orchitis is not established.

Prevention
Measles, mumps, rubella (MMR) immunisation is routine in well-resourced countries, and has reduced mumps by over 90%. The recommended two-dose vaccine schedule has an effectiveness of approximately 90% (range 88–95%).

6.2.G Poliomyelitis

BOX 6.2.G.1 Minimum standards
- Immunisation.
- ABC, including airway protection if there is bulbar palsy.
- Public health measures.
- Bed rest and physiotherapy.
- Nutritional support and hydration.
- Nasogastric feeding and airway protection if there is bulbar palsy.

Introduction

Poliomyelitis is caused by polioviruses type 1, 2 and 3, which are ingested and then multiply in the tonsils and Peyer's patches of the gut. In most cases, infection is contained at this point and the child is asymptomatic.

Due to both vertical and mass vaccination campaigns, the number of reported cases has fallen by 90% since 1988. Wild poliovirus is now mainly found in Afghanistan and a few countries in sub-Saharan Africa.

Severity

Minor illness

This is associated with viraemia and non-specific symptoms, such as nausea, vomiting, abdominal pain and sore throat.

Major illness

Non-paralytic poliomyelitis

This occurs in a minority of symptomatic children. Incubation period is 10–14 days and symptoms include: fever, headache and two to five days later, signs of meningeal irritation with severe pain and stiffness of neck, back and limbs.

Paralytic poliomyelitis

- Paralysis occurs within the first 2 days of major illness.
- It can affect any muscles, but particularly large ones and those of the lower limbs.
- Asymmetrical paralysis, flaccid muscles and absent tendon reflexes are characteristic. There is intact sensation. Paralysis is maximal within 3–5 days of onset, and rarely extends once the temperature has settled.
- In **bulbar form**, the involvement of cranial nerve nuclei and vital centres in the brainstem results in paralysis of the facial, pharyngeal, laryngeal and tongue muscles, causing swallowing difficulties, aspiration and respiratory failure.
- Hypertension may occur, as well as transient bladder paralysis.

Diagnosis

CSF initially shows neutrophil predominance, but after 5–7 days is mainly lymphocytic. CSF protein levels are normal or slightly elevated. CSF glucose levels are normal. Virus can be isolated from throat and stool for up to 3 months after onset. The differential diagnosis includes other causes of acute flaccid paralysis (*see* Section 5.16.F).

Prognosis

- This depends on the extent of paralysis and the quality of care during the acute phase.
- Early identification of and intervention for respiratory and bulbar paralysis will reduce mortality to 5–10%.
- With appropriate physiotherapy, improvement in the function of paralysed muscles can occur for up to 18 months.
- Factors that adversely affect outcome include intramuscular injections, muscle fatigue, corticosteroid therapy and immunocompromised states. Removal of tonsils or teeth during the incubation period increases the risk of bulbar paralysis.

Management

Acute phase

- Absolute bed rest is mandatory. Avoid intramuscular injections and exercise.
- Analgesics should be given for severe pain. Keep paralysed muscles in a neutral position to prevent contractures.
- Gentle passive exercises and warm compresses should be used to help to relieve pain. Active exercises are introduced a few days after the temperature has settled.
- Respiratory paralysis requires ventilatory support (if available) (*see* Sections 1.25 and 8.3).
- Bulbar paralysis requires nasogastric tube feeding and, to protect the airway, may require tracheostomy.

Convalescent phase

- Aim to improve motor function, prevent deformities and generally reintegrate the child into society.
- Encourage active participation by the parents in the rehabilitation process. The educational and emotional needs of the child must not be neglected. The services of an orthopaedic surgeon and an orthoptist may be required.
- *See* Sections 4.2.C, 4.2.D and 4.2.E for further information on the long-term care of children with a disability.

Prevention

See Section 1.17 on immunisation.

6.2.H Rabies management and prevention after animal bites

BOX 6.2.H.1 Minimum standards
- Palliative care, including morphine.
- Wound care.
- Rabies vaccine.
- Rabies immunoglobulin.

Rabies encephalitis

Furious and paralytic (dumb) forms of human rabies can occur. Furious rabies is characterised by agitation, hyperexcitability and hydrophobia, which is due to spasms of the inspiratory muscles, accompanied by an inexplicable feeling of terror. Spasms occur on attempting to drink water or from a draught of air. Flaccid paralysis without hydrophobia occurs in some patients, but this paralytic rabies is rarely recognised. It is likely to be misdiagnosed as another encephalitis or cerebral malaria. Once symptoms of encephalitis have begun there is no treatment. The disease is always fatal in Asia, Africa and Europe. A very few patients have survived infection after contact with bats in the Americas. North and South American bat rabies viruses appear to be less pathogenic.

Management

The treatment of established rabies is palliative. Sedatives (e.g. diazepam, midazolam) and strong analgesics (e.g. morphine) may be given parenterally to control symptoms and relieve anxiety. An IV infusion assuages the feeling of thirst. Relatives and staff should wear gloves when handling the child, their vomitus or their saliva. Close attendants are at risk of exposure to the virus, but there is no documented case of transmission of rabies to a carer. However, if anti-rabies vaccine is available it should be offered to them, but rabies immunoglobulin (RIG) is not needed.

Rabies prophylaxis

Dog bites are the usual cause of rabies in humans, but cats, foxes, bats, jackals, wolves, mongooses and domestic mammals may also transmit the infection.

Estimating the risk of exposure to rabies

1 Is there a bite wound with broken skin? Have mucous membranes or an existing skin lesion been contaminated by virus in the animal's saliva? Intact skin is a barrier against the virus.
2 How did the animal behave? An unprovoked attack by a frantic dog is a high risk, but so is contact with a paralysed animal, or an unusually tame wild mammal.
3 Is rabies known to occur in the biting animal species?
4 Regularly vaccinated animals are unlikely to be rabid, but vaccinated dogs or cats can transmit the infection.
5 Try to have the animal's brain examined for rabies. If this is not possible, the animal may be kept under safe observation, but post-exposure treatment must not be delayed. If the animal is still healthy after 10 days, vaccine treatment of the patient can be stopped.

Post-exposure treatment

Table 6.2.H.1 lists the criteria for initiating treatment. All three parts of post-exposure therapy are always **urgent**. The aim is to chemically kill or neutralise the rabies virus at the wound site before it can enter a nerve ending and travel to the brain. Neutralising antibody is provided by local injection of rabies immunoglobulin, or it may be present already in previously vaccinated individuals.

1 Wound care: this is important for all bites, irrespective of the rabies risk.
2 Rabies vaccine (active immunisation).
3 Rabies immunoglobulin (RIG) is passive immunisation which provides antibody locally for the first week, until the vaccine-induced antibody appears.

Wound care

- Scrub and flush the lesion repeatedly and energetically with **soap or detergent and water.** Remove any foreign material. Local analgesia may be necessary.
- Apply povidone iodine (or 70% ethyl alcohol, but this is painful).
- Do not suture the wound, or at least delay suturing.
- Give tetanus immunisation if appropriate.
- Treat bacterial infection of wounds with an oral antibiotic, such as amoxicillin/clavulinic acid or tetracycline.

Rabies vaccine

Active immunisation with vaccine should be given whenever there is a risk from contact with a suspect rabid animal. Rabies vaccines are suitable for people of all ages, including pregnant women.

Vaccines accredited by the WHO include the following:

- Purified chick embryo cell vaccine (PCEC) (Rabipur®, RabAvert®) (1.0 mL/ampoule).
- Purified vero cell vaccine (PVRV) (Verorab®) (0.5 mL/ampoule).
- Purified duck embryo vaccine (PDEV) (Vaxirab®) (1.0 mL/ampoule).
- Human diploid cell vaccine (HDCV) by Sanofi (1.0 mL/ampoule).

These vaccines are interchangeable, so a change may be made to a different vaccine during a course of treatment.

The side effects of these vaccines are mild local or non-specific generalised symptoms. Transient maculopapular or urticarial rashes are occasionally seen.

Other vaccines

1 Tissue culture rabies vaccines not listed above should be used according to the manufacturer's instructions.
2 Vaccines of nervous tissue origin (e.g. Semple vaccine and suckling mouse brain vaccine) should only be used if no other vaccine is available.

*Three post-exposure regimens (***see *Table 6.2.H.2)***

Standard five-dose intramuscular (IM) 'Essen' regimen

- Days 0, 3, 7, 14 and 28: Inject one IM dose (1 mL or 0.5 mL) into the deltoid or antero-lateral thigh in small children. Do not inject into the gluteal region.

Economical four-site intradermal (ID) regimen

The intradermal dose is **0.1 mL per site for vaccines containing 0.5 mL/ampoule** (e.g. Verorab®), and **0.2 mL per site for vaccines containing 1 mL/ampoule** (e.g. Rabipur®).

- Day 0: draw up a whole ampoule of vaccine into a 1-mL (Mantoux-type) syringe. Give intradermal injections at four sites (deltoid, and either thigh or suprascapular areas) using all of the vaccine.
- Day 7: give an intradermal dose (**0.1 mL or 0.2 mL**) at two sites (deltoid areas).
- Day 28: give one intradermal dose.

Practical points

- Intradermal injections should raise a **papule** as with BCG vaccine.
- Inject using strict aseptic precautions. If ampoules are shared, use a new **sterile needle and syringe** for each patient. If there is difficulty in injecting 0.2 mL intradermally, withdraw the needle and inject the remainder at an adjacent site.
- **Do not waste vaccine.** Ampoules shared between patients must be stored at 5°C and used on the same day.
- If few patients are treated, on day 0 ask the patient to bring their relatives and friends for pre-exposure vaccine on day 7.
- If vaccine is very scarce or unaffordable, and 1-mL vaccines (e.g. Rabipur®) are used, half the dose (i.e. 0.1 mL per intradermal site) may be used.
- The timing of the final dose can be varied for economy. A clinic could assign 1 or 2 days a week for intradermal rabies vaccination for the day 28 doses and pre-exposure immunisation (see below).
- This is the **most economical** rabies post-exposure regimen both for the healthcare provider and for the patient.
- This regimen is as immunogenic as IM vaccination, and may become the treatment of choice in Asia and Africa.

Economical two-site ID regimen

The **intradermal dose is 0.1 mL per site for vaccines containing 0.5 mL/ampoule** (e.g. Verorab®). The equivalent dose is **0.2 mL for vaccines containing 1 mL** (e.g. Rabipur®), but half the dose (i.e. 0.1 mL per site) is used.

- Days 0, 3, 7 and 28: give an intradermal dose at two sites (deltoids).

The same precautions for intradermal use as described above apply. This regimen is less economical if few patients are being treated. It has mainly been used in large clinics.

Rabies immunoglobulin (RIG)

- Passive immunisation with RIG is recommended to accompany vaccine following contact with suspected rabid animals where the skin has been broken or mucous membranes have been contaminated (*see* Table 6.2.H.2).
- It is vital for bites with a high risk of infection (on the head, neck or hands) or for multiple bites.
- If supplies are limited, ensure that the high-risk, severely exposed patients have access to RIG.
- If RIG is not available immediately, it should be given up to 7 days after the first dose of vaccine. After that it is no longer needed.
- RIG is not required if a course of vaccine has been completed previously.

Dosage: equine RIG (40 IU/kg) or human RIG (20 IU/kg) is infiltrated into and around the wound on day 0. If this is not anatomically possible (e.g. on a finger), inject any remainder IM, at a site remote from the vaccine site, but not into the gluteal region.

- Skin tests are **not** useful for predicting anaphylactoid reactions to equine RIG, and should not be used.
- In very rare cases there may be **anaphylaxis**.

*Anaphylaxis treatment (***see also *Section 5.1.B)***

Adrenaline (epinephrine) intramuscular treatment is essential.

Dosage:

- Age < 6 years: 150 micrograms or 0.15 mL of 1:1000 (1 mg/mL).
- Age 6–12 years: 300 micrograms or 0.3 mL of 1:1000.
- Age > 12 years: 500 micrograms or 0.5 mL of 1:1000.

The dose can be repeated at 5-minute intervals if necessary.

In addition, if available give the following:

Chlorpheniramine maleate IM or by slow IV injection

Dosage:

- Age 6 months to 6 years: 2.5 mg.
- Age 6–12 years: 5 mg.
- Age > 12 years: 10 mg.

Hydrocortisone sodium succinate by slow IV injection or IM

Dosage:

- Age 1–5 years: 50 mg.
- Age 6–12 years: 100 mg.
- Age > 12 years: 200 mg.

Post-exposure treatment for previously vaccinated adults

Thorough wound care and vaccine treatment are always **urgent** following possible exposure to a rabid animal. Patients who have previously had a complete pre-exposure (three doses) or post-exposure course of vaccine only require a short booster course, and RIG is not necessary.

*Two post-exposure booster regimens (***see *Table 6.2.H.2)***

Standard two-dose IM regimen

- Days 0 and 3: inject one IM vaccine dose.

Economical single-day four-site ID regimen

- Day 0: Give 0.1 mL intradermal injections at four sites (deltoids, and either thigh or suprascapular areas).
- The intradermal dose is 0.1 mL, which is sufficient for vaccines of any volume. For Verorab® (0.5 mL/ampoule) a whole ampoule is used.
- For 1 mL vaccines, the total dose is half an ampoule. **Do not waste vaccine.** Ampoules may be shared between patients or used as pre-exposure prophylaxis for relatives, hospital staff, etc. on the same day. **See above for precautions when sharing ampoules.** If the ampoule cannot be shared, give the whole 1 mL to the patient at four sites, as for the primary four-site intradermal regimen described above.

Pre-exposure treatment

Pre-exposure vaccination is the best means of rabies prophylaxis. No one who has had pre-exposure treatment and a post-exposure booster injection is known to have died of rabies.

Indications for pre-exposure rabies prophylaxis

People working with dogs, bats or other wild mammals should be immunised. Anyone in an area where dog rabies is enzootic is at risk of infection, especially children. Ideally, rabies should be included as part of the routine Expanded Programme on Immunisation (EPI). Pre-exposure vaccine should be given whenever it is affordable to residents of dog rabies areas, and should be strongly encouraged if RIG may not be available locally.

Pre-exposure three-dose regimen (see Table 6.2.H.2)

Days 0, 7 and 28: Inject one dose of a vaccine IM (1 ampoule) or intradermally (0.1 mL). Variation in timing does not matter. The final dose may be given from day 21 to months later, but aim for a total of three doses. Having had one or two doses is still an advantage if the individual is exposed to rabies in the future, especially if RIG may not be available.

- Patients on chloroquine, steroids or other immunosuppressive drugs should have IM not intradermal injections for pre-exposure treatment.
- Patients who have been vaccinated should keep a record of their immunisations.
- Routine booster doses are only recommended for people at high occupational risk of exposure.
- If contact with a rabid animal occurs, **post-exposure booster vaccine treatment is still required**.

TABLE 6.2.H.1 Recommended criteria for post-exposure treatment

Type of exposure	Criteria	Action
No exposure*	Touching animals, or being licked on intact skin	No treatment
Minor exposure, WHO Category II	Nibbling (tooth contact) with uncovered skin, or minor scratches or abrasions without bleeding	Start vaccine immediately
Major exposure, WHO Category III	Single or multiple bites or scratches that break the skin, or licking on broken skin, or licking or saliva on mucosae, or physical contact with bats	Immediate rabies immunoglobulin and vaccine
Severe exposure, WHO Category III	Bites on the head, neck or hands, or multiple bites	Immediate rabies immunoglobulin is mandatory with vaccine

For all cases:

- Stop treatment if the dog or cat remains healthy for 10 days.
- Stop treatment if the animal's brain is shown to be negative for rabies by appropriate investigation.

*The confusing term 'WHO Category I' should be avoided, as misunderstanding leads to unnecessary treatment.

Summary

- The only treatment for rabies encephalitis is palliative care.
- Rabies can be prevented by education about the dangers of animal contact, the need for vaccination of pets, first-aid cleaning of wounds with soap, and the need to attend a clinic for vaccine.
- Pre-exposure vaccination should be encouraged, especially for children and if RIG is not available locally.
- Post-exposure prophylaxis is urgent.
- If rabies vaccine is unaffordable or in short supply use robust economical ID regimens that are suitable for use globally.

This scheme is a modification of WHO recommendations.

TABLE 6.2.H.2 Selected standard intramuscular and economical intradermal rabies vaccine regimens

Vaccine regimen and route	Days of injection (number of sites injected denoted by superscript number)	Visits to clinic	Total vaccine used (ampoules)
Pre-exposure:			
IM	0 7 28	3	3
ID 0.1 mL‡	0 7 28	3	< 1–3
Post-exposure (+ RIG day 0):			
IM five-dose	0 3 7 14 28	5	5
ID four-site†	04 7^2 28	3	< 2–3
Post-exposure booster if previous vaccine course:			
IM	0 3	2	2
ID*	0^4	1	1 (or < 1)*

IM, intramuscular; ID, intradermal.

* 0.1 mL/site, whole ampoule used for 0.5 mL vaccines. For 1 mL ampoules share between two, or alternatively use the whole dose to avoid wastage.

† Intradermal doses are 0.1 mL/site for PVRV vaccine (0.5 mL/ampoule) or the equivalent dose, 0.2 mL/site of injection, for PCECV vaccine (1.0 mL/ampoule).

‡ Intradermal doses are all 0.1 mL/site of injection.

6.2.I Viral haemorrhagic fevers

BOX 6.2.I.1 Minimum standards
- ABCD.
- Management of shock.
- Blood transfusion and clotting factors.
- Isolation and infection control.
- Public health measures.

Introduction

Viral haemorrhagic fevers (VHFs) are a group of severe infections caused by viruses that normally affect animals. Human infection is characterised by high fever and, in a proportion of cases, haemorrhage. Animal hosts such as rodents are usually asymptomatic and are often infected with virus from birth, excreting it in urine or body fluids throughout life.

In primary cases, transmission to humans occurs by a variety of routes, such as food contaminated with urine (e.g. Lassa, Junin, Machupo and Hantaan fevers) via arthropod vectors such as ticks (e.g. Crimean-Congo and Omsk fevers) or mosquitoes (e.g. Rift Valley fever). The hosts for Ebola and Marburg haemorrhagic fevers are not yet known.

Humans with disease are usually highly infectious. Most VHFs cause severe disease with a high mortality, especially following human-to-human spread (secondary cases). Some (e.g. Lassa fever) may also cause asymptomatic or mild illness.

Symptomatic disease is commonly mistaken for other febrile illnesses, typically malaria, typhoid fever or *Shigella* dysentery, which fail to respond to treatment. Individual VHFs are geographically restricted in distribution. As with all geographical illnesses, clinicians only need to know of those present in the local area. VHFs are fortunately rare.

Lassa fever

- Distribution: West Africa (Nigeria, Sierra Leone, Liberia and Guinea).
- Host: Mastomys rat (habitat is rural).
- Transmission:
  - **Primary:** mainly from contact with host (rat) urine. Food may be contaminated.
  - **Secondary:** transmission from patient to carer, or to hospital and laboratory staff is common, particularly from haemorrhagic cases. Maternal illness is particularly severe, with a high risk of vertical transmission to the baby (which is invariably fatal).

Prevalence

This disease is relatively common. Most primary human infections are not severe, and many are subclinical. Childhood seroprevalence in Sierra Leone can be as high as 20% in some rural villages. Outbreaks may occur in displaced communities or when humans enter host habitat.

Clinical features

- High fever (>39°C) with cough and vomiting in 65% of hospital cases.
- Abdominal pain and diarrhoea are common (around 35% of cases).
- In children, wheeze and pleural effusions are more frequent than in adults.
- Sore throat and pharyngeal ulcers occur less frequently in children than in adults, but are highly suggestive of Lassa fever.
- In children, oedema (especially of the face) and overt bleeding are seen in 10% of cases, and in a febrile child from an appropriate area should suggest Lassa fever.
- At the epicentre of the transmission area, Lassa fever is a common cause of a febrile child with convulsions.

Diagnosis of Lassa fever

Clinical case diagnosis

- An unexplained febrile illness compatible with Lassa fever, in a child from an area of known transmission, with no response of either fever or illness to an anti-malarial drug plus a broad-spectrum antibiotic (e.g. chloramphenicol).
  - Note that malaria parasitaemia in an area of endemic malaria transmission is not sufficient to exclude other causes of fever (e.g. VHF) as the cause of a febrile illness, as many adults and older children may have coincidental asymptomatic malaria parasitaemia as the cause of a febrile illness.

Supportive indirect laboratory tests

- Raised liver transaminases (AST/SGOT) (in adults this reflects a poorer prognosis).
- Low initial white blood cell counts, but often a normal platelet count.

Confirmation of diagnosis

- **Positive specific IgM serology** (on admission only 50% of cases are positive).
- **Rising IgG titres** to Lassa on acute and convalescent serum.
- Isolation of virus: this is rarely appropriate and, **due to the high risks of laboratory infection, samples should not be taken without senior expert advice**.
  - Samples must be marked as high infection risk, ideally with standard yellow hazard tape, and sent in two sealed plastic bags. Samples should only be taken if laboratory staff are aware of the potential risks, and are able to take the necessary precautions to handle such specimens safely. The laboratory should be informed that the specimen has been sent.

Management

- Appropriate symptomatic management of fever, distress and pain.
- Fluid and nutritional requirements.
- Supportive care includes oxygen (if hypoxic) and initial IV volume replacement if the patient is hypovolaemic (*see* Section 5.5).
- Blood transfusion may be required for a falling PCV or haemorrhage. Fresh-frozen plasma (FFP) may not be of benefit, as inhibitors of clotting factors may cause bleeding.
- **Early ribavirin can improve the prognosis in severe disease, but is very expensive.**

Infection control

See below and Section 1.2.

Ebola

- Distribution: Central Africa (Sudan, Democratic Republic of the Congo, Gabon, Cote d'Ivoire, Uganda) and West Africa (Guinea, Liberia and Sierra Leone).
- Host: the main animal reservoir is unknown.
- Transmission:
  - **Primary:** infection occurs mainly in adults trekking in tropical Central African forests. Transmission from primates to humans has been recorded.
  - **Secondary:** patients with advanced disease are viraemic and highly infectious. Once in a human host, transmission to carers, hospital and laboratory staff is frequent (30% of doctors developed Ebola during an outbreak in Kikwit, Democratic Republic of the Congo). However, once effective infection control measures have been implemented, secondary cases are rare.

The disease is invariably severe, with a high death rate, but only 20% of cases in the Democratic Republic of the Congo outbreak were under 15 years of age. Children are at low risk in the community, and boys have half the incidence of girls, possibly because they are less involved in the care of sick adults.

Invariably, in children, there is a history of contact with a primary case, and an outbreak of an illness that could be Ebola is present in the hospital and/or community. Post-mortem transmission does occur, possibly through skin contact.

Prevalence

Prevalence is low: the disease occurs sporadically in well-localised outbreaks.

Clinical disease (data for adults)

- Fever is invariably present, and diarrhoea occurs in 85% of cases. This is bloody in 20% of cases, and can be confused with *Shigella* dysentery.
- Vomiting and abdominal pain are common (75% of cases).
- Headaches, myalgia or arthralgias are reported in 50% of cases.
- Sore throat occurs in 50% of cases, and is a distinguishing feature, as is conjunctival injection (45%).
- A maculopapular rash, although poorly visible on black African skin, is common.
- Cough occurs in 10% of cases.
- Bleeding is seen in 40% of cases, and is usually either gastrointestinal, oral, at injection sites or as skin petechiae. This is a major diagnostic sign.
- Hospital mortality is around 80%. Recovery starts 2 weeks into the illness.

Diagnosis of Ebola

Clinical diagnosis

- **Suspected clinical case (during epidemic):** any febrile illness associated with haemorrhage. No contact history is required.
- **Probable case (during epidemic):** a febrile illness occurring within 3 weeks of contact with a case of Ebola

or

  a febrile illness in which three or more of the above clinical features are present.
- **Possible clinical case (non-epidemic):** an unexplained severe febrile illness, particularly with haemorrhage, in an area of Ebola transmission, with no response to an antimalarial drug plus a broad-spectrum antibiotic (e.g. chloramphenicol).

Indirect laboratory tests supportive of diagnosis

- Raised liver transaminases (AST/SGOT).
- Low or normal initial white blood cell count.

Confirmation of diagnosis

Early serological tests were difficult to interpret, but newer specific IgM ELISAs may allow diagnosis of acute cases on a single positive test. However, IgM is not always positive at presentation.

- **Specific IgG (by ELISA) rises too slowly to be used as a test of acute infection, but may be useful in epidemiological surveys.**
- **Isolation of the virus is not appropriate outside a specialised laboratory.**
- **A post-mortem skin biopsy (in formalin at room temperature) is not infectious, and can allow a diagnosis to be made using immunohistochemistry.**

Samples need to be marked as **high infection risk**, ideally with standard yellow hazard tape, and sent in two sealed plastic bags. Samples should only be taken where laboratory staff are aware of the potential risks and can take the necessary precautions to handle such specimens safely. The laboratory should be informed that the specimen has been sent.

Infection control

See below and Section 1.2.

Notification

Consider formal identification of a possible outbreak of Ebola if there is a new illness of high mortality in adults in a recognised area of transmission, particularly if hospital-acquired secondary cases have occurred.

Management

- Apart from supportive care, particularly with regard to adequate fluid and nutritional intake, there are no specific treatments that modify the course of the illness.
- Antimalarial and antibiotic therapy should be given routinely, directed at treating possible alternative diagnoses (e.g. shigellosis, typhoid).

Infection control of VHFs

At increased risk are laboratory staff, midwives, and those staff and family members who are handling body fluids and excreta. High-risk patient groups are those with active haemorrhage, those who are confused and agitated, and pregnant mothers.

Barrier nursing

- Secondary spread is usually by contact with blood, urine-infected secretions, used needles or stool, but

some viruses (e.g. Ebola) have also been found on patients' skin.
- There is little clinical evidence of respiratory aerosol spread for the VHFs, although virus may be present in the nose and oropharynx.
- Surgical and obstetric procedures carry a particularly high risk of infection for staff.
- **Transmission is substantially reduced by strict adherence to barrier nursing, disinfection of excreta, and clear labelling of 'at risk' specimens.**
  - **Only essential samples should be taken.**
  - The laboratory should be aware of and prepared to receive specimens.
  - Family contact should be restricted to the minimum required for care.
  - Soap and water should be available for hand washing before and after patient contact.
  - **For all carers, including family members, careful barrier nursing with gloves and plastic aprons is mandatory, and stocks of these must be readily to hand.**
  - Hospital staff and carers are advised to wear double gloves, plastic aprons, gowns (with boots), a head covering, HEPA-type face masks and goggles or eye shields. However, in a tropical setting these can only be tolerated for a few hours at a time, so arrange work to account for this.
  - If outer gloves are not changed between patients, gloved hands should be washed in 1:100 bleach.
  - Appropriate disposal of excreta and clinical waste is essential, so incinerate burnable clinical waste daily, and flush excreta down a dedicated toilet, having added 1:10 household bleach (0.5% chlorine) first.

(a) Disinfect bedpans and urine bottles with 1:10 bleach.
(b) Disinfect beds and equipment with 1:100 bleach.
(c) Disinfect the dead with 1:10 bleach before burying in a sealed plastic bag.

Consider using seropositive staff to nurse these patients. The identification and involvement of these staff has been successful in some outbreaks. They must follow the ward infection control measures. Remember that convalescent patients may continue to excrete virus for many months (in both Lassa and Ebola).

Fear among staff and the community needs to be addressed openly, and staff and carers must be educated about the role of barrier nursing measures, and the risks involved if these are not implemented.

Careful attention should be paid where local culture and customs (e.g. burial rites, 'widow cleansing', care of the sick, etc.) cause 'high-risk' activity. Education and participation of community leaders is important to ensure safe practice.

Which patients should be isolated?

Isolation of all patients who are likely to have a VHF on admission

- The different categories of **clinical diagnostic probability** are based on fever, contact history, haemorrhagic and non-haemorrhagic clinical signs, initial laboratory tests and geography. These categories are as follows:
  - suspected clinical VHF
  - probable VHF
  - illness probably not a VHF.
- Distinguishing signs (e.g. conjunctivitis in Ebola) are particularly helpful for categorising cases.

Isolation of suspected and probable cases on presentation to hospital

- Isolation should ideally be in single rooms, but an identified separate communal ward for probable and confirmed cases is often all that is available.
  - This should have an adjoining toilet, for safe waste disposal.
  - There should be a separate adjoining area for changing into and storing isolation clothing.
  - Supplies of gloves, gowns, etc. need to be readily available.
  - Hand-washing facilities are mandatory.
- The area should be marked as 'access restricted' to only those trained in VHF isolation precautions, and attention should be paid to screening windows.

Written infection control measures should be clearly displayed on the ward.

Differential diagnosis of VHFs

- The important differential diagnoses are, depending on geography, falciparum malaria, typhoid, meningococcaemia, *Shigella* or non-specific bloody dysentery, severe sepsis, leptospirosis, plague, yellow fever and dengue.
- It is crucial to exclude other treatable disease in patients presenting with symptoms suggestive of a VHF, and to initiate therapy directed at these.
- All patients should therefore receive a broad-spectrum antibiotic (e.g. chloramphenicol), and in some areas an antimalarial drug.
- In an endemic area, or during a known outbreak, the clinical diagnosis of a VHF is relatively straightforward. Difficulty arises when sporadic or new cases occur.
- A history of contact with a case in the previous 3 weeks and a history of recent travel to a transmission area should be sought. As no VHF has an incubation period longer than 3 weeks, travellers or contacts of known or suspected cases who are well after this period are unlikely to be infected.

Further reading

The following very practical resources are for those who require additional VHF control information.

Medicins Sans Frontieres 2014 on the Ebola epidemic in West Africa www.msf.org.uk/ebola

WHO fact sheet on Ebola 2014 www.who.int/mediacentre/factsheets/fs103/en/

World Health Organization Global Alert and Response on the Ebola epidemic 2014. www.who.int/csr/disease/ebola/en/

World Health Organization (1997) *WHO Recommended Guidelines for Epidemic Preparedness and Response: Ebola Haemorrhagic Fever (EHF).* www.fas.org/nuke/intro/bw/whoemcdis977E.pdf

6.2.J Yellow fever

BOX 6.2.J.1 Minimum standards
- Immunisation.
- Intensive supportive care.
- Blood transfusion.
- Vector control.
- Internationally notifiable.

Introduction

Yellow fever is a flavivirus infection spread by the bite of *Aedes* and other mosquitoes.

Epidemiology

- Yellow fever is currently confined to tropical Africa and parts of South America, especially around the Amazon basin. It does not occur in Asia.
- A reservoir of infection exists in jungle primates, and mosquitoes which bite the animals in the tree canopy.
- Three transmission cycles are recognised:
  - sylvatic (jungle), in which a reservoir is maintained among jungle primates by mosquitoes, with humans being infected incidentally
  - intermediate (savannah), the commonest cycle occurring in Africa, in which semi-domestic mosquitoes may cause small epidemics in rural villages
  - urban, in which infected humans introduce infection to urban areas, where the day-biting *Aedes aegypti* flourishes and may cause major epidemics in unvaccinated populations.

Pathophysiology

Symptoms are due to toxic effects on the liver, kidneys and sometimes other organs, such as the heart and brain. Asymptomatic infections may also occur.

Clinical features

- The incubation period is 3–6 days.
- Many patients have an initial febrile illness, with chills and muscle pains, from which they recover.
- Others, after an illness of about 5 days, have a brief period of apparent improvement followed by deterioration and the following complications:
  - vomiting: first bilious and then black ('coffee grounds')
  - jaundice, liver failure and hypoglycaemia
  - bleeding of the gums, nose and stomach
  - proteinuria, oliguria and renal failure
  - delirium and coma.
- Mortality among complicated cases is 20–50%.

Laboratory diagnosis

- Leukopenia, thrombocytopenia, initial haemoconcentration and then haemodilution.
- Raised transaminases and bilirubin levels.
- Abnormal clotting.
- Proteinuria and impaired renal function.
- Rapid detection methods for yellow fever virus include PCR and antigen detection.
- The serum IgM-ELISA assay is 95% sensitive if performed within 7–10 days of clinical onset.
- **A probable case is defined as positive IgM-ELISA taken within days 3–10** of symptoms.
- A confirmed case is defined as a clinically compatible case plus a fourfold rise in antibody titre in a patient with no history of recent yellow fever vaccination and having excluded cross-reactivity with other flaviviruses.
- Post-mortem liver biopsy specimens show mid-zone necrosis of hepatic lobules, often with eosinophilic Councilman bodies. Antigen may also be detected in tissue.

Management

- **Universal cross-infection precautions**, careful nursing and symptom control.
- Nurse suspected patients under permethrin-treated bed nets, as blood may remain infective for mosquitoes up to 5 days after onset.
- Supportive management, fluids, blood transfusion, fresh-frozen plasma, inotropes, dialysis, and ventilation if required.
- No specific antiviral treatment is available. Caution in prescribing and beware risk of bleeding, hepatic and renal impairment. H2-receptor antagonists may reduce risk of gastric bleeding.
- **Suspected cases of yellow fever must be notified within 24 hours** to national public health authorities, which in turn notify the WHO.

Prevention

- Elimination of the breeding sites of *Aedes aegypti* mosquitoes around human dwellings.
- Immunisation of the local population with live attenuated 17D yellow fever vaccine. Immunisation becomes effective after 10 days. Vaccine may be given to children aged 6 months or older unless there are specific contraindications (e.g. if they are immunocompromised).

6.3 Other parasitic infections

6.3.A Systemic protozoal infections

6.3.A.a African trypanosomiasis

BOX 6.3.A.A.1 Minimum standards
- Hydration, nutritional support, and treatment of intercurrent infections.
- Confirm the diagnosis, including lumbar puncture for clinical staging.
- Pentamidine, suramin, melarsoprol, eflornithine and nifurtimox.
- Prednisolone.
- Public health measures and vector control.

Introduction

Gambian trypanosomiasis, caused by *Trypanosoma brucei gambiense*, is a slowly progressive disease of West and Central Africa. Rhodesian trypanosomiasis, caused by *T. b. rhodesiense*, is a subacute infection found in East and Southern Africa. Trypanosomiasis of wild and domestic animals is often caused by other 'subspecies' of *T. brucei* which are indistinguishable morphologically from those that cause human infection.

Transmission

- By the bite of infected tsetse flies (*Glossina*).
- Riverine tsetse (*Glossina palpalis* group) are responsible for transmission of *T. b. gambiense*, chiefly from a human reservoir. Infection may be endemic or epidemic.
- Savannah tsetse flies (*Glossina morsitans* group) are mainly responsible for sporadic transmission of *T. b. rhodesiense* from animals to humans.
- Congenital transmission is also well recognised.

Clinical features

A painful bite lesion (the trypanosomal chancre) may form at the site of the infected bite and last for up to 3 weeks. Among indigenous people in endemic areas, this is more commonly seen in *T. b. rhodesiense* (19%) than in *T. b. gambiense* infections. However, a chancre may be seen in 25–40% of early presentations of *T. b. gambiense* among expatriates. Clinical staging is essential for planning treatment, and depends on evidence of CNS involvement based on lumbar puncture findings.

Haemolymphatic stage 1

- Symptoms of fever and malaise that last for about a week are associated with waves of parasitaemia. Lymph nodes (especially those at the back of the neck in Gambian disease) become enlarged.
- There may be short-lived oedematous swellings of the face or limbs, and sometimes a patchy circular erythematous rash or skin itching.
- Early symptoms are often milder in Gambian disease, and this stage may last for months to years.
- In Rhodesian disease, patients are usually more ill with tachycardia, high fever, hepatosplenomegaly, myocarditis, anaemia and sometimes jaundice.

Meningo-encephalitic stage 2

- Severe headache and altered behaviour are often seen.
- Patients may become apathetic, depressed or frankly psychotic.
- Sleep is disturbed, so that patients are often awake during the night and sleep by day; eventually deep coma results.
- Ataxia and cerebellar signs are frequent.
- Delayed response to pain after deep pressure, the appearance of primitive reflexes and altered tendon reflexes may be seen.
- Death often results from intercurrent infection.

Diagnosis

- In *T. b. rhodesiense* infections, trypanosomes can usually be observed in thick blood films. These are also useful for *T. b. gambiense* infections, but may be negative during periods of low parasitaemia.
- More sensitive methods of examining the blood include microhaematocrit centrifugation, use of the quantitative buffy coat (QBC) technique, and the mini-anion exchange column method.
- When there are enlarged lymph nodes, particularly posterior cervical nodes in *T. b. gambiense* infections (Winterbottom's sign), microscopy of a node aspirate may demonstrate trypanosomes.
- **Serological methods: The card agglutination test for trypanosomiasis (CATT) is useful only for population screening for *T. b. gambiense* infections. Positive results need to be confirmed by the finding of parasites. Other serological tests exist that may be useful for screening suspected cases of *T. b. gambiense*, but are rarely available in resource-limited settings.** Seropositives require parasitological confirmation. Negative serology does not exclude the diagnosis. Always search for

parasites. No serological screening tests are currently available for *T. b. rhodesiense*.

- Treatment depends on evaluation of the stage of infection, so lumbar puncture is essential. Criteria for stage 2 disease in a previously untreated patient include either the presence of trypanosomes in the CSF, or a raised CSF lymphocyte count (> 5 cells/mm^3) in the absence of another cause. CSF protein levels are usually raised. CSF IgM (if available) may be useful as an early marker of CNS invasion.

Treatment

Drug resistance is becoming more widespread. Check local resistance patterns and treatment recommendations.

The drugs used for treatment are toxic. They should only be started after a parasitological diagnosis has been confirmed and, particularly in stage 2 *T. b. gambiense* disease, after the patient's general condition has been improved by attention to hydration, nutrition and intercurrent infections.

T. b. gambiense stage 1

- Give pentamidine isethionate 4 mg/kg IM daily for 7–10 days.
- Children should be given a meal or a sweet drink 1 hour prior to treatment (to reduce the risk of hypoglycaemia), and must lie down for an hour after an injection and have careful checks of pulse and blood pressure (there is a **risk of severe hypotension**).
- **Side effects:** hypoglycaemia (may occur up to 7 days after treatment), arrhythmias, bone-marrow suppression, electrolyte disturbances (low K^+, Ca^{2+}, Mg^{2+}). Monitoring is recommended if possible.

T. b. gambiense stage 2

- **Recommended treatment is nifurtimox–eflornithine combination treatment (NECT).**
- Give nifurtimox 5 mg/kg orally three times daily for 10 days plus eflornithine 200 mg/kg every 12 hours by IV infusion (over 2 hours) for 7 days.
- Second choice, if nifurtimox is not available and the patient is under 12 years of age, is to give eflornithine 150 mg/kg every 6 hours by IV infusion (over 2 hours) for 14 days. If the patient is over 12 years of age, give eflornithine 100 mg/kg every 6 hours by IV infusion (over 2 hours) for 14 days.
- There is a risk of infection and phlebitis at the IV site. Care is needed with regard to sterile procedures and securing the IV line. Change the IV site every 2 days.
- Side effects include **CNS abnormalities (due to nifurtimox), convulsions**, and bone-marrow suppression (due to eflornithine).
- **Relapse after NECT or eflornithine:** Give **melarsoprol**, 2.2 mg/kg/day slowly IV for 10 days. **Encephalopathy occurs in up to 15% of patients treated with melarsoprol, and is associated with a 50% case-fatality rate. Co-administration of prednisolone reduces the risk of encephalopathy to less than 5%. Prior to the first dose of melarsoprol, start prednisolone** orally 1 mg/kg (maximum 40 mg/day) daily for 10 days, then taper and stop over 3 days.
- **Side effects include encephalopathy, peripheral neuropathy, skin reactions including Stevens–Johnson syndrome, and phlebitis.** Note that melarsoprol IV is very painful, particularly if extravasation occurs, and may cause tissue necrosis.

T. b. rhodesiense stage 1

- **Suramin:** initial test dose of 4–5 mg/kg slowly IV over 5 minutes on day 1, then 20 mg/kg slowly IV on days 3, 10, 17, 24 and 31. Maximum single dose 1 g/injection.
- The initial test dose is to reduce the risk of idiosyncratic anaphylactic reactions to suramin. Have IM adrenaline available (*see* Section 5.1.B).
- Test the urine for albumin before each dose, and modify the regime if more than a trace of protein is seen.
- This regime may also be used for **stage 1 *T. b. gambiense* if pentamidine is unavailable.**
- **Side effects include hypersensitivity, nephrotoxicity** (monitor urine albumin levels before each dose, and modify the regime if more than a trace of protein is seen) and peripheral neuropathy.

T. b. rhodesiense stage 2

- **Melarsoprol:** 3.6 mg/kg slowly IV for 3 or 4 days repeated three or four cycles with an interval of 7–10 days between treatment series.
- **Prednisolone:** 1 mg/kg (maximum 40 mg/day) orally daily throughout the course of melarsoprol, then gradually taper and stop. Note that the recommendation for use in *T. b. rhodesiense* stage 2 is largely based on evidence for use in *T. b. gambiense* stage 2.
- Side effects: see previous notes.

Follow-up

- **Notify all cases** so that effective surveillance and public health action is taken.
- All patients should have follow-up lumbar puncture for 2 years (*T. b. gambiense*, lumbar puncture 6-monthly; *T. b. rhodesiense*, 3-monthly for 1 year and then 6-monthly).

  If initially stage 1 but at follow-up:

  (i) CSF 6–19 white blood cells/mm^3: repeat lumbar puncture in 1–2 months.

  (ii) CSF ≥ 20 white blood cells/mm^3: treat as stage 2.

  If initially stage 2, CSF white cell count trend at follow-up is more important than the actual value.
- Drug resistance is increasing – if suspected seek expert advice.

6.3.A.b American trypanosomiasis (Chagas disease)

BOX 6.3.A.B.1 Minimum standards
- Bed nets.
- Vector control.
- Benznidazole.
- Nifurtimox.

Introduction

American trypanosomiasis is potentially life-threatening and is caused by the protozoan parasite, *Trypanosoma cruzi*.

An estimated 10 million people are infected worldwide, mostly in Latin America, where it is endemic. In 2008 it killed more than 10 000 people. It is increasingly being detected in the USA, Canada, many European and some Western Pacific countries.

In Latin America, *T. cruzi* is mainly transmitted by the infected faeces of blood-sucking triatomine bugs. These bugs typically live in the cracks of poorly constructed homes in rural or suburban areas. They become active at night when they feed on human blood by biting an exposed area of skin such as the face, where the bug defecates close to the bite. The parasites enter the body when the person instinctively smears the bug faeces into the bite, the eyes, the mouth, or any break in the skin.

T. cruzi can also be transmitted in the following ways:
- via food contaminated with the parasite through, for example, contact with triatomine bug faeces
- by blood transfusions from infected donors
- by transmission from an infected mother to her newborn during pregnancy or childbirth.

Clinical management

Signs and symptoms

The disease presents in two phases. The initial acute phase lasts for about 2 months after infection. During the acute phase, a high number of parasites circulate in the blood. In most cases, symptoms are absent or mild, but can include fever, headache, enlarged lymph glands, pallor, muscle pain, difficulty in breathing, swelling and abdominal or chest pain. In less than 50% of people bitten by a triatomine bug, the characteristic first visible signs can be a skin lesion or a purplish swelling of the lids of one eye.

During the chronic phase, the parasites congregate in the heart and digestive tract. Up to 30% of patients suffer from cardiac disorders, and up to 10% suffer from digestive (typically enlargement of the oesophagus or colon), neurological or mixed pathology. The infection can lead to sudden death or heart failure caused by progressive destruction of the heart muscle.

Treatment

Benznidazole and nifurtimox are both almost 100% effective in curing the disease if given soon after infection. However, the efficacy of both diminishes the longer a person has been infected. Treatment is also indicated for those in whom the infection has been reactivated (e.g. due to immunosuppression), for infants with congenital infection, and for patients during the early chronic phase. The potential benefits of medication in preventing or delaying the disease should be weighed against the long duration of treatment (up to 2 months) and possible adverse reactions (occurring in up to 40% of treated patients).

Benznidazole and nifurtimox should not be taken by pregnant women or by people with kidney or liver failure. Nifurtimox is also contraindicated in people with a history of neurological or psychiatric disorders. In addition, specific treatment for cardiac or digestive manifestations may be required.

Benznidazole 100 mg tablets

Acute or early chronic phase:
- Full term newborn infant give 5 mg/kg daily in 3 divided doses increasing after 3 days to 10 mg/kg daily if no leukopenia or thrombocytopenia occurs. Treat for 60 days.
- Infant or child, 40 kg body weight give 7.5 mg/kg daily in 2–3 divided doses for 60 days.
- Child > 40 kg give 5 mg/kg daily in 2–3 divided doses for 60 days.

Chronic phase:
Infant or child 5 mg/kg daily in 2–3 divided doses for 60 days.

Nifurtimox Tablets 30, 120 and 250 mg

Acute or early chronic phase:given after meals
- Neonate, infant or child < 40 kg give15–20 mg/kg daily in 3 divided doses for 60 days
- Child > 40 kg 12.5–15 mg/kg daily in 3 divided doses for 60 days

Chronic phase:
Infant or child 8–10 mg/kg daily in 3 divided doses for 60 days.

Vector control and prevention

There is no vaccine for Chagas disease. Vector control is the most effective method of preventing this disease in Latin America. Blood screening is necessary to prevent infection through transfusion.

The WHO recommends:
- insecticide spraying of houses and surrounding areas
- house improvements to prevent vector infestation
- personal preventive measures such as bed nets
- good hygiene practices in food preparation, transportation, storage and consumption
- screening of blood donors
- screening of newborns from infected mothers, and of siblings of infected children to provide early diagnosis and treatment.

6.3.A.c Leishmaniasis

BOX 6.3.A.C Minimum standards

- Public health measures and vector control.

Leishmaniasis: visceral

- Bone-marrow, splenic and lymph-node aspirate.
- Pentavalent antimonials.
- Amphotericin B.
- Paromomycin.

Leishmaniasis: cutaneous and mucocutaneous

- Pentavalent antimonials.
- Topical 15% aminosidine plus 12% methyl benzethonium.
- Ketoconazole.

Introduction

Leishmaniasis is caused by *Leishmania*, a protozoon whose reservoir is in animals, including rodents and dogs, and in some areas (e.g. India) in humans. The vector is the female sandfly.

There are three main clinical types of disease:

- cutaneous (CL)
- mucocutaneous (MCL)
- visceral leishmaniasis (VL) or kala-azar.

Parasite and life cycle

- About 21 of the 30 or more species of *Leishmania* infect humans. They are morphologically similar and can only be differentiated by isoenzyme analysis which identifies the zymodeme in the cultured parasite.
- In animals and humans, *Leishmania* lives in macrophages in the reticulo-endothelial system in the form of amastigotes (Leishman–Donovan bodies). When taken up by the biting sandfly it transforms into a promastigote, which has a flagellum.
- There are two main genera of sandfly responsible for transmission, *Phlebotomus* in the Old World and *Lutzomyia* in the New World (Central and South America). Sandflies breed in organic material in dark moist sites, such as cracks in masonry, termite hills, or leaves on the forest floor. The female obtains her blood meal at night by feeding on animals, and also on humans if they are living or working in the vicinity.

Epidemiology

The Old World comprises Africa, Asia and Europe (collectively known as Afro-Eurasia), plus the surrounding islands. It is used in the context of, and contrast with, the 'New World' (i.e. the Americas and sometimes Oceania). Old world CL and VL are found in the Mediterranean basin, the Middle East, the Sudan, Ethiopia, Kenya, Afghanistan, the Indian subcontinent, and southern regions of the former Soviet Union, and China. Where HIV infection and VL coexist, there are major problems in the treatment of VL. Drug resistance in VL is a serious concern in India and the Sudan. Bihar State has 90% of VL in India and 45% of world cases.

In the New World, CL and MCL are the main forms of infection. VL occurs mainly in North-East Brazil.

Currently, leishmaniasis occurs in four continents and is considered to be endemic in 88 countries, 72 of which are resource-limited:

- 90% of all visceral leishmaniasis cases occur in Bangladesh, Brazil, India, Nepal and Sudan
- 90% of mucocutaneous leishmaniasis cases occur in Bolivia, Brazil and Peru
- 90% of cutaneous leishmaniasis cases occur in Afghanistan, Brazil, Iran, Peru, Saudi Arabia and Syria.

Leishmaniasis is a disease of poverty associated with malnutrition, displacement, poor housing and migration of non-immune people to endemic areas. It is linked with deforestation and urbanisation.

Immunology

- A strong cell-mediated immune (CMI) response is required for control of and recovery from disease. Polyclonal stimulation of B cells results in high levels of IgG.
- Subclinical infection is common. CL usually heals spontaneously, but untreated MCL will progress, and VL will result in death. Development of VL indicates that the host's CMI is unable to control the infection, and if untreated, progressive immunosuppression will develop.
- Death is usually due to a secondary infection (e.g. respiratory tract or gut infection).

Cutaneous and mucocutaneous leishmaniasis

Cutaneous leishmaniasis

The species responsible are *L. tropica*, *L. major*, *L. aethiopica* in the Old World, and *L. mexicana* and *L. amazonensis* in the New World. Single or multiple nodules develop on exposed areas, especially the face or extremities, and usually ulcerate. Most heal spontaneously within months to a year or so, leaving scars.

Mucutaneous leishmaniasis

The species responsible is *L. braziliensis.* A nodule develops initially, as in CL, but at about the time of healing, metastatic lesions occur on mucosal surfaces, such as the nasal mucosa and oropharynx. If these are left untreated, progressive destruction of local tissue occurs.

Diagnosis

- Slit skin smear or aspiration should be undertaken from the raised margin of the lesion (not the base of the ulcer). Material is spread on a slide, dried, fixed in methanol and stained with Giemsa or Leishman.
- If a biopsy is undertaken (e.g. in MCL), impression smears should be done before fixing.
- If available, the specimen should be cultured.

Management

Most CL lesions are self-limiting. Treatment is indicated for

multiple, large and disfiguring lesions and all MCL. Clean the lesion, and give antibiotics if necessary.

Standard treatment for CL and MCL is with pentavalent antimonials (Sb): **sodium stibogluconate** (Pentostam, 100 mg Sb/mL) or **meglumine antimoniate** (Glucantime, 85 mg Sb/mL). **It is essential to remember that the doses of these two drugs are different, because they contain different concentrations of antimony (Sb).** Give 20 mg Sb/kg/day IV or IM in a single dose for 20–28 days depending on the species of *Leishmania* (e.g. MCL requires 28 days or more). The IV infusion is stopped if coughing or substernal pain occurs. Urinary excretion of Sb is rapid (its half-life is 2 hours), although slow accumulation occurs.

For *L. major*, weekly or twice weekly intra-lesional injections of Sb (which are painful) may be administered (1 mL/lesion at four sites per ulcer) to adolescents or adults, using a 1-mL syringe and a fine (24-gauge) needle, for 4–8 weeks. A topical ointment containing 15% aminosidine and 12% methylbenzethonium chloride applied twice daily for 10–20 days may be tried. Efficacy is variable, but it may be combined with intra-lesional Sb injections.

Oral fluconazole, 3 mg/kg once daily (maximum 100 mg) for up to 6 weeks, may be effective, but there is a **danger of liver dysfunction**.

In areas where there is antimonial resistance, pentamidine (IM 2 mg/kg every second day for seven injections), amphotericin B and oral miltefosine may be required (see management of VL below).

All three of these drugs have potentially serious side effects.

Visceral leishmaniasis (kala azar)

Epidemics occur in situations of famine, complex emergencies and mass movements of populations. It has a high fatality rate if untreated. It is estimated that there are 360 000 new cases every year globally, of which more than 60% occur in Northern India (Bihar).

The species responsible are *L. donovani* and *L. infantum* in the Old World, and *L. chagasi* in the New World.

- The major presenting features include the triad of prolonged fever, anaemia and moderate to marked splenomegaly. In the early stages the child is often only mildly unwell and may have a reasonable appetite. In a minority of cases, the onset may be acute, with a high temperature, toxaemia and mild splenomegaly.
- Pancytopenia is the main laboratory finding.

Diagnosis

- In children, the diagnosis is usually confirmed by demonstrating amastigotes on bone-marrow aspirate.
- Splenic aspirates have a higher sensitivity, and this procedure is safe in skilled hands so long as the platelet count is above 40×10^9/litre and coagulation is normal.
- Repeat bone-marrow or splenic aspiration to monitor progress if required.
- If there is lymphadenopathy, diagnosis may be attempted by fine-needle aspiration.
- **Serological antibody tests such as ELISA have a high sensitivity, and are particularly helpful if a parasitological diagnosis cannot be obtained.**
- If a microscopic diagnosis cannot be made, **the polymerase chain reaction (PCR) should be undertaken. The value of the PCR is being evaluated**.

Differential diagnosis

- Differential diagnosis of marked hepatosplenomegaly, anaemia and pancytopenia includes hyper-reactive splenomegaly (tropical splenomegaly) syndrome and schistosomiasis, as well as myeloid leukaemia and myelofibrosis.
- In acute-onset disease, malaria, disseminated tuberculosis, typhoid, brucellosis, African trypanosomiasis, relapsing fever and leukaemia should be considered.
- **HIV infection greatly increases the risk of visceral leishmaniasis, and thus co-infection is common.**

TABLE 6.3.A.C.1 Clinical features of visceral leishmaniasis

Incubation period: 2–4 months (weeks to two years)
Fever: intermittent at first
Anaemia: bone-marrow depression, hypersplenism
Splenomegaly: progressive enlargement
Hepatomegaly
Weight loss
Epistaxis: haemorrhage from other sites may occur in advanced disease
Diarrhoea: invasion of gut by amastigotes, secondary infection
Cough
Oedema: hypoalbuminaemia
Hair and skin signs of malnutrition in chronic forms
Lymphadenopathy: in some African countries

TABLE 6.3.A.C.2 Clinical pathology of visceral leishmaniasis

Haemoglobin: low; normochromic, normocytic film
White blood cells: low, 2–3 × 10^9/litre Eosinophils low
Platelets: low, < 100 × 10^9/litre
Reticulocytes: low
Serum albumin: low
Serum globulin: elevated
Liver transaminases and serum bilirubin: normal

Management of visceral leishmaniasis

Consider HIV co-infection and secondary disorders such as malaria, respiratory and gut infections, and tuberculosis. Blood transfusion for anaemia is seldom required, as the child has usually adapted to the low haemoglobin level. Give haematinics and vitamin supplements during nutritional rehabilitation and convalescence.

Liposomal amphotericin B used to be expensive, but following a campaign the WHO has brought about a 90% reduction in price, and consequently this is now the treatment of choice.

The alternative treatment is with antimoniates (Sb), for which again the WHO has obtained a substantial reduction in cost. Meglumine antimoniate and sodium stibogluconate are available. The duration of Sb treatment is usually 4 weeks, but prolonged treatment (up to 6 weeks) may be necessary in resistant cases (*see* Table 6.3.A.c.3).

For relapse, a second course can be given after a few weeks. Serious toxicity is rare in children, but if a prolonged course of high dosage is required, or toxicity is suspected, liver function tests and an ECG looking for conduction

disorders should be undertaken. Serious toxicity may require dimercaprol to chelate and remove the antimony.

In areas where there is resistance to Sb, such as Bihar state in India, and the Sudan, alternative drugs are required as follows: amphotericin B by slow infusion; paromomycin (aminoglycoside, identical to aminosidine); or oral miltefosine. Combinations of drugs (e.g. paromomycin and Sb) may be more effective. In patients with HIV/VL co-infection, management is difficult because of frequent relapse when treatment is stopped. HAART combined with maintenance anti-leishmanial therapy is important.

TABLE 6.3.A.C.3 Drugs used in the treatment of visceral leishmaniasis

Drug	Doses	Contraindications and cautions	Side effects
Liposomal amphotericin B	4 mg/kg IV over 30–60 minutes once daily by IV infusion on days 1, 2, 3, 5 and 10	An initial test dose of 100 micrograms/kg (maximum 1 mg) is infused over 15 minutes. Observe for 1 hour to ensure that anaphylaxis does not occur, then proceed	May produce hypotension, fever, vomiting, headache, and muscle and joint pain. Less commonly, chest pain, hypoxia, severe abdominal pain, flushing, urticaria, and flank or leg pain
Sodium stibogluconate (100 mg Sb/mL) or meglumine antimoniate (81 mg Sb/mL)	20 mg/kg (minimum 200 mg) IV infusion or deep IM injection over over 5–10 minutes once daily for 28 days Prolonged treatment for 6 weeks in resistant cases	Pre-existing severe cardiac, liver, renal, pancreatic or haematological abnormalities Not to be given during pregnancy Filter solution through 5-micron filter immediately before infusion	Vomiting, abdominal pain, myalgia and arthralgia, headache, metallic taste. Rarely sudden death with prolonged QT interval; therefore monitor ECG and stop infusion if QT exceeds 0.5 seconds
Conventional amphotericin B	Slow IV infusion, 1 mg/kg every second day for 15 days, or daily for 20 days. (daily dose must never exceed 1.5 mg/kg)	An initial test dose of 100 micrograms/kg (maximum 1 mg) is infused over 15 minutes. Observe for 1 hour to ensure that anaphylaxis does not occur, then proceed	May produce hypotension, fever, vomiting, headache, and muscle and joint pain
Paromomycin	Daily IV or IM injections 16–20 mg/kg/day for 21 days	Do not give at the same time as gentamicin or other aminoglycosides. Avoid if there is renal impairment	Vomiting, diarrhoea, abdominal pain, fever and ototoxicity
Miltefosine	2.5 mg/kg/day orally for 28 days	Not in pregnancy	Nausea and vomiting

A limited stock of the above drugs is kept by the WHO in Geneva for rapid response to an epidemic.

A study looking at the effectiveness of a single-dose treatment (by IV infusion) using liposomal amphotericin B is currently in progress in India.

Follow-up and prognosis

Symptomatic improvement usually occurs within a few days, and a haematological response occurs within 2 weeks. Splenomegaly slowly regresses, but may take a year or more to resolve. Prolonged follow-up (at least 1 year) is necessary to detect relapse. Relapse is treated with a repeat prolonged course of antimonials (up to 8 weeks). Unresponsiveness will require alternative drugs such as liposomal amphotericin B (if available), aminosidine, standard amphotericin B or pentamidine. Trials of miltefosine are in progress.

Prevention and control

Prevention is similar to that of malaria, and includes insect repellents and the use of fine-mesh bed nets impregnated with permethrin. Control includes spraying of sandfly resting sites and human dwellings, destruction of animal reservoirs and treatment of cases.

Further reading

Murray HW, Berman JD, Davies CR *et al*. (2005) Advances in leishmaniasis. *Lancet*, **366**, 1561–77.

World Health Organization (2014) *Leishmaniasis*. www.who.int/leishmaniasis/en/

6.3.A.d Malaria

BOX 6.3.A.D.1 Minimum standards for an effective malaria control programme

1 Prevention:
   - Impregnated bed nets (ITNs), preferably long-lasting insecticidal nets (LLINs).
   - Where appropriate, intermittent preventive treatment in infants (IPTi) and seasonal malaria chemoprevention (SMC) for older children.
   - Other methods of vector control, such as indoor residual spraying (IRS), personal protection (e.g. mosquito coils, impregnated clothing, repellents, etc.).

2 A well-informed population to improve early care seeking and adherence to treatment and preventive regimes.

3 Good case management:
   - Early accurate diagnosis: all patients should have a biological test before treatment:
     — Quality-assured thick blood film and/or rapid diagnostic test (RDT).
     — Haemoglobin measurement to detect and treat malaria anaemia (e.g. using a haemocue machine).
     — In severe disease, facilities to measure blood glucose levels and provide safe blood transfusion.
   - Effective treatment:
     — Treatment for simple malaria.
       » Artemisinin combination therapy (ACT) (following the national protocol for recommended ACT).
     — Treatment for severe disease.
       » IV or IM artesunate (IM artemether, rectal artesunate, or IV or IM quinine if artesunate is not available).
     — Pre-referral treatment.
       » Rectal artesunate (if artesunate is not available, rectal quinine) or if injections are safe IV or IM artesunate or IM artemether, or IM quinine.

4 Accessible, acceptable and affordable care:
   - Consider training community health workers in remote areas to diagnose and treat malaria.
   - Make treatment free for pregnant girls and children under five.
   - Set up a good referral system from community and first-level health facilities to facilities with means to treat severe cases, including transport and facilities to access resources to pay for treatment if needed.

BOX 6.3.A.D.2 Minimum standards for hospital treatment of severe malaria

- A triage system.
- RDTs and microscopy for initial diagnosis, plus laboratory facilities to determine levels of parasitaemia.
- Antimalarial drugs for IV, IM and oral treatment.
- Oxygen.
- Antibiotics and anticonvulsants.
- Safe blood transfusion services.
- Nasogastric feeding.
- Good nursing care (monitoring of vital signs and fluid balance, nasogastric feeding).

Introduction

Malaria is an extremely important public health burden in Africa, disproportionately affecting the youngest and most vulnerable. Children under 5 years and pregnant women, especially in the first pregnancy, suffer from severe forms of the disease. In Asia, the disease is more common in men and older children.

- Nearly 80% of the world's malaria burden is in Africa. Malaria is estimated to cause at least 650 000 deaths each year, mostly among African children.
- Unlike anywhere else in the world, children aged 6–24 months in Africa are most at risk of the worst forms of malaria. Every 30 seconds an African child dies of malaria.

There are five *Plasmodium* species known to be infective to humans, namely *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi.*

P. falciparum causes severe disease and is the most prevalent form in sub-Saharan Africa (most sub-Saharan Africans are protected against *P. vivax* due to lacking a protein in their red blood cells (the Duffy antigen)). *P. falciparum* differs from the other species in that infected erythrocytes adhere to capillary epithelium, thus disappearing from the circulation and evading destruction by the spleen.

P. vivax and *P. ovale* can cause recurrent malaria attacks due to the formation of a dormant form existing as hypnozoites in the liver, which are periodically released into the blood. Drugs to eliminate the hypnozoites from the liver are limited (primaquine).

P. malariae can cause long-term problems, including kidney failure, and *P. knowlesi* is a newly emerging form which has caused severe disease in Asia (Papua New Guinea and Thailand).

Life cycle

The infected *Anopheles* female mosquito injects sporozoites into the bloodstream of an individual. Sporozoites circulate for less than 30 minutes before being phagocytosed or entering liver parenchymal cells. The blood and liver phase prior to re-entry into the circulation is called the pre-erythrocytic phase, and it varies in length according to the species. At the end of this phase, merozoites invade the red blood cells and begin the erythrocytic phase. Parasites rapidly multiply within the red blood cells, which finally burst, releasing more merozoites into the bloodstream to invade further red blood cells.

Periodic bouts of fever are associated with the release of the merozoites. After some time, sexual forms of the parasites (gametocytes) are formed which are then ingested by a female mosquito to complete the cycle in humans. In the mosquito stomach, the gametocytes merge and eventually form sporozoites which migrate to the salivary

glands, where they are injected into the bloodstream by the mosquito as it takes a blood meal to support its own reproductive effort.

In two species (*P. vivax* and *P. ovale*) some hepatic-stage parasites remain within the liver cells with the formation of the dormant phase, called hypnozoites. For various reasons (perhaps including waning immunity), at a later date the dormant phases activate and reseed blood. This leads to manifestations of malaria not from a new infection but from the latent exo-erythrocytic phase.

P. falciparum differs from the other species in that infected erythrocytes adhere to capillary epithelium, thus disappearing from the circulation and evading destruction by the spleen.

P. falciparum is the most likely species to cause life-threatening disease, and is a major cause of mortality in children.

Plasmodium falciparum

Clinical features

- Typical symptoms include high-grade fever alternating with cold spells, rigors, chills and sweating. There are usually associated myalgias and arthralgias.
- However, features in children under 5 years of age may be non-specific, with fever, vomiting, diarrhoea and abdominal pain being the main symptoms.
- In older immune individuals the only symptoms may be fever with headache and joint pains.
- All fevers in children from a malaria-endemic area are therefore due to malaria until proven otherwise.

Diagnosis

Microscopy

- Blood smear for malaria remains the gold standard: a thick film for diagnosis, and a thin film to confirm the type of malarial parasite. Typically species-specific ring forms inside red blood cells are seen, but there may also be gametocytes.
- The level of parasitaemia is usually scored as 1–5+. If the malarial smear is 3+ or more, there is a high level parasitaemia. In areas where parasitic density is measured the smear is reported as parasites/mm^3.
- Malaria microscopy in district hospitals can be of very poor quality. A quality assurance programme should be in place that includes the following:
  - a properly trained and regularly updated microscopist
  - adequate time to look at slides, particularly for low-level parasitaemia
  - the correct stains and good-quality slides
  - a binocular microscope that is properly serviced and maintained
  - a system of internal and preferably external cross-checking of a sample of slides, especially the low parasitaemias and negative slides.
  - If possible examination requires a reliable electricity supply or good lighting near a window in the day time. Many modern microscopes have an inbuilt LED light.

Rapid diagnostic tests

Antigen-capture test kits use a rapid simple dipstick test from a finger-prick blood sample to give a result in 10–20 minutes. RDTs should be used in circumstances where microscope facilities and/or diagnostic expertise are limited.

There are two main forms of rapid test.

Histidine-rich protein 2 (HRP2) tests

These only detect *P. falciparum.* HRP2 tests have a sensitivity of 97–100% (i.e. there are very few false-negative results). These tests can lack specificity (which may be as low as 59% in some studies), so there can be a high frequency of false-positive results, especially in a high transmission zone where malaria infection is frequent (children can have as many as six attacks a year). HRP2 remains in the bloodstream for at least 2 weeks after all viable parasites have been killed, and often for considerably longer (6–8 weeks), so patients returning with fever within 4 weeks after treatment cannot be diagnosed using an HRP2-based RDT. However, a presumptive diagnosis that fever equals malaria has an even lower specificity.

HRP2 tests are very heat stable, but are sensitive to humidity. They have a shelf-life of 2 years, and their use can be taught to healthcare workers, even at village level, in a few hours. They are especially suitable for use in sub-Saharan Africa, where other species of malaria are rare.

Parasite lactate dehydrogenase (pLDH) tests

The parasite lactate dehydrogenase (pLDH) antigen is produced by all four *Plasmodium* species. The pLDH-based tests detect the antigen using a panel of monoclonal antibodies. They can have high sensitivity for *P. falciparum*, and are more specific than HRP2. They return to negative in 3–14 days (the majority do so within 7 days).

Some pLDH tests are able to differentiate between *P. falciparum* and other *Plasmodium* species, and between viable and non-viable parasites, thereby enabling their use for monitoring therapy and for detecting new infections within 2 weeks of successful treatment.

The tests currently on the market are available in two forms. The first has a pan-pLDH antibody that can detect any species of malaria. When positive, it produces a single test line. The second produces two test lines, a pan-specific line and a line that detects *P. falciparum*. In theory, there are monoclonal antibodies that can individually detect all of the different species, but these have not yet been validated.

pLDH tests are not as heat stable as HRP2 tests. Although pLDH has a high sensitivity for *P. falciparum*, its sensitivity for *P. vivax* appears to be less satisfactory if the patient has a low parasitaemia. pLDH tests are more expensive than HRP2 tests, and are not therefore recommended in sub-Saharan Africa, where 97% of infections are due to *P. falciparum.*

Advantages of RDTs over microscopy

- The result is available within 15–20 minutes and one person can set up a new test every 1 or 2 minutes. In contrast, there are more steps involved in microscopy (i.e. slide preparation, drying, staining, and drying stained slides), and a negative slide requires 6 minutes of reading time (a microscopy report can be delayed up to an hour from collecting the blood).
- Training takes 2 hours with minimally educated workers.
- Many more tests can be done in one clinic or outreach session.

A quality control/quality assurance system for RDTs should be in place at the level of importation where the Compliance

with last Malarial Treatment (CMT) is based, and at project level after transportation, to ensure that tests remain in good condition (lot testing). Monitoring of the conditions to which the tests are subjected during transportation may account for problems with their function at project level.

Field teams need to monitor the performance of healthcare staff regularly to ensure that tests are performed properly.

Other diagnostic tests that should be available in malaria programmes

- Haemacue to determine haemoglobin levels.
- Tests to deliver safe transfusion: two instant HIV tests, syphilis, hepatitis B and hepatitis C screen.
- Tests for G6PD deficiency if primaquine is to be used for radical treatment to eliminate hypnozoites and/or gametocytes of *P. falciparum*.
- Polymerase chain reaction (PCR) tests. These can be used to detect very low levels of parasitaemia. Work is progressing to develop a bedside PCR detection machine. PCRs are very important in elimination scenarios to detect very low parasitaemias, and in drug efficacy studies.

Case definitions of malaria

Suspected malaria: a patient with a fever or history of fever in the last 48 hours who lives in or has come from a malaria-endemic area.

Uncomplicated (simple malaria): a patient with a fever or history of fever in the last 48 hours who has a positive biological test and no symptoms of severe disease.

Complicated malaria: a patient with the signs and symptoms of simple malaria who is unable to take oral drugs.

Non-severe malaria may be associated with a variety of other symptoms, including cough, vomiting, diarrhoea, abdominal pain, myalgia, headache, sweating and rigors.

Severe malaria

A patient with one or more of the following signs or symptoms, with biologically confirmed *P. falciparum* infection (and occasionally *P. vivax*) and parasitaemia:

- prostration (inability to sit, or to drink or breastfeed)
- impaired consciousness (cerebral malaria)
- respiratory distress
- multiple convulsions
- circulatory collapse
- severe anaemia (haemoglobin concentration < 5 grams/dL or haematocrit of < 15%) may be the presenting symptom, especially in children and pregnant women, and can rapidly lead to death.

Other conditions that may be associated with severe malaria

Hyperparasitaemia may be associated with severe malaria, but is not pathognomonic of severe disease in itself. It has been associated with a higher risk of mortality and needs to be rigorously treated, preferably in the first instance with parenteral medications. If there are no other signs of severity, the patient may not need hospital admission.

Hypoglycaemia often causes unconsciousness or death if not detected and treated rigorously. It is especially dangerous in children, malnourished patients and pregnant women, and is exacerbated by quinine treatment.

Pulmonary oedema is a grave and often fatal complication of malaria. It can occur spontaneously (particularly during pregnancy), but it is often a result of fluid overload during treatment.

Metabolic (lactic) acidosis: see section on severe malaria below.

Abnormal bleeding is associated with thrombocytopaenia, and leads to bleeding of gums and epistaxis, and sometimes more severe internal bleeding.

Jaundice is more common in adults than in children. Mild jaundice only reflects haemolysis, whereas very high bilirubin levels suggest hepatic dysfunction.

Haemoglobinuria is common, but its more extreme form, blackwater fever, is rare. It is associated with quinine therapy.

Oliguria/anuria can be a sign of renal dysfunction, but make sure that the patient is adequately rehydrated before commencing therapy for renal failure. **Fluid balance charts should be instituted and monitored closely for all patients with severe malaria.**

Uncomplicated/simple malaria

There is a fever and a positive blood smear. There is no evidence of altered consciousness, hypoglycaemia, severe anaemia, jaundice or respiratory difficulties.

Management

Management of children who have always lived in an endemic area

- There is no need to admit the child to hospital (unless they are under 4 months of age or less than 5 kg in weight, or pregnant).
- A diagnostic test should be done before treatment (microscopy if available and quality assured, or an RDT). This will confirm malaria and also ensure that patients who do not have malaria receive appropriate treatment. **Note that malaria is frequently accompanied by other serious infections, such as pneumonia.** Signs of bacterial or viral infections should be looked for and treated appropriately even if the malaria diagnostic test is positive.
- Give first-line antimalarial treatment (ACTs) as recommended in local national guidelines.
- Ensure that tablets or syrup are swallowed and not vomited.
- Give the first dose under direct observation and advise the carer on how to administer the drug to young children by dissolving tablets in breast milk or syrup and giving this slowly with a syringe.
- If the child vomits within the first 30 minutes, repeat the full dose. If they vomit after 1 hour give a half dose. Advise the carer to return if further doses are vomited. Remember to advise the carer to give the dose with food if artemether/lumefantrine is used, to improve absorption of the lipophilic lumefantrine.
- Encourage oral fluid intake and continued feeding with light nutritious foods plus catch-up meals when the child recovers. Measures to lower the body temperature may be necessary (tepid sponging and paracetamol).
- Test for iron deficiency, and if the patient is pale and anaemic (based on palmar and conjunctival examination and/or haemoglobin test), give haematinics (iron

and folic acid, **but** if sulfadoxine-pyrimethamine has been used for malaria treatment, do not give folic acid for 2 weeks).

Management of children visiting or returning from an endemic area for the first time

Hospital admission for management of *P. falciparum* is always advisable.

Treat with an ACT

The WHO recommends the use of **fixed-dose combinations (FDCs)** if available, or pre-packaged drugs if FDCs are not available. **The WHO discourages the use of monotherapies, to reduce the risk of resistance developing.** In particular, the use of artesunate monotherapy, which is commonly available on the private market, is strongly discouraged.

ACTs recommended by the WHO

- Artesunate/amodiaquine (AS/AQ FDC).
- Artesunate + mefloquine (AS+MQ or AS/MQ FDC).
- Artesunate + sulphadoxine/pyrimethamine (AS + SP).
- Artemether + lumefantrine (AM/LM FDC).
- DHA/piperaquine (Duo-Cotecxin, Eurartesim) FDC.
- Artesunate/pyronaridine (Pyramax) FDC.

Non-ACTS

- Malarone (atovaquone/proguanil) FDC: this is very expensive and usually only used where there is artemisinin resistance, or for prophylaxis in western travellers.
- Quinine tablets in IV, IM and rectal forms: for true treatment failures.
- Chloroquine: only for non-*P. falciparum* malaria.
- Primaquine and its derivatives (tafenoquine): for radical treatment of *P. vivax* (and *P. falciparum* in elimination areas).

Paediatric formulations

- AS/AQ infant dose is dispersible, and suitable for children who weigh 4.5–8 kg.
- Paediatric Coartem® (AM/LM) is dispersible and available as cherry-flavoured tablets for children who weigh 5–25 kg.
- Artequin (Mepha) FDC AS/MQ is available as mango-flavoured pellets/granules that can be swallowed directly without water. It is not WHO prequalified.
- AS/MG FDC produced in Brazil for Drugs for Neglected Diseases (DNDi).

Drugs frequently available but not WHO prequalified

- ASMQ Artequin (also in paediatric granules).
- Artemisinin/piperaquine (Artequick).
- Artemisinin and naphthoquine.

Drugs in development

- Artemisone (partner drug not yet decided).
- Synthetic AS called OZ (Sanofi Aventis).
- Semi-synthetic artemisinin (One World Health).

Advice for carers

Discuss preventive efforts with carers (e.g. bed net at night, ideally impregnated with insecticide). Give LLIN if possible.

Tell the mother to return after 2 days if fever persists, and earlier if the child deteriorates.

If the child is repeatedly vomiting and the area is remote and admission to hospital difficult, give rectal artesunate until the vomiting settles. Then give a full 3-day course of ACT.

Management of severe malaria

Severe malaria is a complex multi-system disease that constitutes a medical emergency.

Mortality approaches 100% without treatment, and death often occurs within the first few hours. Prompt initiation of antimalarial treatment in peripheral healthcare facilities and comprehensive management in hospital are necessary to prevent deaths.

Neurological sequelae of cerebral malaria affect about 10% of African children who survive cerebral malaria. These sequelae are severe and permanent in up to 19 000 children annually, and include spastic paresis and epilepsy.

Care should be provided within 15 minutes of arrival at a healthcare facility. Triage systems should be in place in health centres and hospitals to pick up severely ill patients, referral should be rapid, and emergency facilities must be instituted in hospitals, with a high standard of medical and nursing care available 24 hours a day.

Any seriously ill or unconscious patient in a malaria-endemic area must be tested for malaria by RDT (remember that parasites may not be present in the peripheral blood of a patient with cerebral malaria). Malaria should be assumed in any child with severe anaemia, convulsions, hyperpyrexia and/or hypoglycaemia either in hospital or in a peripheral healthcare facility.

Even if a diagnostic test is not available, **the patient should be given an antimalarial drug (IV, IM or rectally, depending on the skill of the staff in the facility) before transfer to the hospital.** This can be repeated if transfer is impossible or is delayed for more than 12 hours. A note of what has been given should be sent with the patient as soon as transfer can be arranged.

If any doubt exists, it is safer to treat than not to treat before transfer.

Immediate measures (in hospital)

- Vital signs: temperature, pulse, blood pressure, and respiratory rate and depth.
- State of hydration.
- Estimate or ideally measure body weight. Estimate of weight by age in well-nourished children:
  - For an infant up to 1 year of age, birth weight doubles by 5 months and triples by 1 year.
  - For children over 1 year, use the following formula: weight (kg) = 2 (age in years + 4).

  Be careful in HIV-endemic areas where body weights are often very different from those derived by this formula. Weigh the child if at all possible.
- Level of consciousness (AVPU or Glasgow or Adelaide coma scales) (*see* Section 5.16.A).
- The depth of coma may be assessed rapidly in children using the coma scale for children or by observing the response to standard vocal or painful stimuli (rub your knuckles on the child's sternum; if there is no response, apply firm pressure on the thumbnail bed with a horizontal pencil).
- RDT and malaria smear (thick and thin film) for diagnosis and for continued monitoring of the progress of the

disease. **Do not wait for a malaria smear result before initiating treatment, as it can take up to an hour. If the RDT is positive, commence treatment immediately.**
- Perform lumbar puncture if the patient is unconscious to eliminate meningitis if there are no contraindications. **Contraindications include papilloedema or suspicion of raised intracranial pressure (irregular breathing and pupillary responses, posturing), bleeding problems or respiratory difficulty such that flexing the back would compromise respiration. In such a situation, give IV antibiotics to treat meningitis as well as malaria.**
- Measurement of glucose (finger prick), haemoglobin and haematocrit (packed cell volume, PCV).
- Group and cross-match blood and search for a suitable donor.

Parenteral IV or IM treatment

In Africa and many other regions, sodium artesunate or quinine are the drugs of choice for severe malaria. In South-East Asia and the Amazon Basin, quinine is no longer always effective and should be accompanied by doxycycline in adults or clindamycin in children. Large trials in mainly Asian Adults (SEAQUMAT study) and in African Children (AQUAMAT study) have proved that parenteral artesunate reduces mortality by over 30% and should be used in preference to quinine.

Initially give treatment intravenously, if possible; otherwise use the IM route. Change to oral therapy as soon as possible.

Especially in the malaria-endemic areas of Africa, the following initial antimalarial medicines are recommended. Artesunate has been shown to reduce mortality compared with quinine, but it is important to use whichever drug is available locally.
- artesunate IV or IM
- artemether IM (its absorption may be erratic in children in shock).
- quinine (IV infusion or divided IM injection)

First-line antimalarial drugs

Sodium artesunate IV or IM

Give 2.4 mg/kg IV (by slow injection) or IM on admission (time 0), followed by 2.4 mg/kg IV or IM at 12 hours and again at 24 hours, and then once daily for a minimum of 3 days until the child can take oral treatment with an ACT.

OR second choice

Artemether IM

Give 3.2 mg/kg IM as loading dose, then 1.6 mg/kg IM once daily (every 24 hours) for a minimum of three days until oral treatment can be taken. Use a 1 mL tuberculin syringe to give the small injection volume (note: absorption may be erratic and therefore only use if quinine and artesunate are not available) and if shocked do not use this drug as absorption is too unreliable.

Intravenous IV quinine (quinine dihydrochloride)

This is the second choice, to be used if sodium artesunate is not available. Give 20 mg/kg quinine dihydrochloride (maximum 1.4 grams) in 5% glucose at a concentration of 1 mg of quinine to 1 mL of 5% glucose over 2–4 hours (never more rapidly than over 2 hours). If possible use an in-line infusion chamber (100–150 mL) to ensure that the loading dose does not go in too quickly. Alternatively, ensure that the IV giving bag contains only the amount needed for each dose. There is a major risk of cardiac side effects if it is infused too quickly.

Subsequently give 10 mg/kg in 10 mL/kg fluid (5% glucose) IV every 12 hours for 24 hours, or longer if the child remains unconscious. These latter doses **must** be given over at least 2 hours.

Never give quinine as an IV bolus. The infusion rate must not exceed a total of 5 mg quinine salt/kg/hour.

If safe control over the rate of infusion of IV quinine is not possible (e.g. there are insufficient or only untrained nursing staff available), give a loading dose intramuscularly (with initial doses of 10 mg/kg quinine salt IM at 0 and 4 hours and then 12-hourly).

For IM injections, dilute the quinine solution to allow better absorption and less pain.

As soon as the child is able to take medication orally, switch to quinine tablets 10 mg/kg every 8 hours for a total of 7 days, or the locally available first-line ACT treatment for malaria.

Side effects:
- Common: cinchonism (tinnitus, hearing loss, nausea and vomiting, uneasiness, restlessness, dizziness, blurring of vision).
- Uncommon: hypoglycaemia, although this is a common complication of severe malaria.
- Serious cardiovascular problems (QT prolongation on the ECG) and neurological toxicity are rare.
- If overdosed by mistake with quinine tablets, give activated charcoal orally or by nasogastric tube as a suspension in water (1 gram/kg).

Chloroquine IV

This drug should never be used to treat severe falciparum malaria but only cases of non-resistant vivax or ovale malaria. Give 5 mg base/kg every 6 hours for a total of 25 mg base/kg (five doses) as an infusion in 5% glucose (give over 2 to 4 hours).

Antimalarial treatment after IV or IM regimes have ended

Following parenteral administration, usually for a minimum of 24 hours or until the child can take oral drugs, the treatment of severe malaria must be completed by giving a full course of one of the artemisinin-based combination therapies (ACT) described below. In some parts of the world, oral quinine combined with clindamycin to complete 7 days of treatment is used

The following ACTs are recommended:
- artemether plus lumefantrine
- artesunate plus amodiaquine
- artesunate plus sulfadoxine-pyrimethamine
- dihydroartemisinin plus piperaquine
- artemether plus clindamycin
- artesunate plus mefloquine.

The choice of ACT in a particular country or region will be based on the level of resistance of the partner medicine in the combination.

In areas of multi-drug resistance (e.g. East Asia), artesunate plus mefloquine, or artemether plus lumefantrine, or dihydroartemisinin plus piperaquine are recommended. In

areas without multi-drug resistance (mainly Africa), any of the ACTs, including those containing amodiaquine, may still be effective. Every country has a national malaria policy in which the first-line therapy is described and should be used.

If possible avoid using mefloquine if the patient has presented with an impaired conscious level.

Treatment for HIV-infected patients with P. falciparum *malaria*

- Patients with HIV infection who develop malaria should receive prompt effective antimalarial treatment regimens as recommended above.
- **Treatment with ACT involving sulfadoxine-pyrimethamine should not be given to HIV-infected patients who are receiving co-trimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis.**
- Treatment of HIV-infected patients who are on zidovudine or efavirenz should, if possible, avoid amodiaquine-containing ACT regimens.

Treatment of P. falciparum *malaria in malnourished patients*

Although there are many reasons why antimalarial pharmacokinetics may differ between malnourished patients and those who are well nourished, there is insufficient evidence to change current mg/kg body weight dosing recommendations.

Always check local guidelines on drug sensitivities.

With all antimalarial drugs, change to an oral therapy when the child can tolerate it.

Additional treatment where needed

- Insert a nasogastric tube to minimise the risk of aspiration pneumonia if the patient's level of consciousness is low. **This can also be used to give food to prevent hypoglycaemia if the child is unconscious for a long period and is unable to eat. Alternatively, sucrose (sugar) can be placed under the tongue.**
- Insert an IV cannula and restore the circulating volume.
  - **Fluids should be given with caution** and the need for them assessed on an individual basis after ascertaining the nutritional status and degree of dehydration present.
  - In general, **children with metabolic acidosis who have not previously received parenteral fluids are dehydrated and should be managed accordingly**.
- Give oxygen if SpO_2 is < 94% (to keep SpO_2 in the range 94–100%) or if there is respiratory distress and no pulse oximeter available.
- Treat severe anaemia with a safe blood transfusion if the child is showing signs of decompensation.
- Give anticonvulsants (diazepam is preferred) if the patient is convulsing (see below) to prevent long-term neurological damage (*see* Section 5.16.E). Convulsions associated with cerebral malaria should be distinguished from febrile convulsions common in children under 4 years of age. The child usually recovers rapidly, within a few minutes, from a febrile convulsion. Convulsions in malaria are common before or after the onset of coma. They are significantly associated with morbidity and sequelae. They may present in a very subtle way. Important signs include intermittent nystagmus, salivation, minor twitching of a single digit or a corner of the mouth, and an irregular breathing pattern.

Prophylactic anticonvulsants have been recommended in the past, but recent evidence suggests that **phenobarbital may be harmful in this situation**.

- Paracetamol, 15 mg/kg of body weight 4-hourly, may also be given orally or rectally as an antipyretic.
- Use tepid sponging and fanning to try to keep the rectal temperature below 39°C. Relatives are usually happy to do this when instructed.
- High-dose IV or IM antibiotics should be given routinely to an unconscious or shocked patient.
- Avoid using harmful ancillary drugs.

The patient will need intensive nursing care at least until they regain consciousness. They may urgently need glucose or a blood transfusion if hypoglycaemia or haemolysis is severe.

Management of associated causes of mortality in severe malaria

Some children with *P. falciparum* malaria go on to develop altered consciousness, severe anaemia, acidosis, or any combination of these. Where transmission of *P. falciparum* is endemic, malaria is the commonest cause of coma in children, especially in those aged 1–5 years.

Cerebral malaria (coma, confusion and convulsions)

Coma develops rapidly, often within 1 or 2 days of onset of fever, and sometimes within hours. Convulsions are usual and may be repeated. Clinical features suggest a metabolic encephalopathy, with raised intracranial pressure. Opisthotonos, decorticate or decerebrate posturing, hypotonia and conjugate eye movements are common. Oculovestibular reflexes and pupillary responses are usually intact. Papilloedema is found in a small minority of cases. A unique retinopathy with patchy retinal whitening and pallor of vessels is found. In fatal cases, brain swelling is commonly present at autopsy, but cerebral herniation is not usually found even in patients who have undergone lumbar puncture.

Hypoglycaemia, acidosis, hyperpyrexia and convulsions (sometimes undetectable without EEG) are common accompaniments of cerebral malaria, and require appropriate management (see below).

No physical signs are diagnostic of coma due to malaria, and incidental parasitaemia is common in endemic areas, so other causes of coma, especially hypoglycaemia and meningitis, must always be carefully sought, and if necessary treated on the basis of presumptive diagnosis.

Even with optimal treatment, the case fatality rate is 15–30%, and about 10% of survivors have residual neurological sequelae (hemiparesis, spasticity, cerebellar ataxia) that may partially or completely resolve over time.

Investigations

- Blood glucose levels (e.g. by blood glucose stick test).
- Lumbar puncture if meningitis is suspected; contraindications include papilloedema or suspicion of raised intracranial pressure (irregular breathing and abnormal pupillary responses, posturing), or respiratory difficulty such that flexing the back would compromise respiration. **In such a situation, give IV antibiotics to treat meningitis as well as malaria.**

Management

Coma

Ensure that the airway is open at all times and that the patient is breathing adequately. Give oxygen by face mask with a reservoir or nasal cannulae (to keep SpO_2 in the range 94–98% if a pulse oximeter is available). If the child stops breathing, give assisted ventilation with a bag-mask of suitable size (500 mL or 1600 mL).

Ensure that a bag-mask is available at all times.

Nurse the patient in the recovery position to avoid aspiration of secretions or vomit.

Exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis).

- Treat convulsions (*see* Section 5.16.A on coma and Section 5.16.E on convulsions).
- Treat hypoglycaemia.

Convulsions

Convulsions are common before and after the onset of coma.

- Ensure that the airway is open, and give oxygen by face mask with a reservoir or nasal cannulae.
- If the child stops breathing, give assisted ventilation with a bag-mask of suitable size (500 mL or 1600 mL).
- Examine all children with convulsions for hyperpyrexia and hypoglycaemia. Treat hypoglycaemia with IV or oral glucose if identified on blood testing, but also treat as for hypoglycaemia if blood glucose levels cannot be measured and the child is drowsy, unconscious or fitting (see below).
- Give anticonvulsant treatment with rectal diazepam or paraldehyde or IM paraldehyde.
- If the patient has a fever of ≥ 39°C (≥ 102.2°F), give paracetamol rectally (if available).
- Treat seizures lasting for more than 5 minutes with drugs. **Ensure that a bag-mask is available at all times in case of apnoea following the use of diazepam. Apnoea is usually short-lived and improves quickly with ventilation via bag and mask.**

Note that seizure activity needs to be looked for carefully, as it may appear as just a twitching of the thumb or mouth.

- Give IV diazepam:
  - **Children**: 300 microgram/kg of body weight as an IV infusion over 2 minutes or 400–500 microgram/kg of body weight intra-rectally. This dose can be repeated after 10–15 minutes if still fitting.
  - **Pregnant girls**: 10 mg rectally or by slow IV injection. This dose can be repeated after 10–15 minutes if still fitting.
  - Do not exceed 10 mg per dose.
- Alternatively, paraldehyde 0.1 mL/kg of body weight may be given by deep IM injection or 0.8 mL/kg of body weight (maximum 20 mL) intra-rectally using a sterile glass syringe (a disposable plastic syringe may be used provided that the injection is given immediately after the paraldehyde is drawn up, and the syringe is never reused).

Hypoglycaemia

Hypoglycaemia is common and is due to poor intake, increased metabolic needs of the patient and parasites and impaired hepatic gluconeogenesis. It is easily overlooked because clinical signs may mimic those of cerebral malaria.

Check for hypoglycaemia in **all** patients who are unconscious, in shock or deteriorating. Also regularly (every hour in the first instance) check pregnant girls, children under 5 years, and the malnourished, and all patients receiving quinine.

Hypoglycaemia is defined as blood glucose levels < 2.5 mmol/litre (< 45 mg/dl).

Prevent hypoglycaemia with a maintenance quantity of 5% glucose in 0.9% Ringer-lactate or Hartmann's solution (50 mL of 50% glucose in a 500-mL bag). If the child develops hypoglycaemia despite this, give maintenance as 10% glucose in 0.9% Ringer-lactate or Hartmann's solution (100 mL of 50% glucose in a 500-mL bag). Do not exceed maintenance fluid requirements for the child's weight (*see* Section 9 Appendix). If the child develops signs of fluid overload, stop the infusion; repeat the 10% glucose boluses (5 mL/kg) if there is hypoglycaemia identified by making regular checks of blood glucose levels.

If IV access is not possible and the child is hypoglycaemic, place an intra-osseous needle (*see* Section 8.4.B).

Treat hypoglycaemia or suspected hypoglycaemia with an IV glucose infusion or bolus:

- **Children:** 1 mL/kg of 50% dextrose, diluted with four times the volume of infusion fluid (usually Ringer-lactate or Hartmann's solution) infused over 5 minutes **or** 5 mL/kg of 10% glucose as a bolus.
- **Pregnant girls:** 50 mL of 50% dextrose diluted with an equal volume of infusion fluid (usually Ringer-lactate or Hartmann's solution) over 15 minutes (irritating to veins).

Re-test 15 minutes after completion of the infusion, and repeat the infusion if blood glucose remains low. Repeat until blood glucose recovers, then infuse with 5–10% glucose in Ringer-lactate or Hartmann's solution (according to hypoglycaemia risk) to prevent recurrence. Ensure regular feeding when oral intake can be sustained. Fluids used to treat hypoglycaemia must be included in daily fluid requirements.

If blood glucose levels cannot be measured and hypoglycaemia is a possibility, always give IV glucose as described above.

If the child is still unable to swallow after 48 hours, start nasogastric feeds. If a gag reflex is present and the child is able to swallow, feed them as soon as this is possible. For young children breastfeed every 3 hours if possible, or give milk feeds of 15 mL/kg 3-hourly if the child can swallow. If they are not able to feed without risk of aspiration, give milk, especially breast milk, by nasogastric tube or sugar sublingually (*see* Section 5.8.B). Continue to monitor the blood glucose levels, and treat accordingly (as described above) if these are found to be < 2.5 mmol/litre or < 45 mg/dL.

Hypoglycaemia is a major cause of death in severe malaria patients, especially in young children and pregnant girls. Remember that quinine will potentiate hypoglycaemia. Young children should receive regular feeding, including by nasogastric tube, if they are unable to take oral foods.

Severe anaemia

This is indicated by severe palmar pallor, often with a fast pulse rate, difficult breathing, confusion or restlessness. Signs of heart failure such as gallop rhythm, enlarged liver

and, rarely, pulmonary oedema (fast breathing, fine basal crackles on auscultation) may be present (see above).

Severe haemolytic anaemia is defined as < 5 grams of haemoglobin/dL or haematocrit < 15%.

Severe anaemia may be the presenting feature in malaria. Patients with severe anaemia, especially pregnant girls, should be tested for malaria.

Give a safe blood transfusion as soon as possible to:

- all children or pregnant girls with a haematocrit of ≤ 12% or Hb of ≤ 4 g/dL
- less severely anaemic children (haematocrit > 12–15%; Hb 4–5 g/dL) with any of the following:
  - clinically detectable dehydration (as well as rehydrating orally if possible)
  - shock
  - impaired consciousness
  - deep and laboured breathing
  - heart failure
  - very high levels of parasitaemia (> 10% of red blood cells parasitised).

Give packed cells (10–20 mL/kg body weight for children and 500 mL for pregnant girls), if available, over three to four hours in preference to whole blood. Allow red blood cells to settle at the bottom of the bag, and stop the infusion when the cells have been used.

If not available, give fresh whole blood (20 mL/kg body weight) over 3–4 hours.

A diuretic is not usually indicated (unless pulmonary oedema or fluid overload is developing), because many of these children have a low blood volume (hypovolaemia).

Check the respiratory rate and pulse rate every 15 minutes. If one of them rises, transfuse more slowly. If there is any evidence of fluid overload due to the blood transfusion, give IV furosemide (1–2 mg/kg body weight) up to a maximum total of 20 mg for children, and give 40 mg IV for pregnant girls.

After the transfusion, if the haemoglobin level remains low, repeat the transfusion.

In severely malnourished children, fluid overload is a common and serious complication. Give whole blood (10 mL/kg body weight rather than 20 mL/kg) once, and only repeat the transfusion if there are no signs of overload.

Perform microscopy following transfusion, and repeat or extend antimalarial treatment if parasitaemia is increasing.

Respiratory distress due to acidosis

This presents with deep laboured breathing while the chest is clear on auscultation, sometimes accompanied by lower chest wall indrawing. It is caused by systemic metabolic acidosis (frequently lactic acidosis) and may develop in a fully conscious child, but more often in children with cerebral malaria or severe anaemia. Always exclude other causes, such as pneumonia or pulmonary oedema.

Metabolic acidosis in severe malaria has been attributed to the combined effects of several factors that reduce oxygen delivery to tissues:

- Increased production of lactic acid by parasites (through direct stimulation by cytokines).
- Decreased clearance by the liver.
- Marked reductions in the deformability of uninfected red blood cells may compromise blood flow through tissues.
- Dehydration and hypovolaemia can exacerbate microvascular obstruction by reducing perfusion pressure.
- Destruction of red blood cells and anaemia further compromise oxygen delivery.
- Mean venous blood lactate concentrations have been found to be almost twice as high in fatal cases as in survivors, and to correlate with levels of tumour necrosis factor and interleukin 1-alpha. The lactate concentrations fell rapidly in survivors but fell only slightly, or rose, in fatal cases. Sustained hyperlactataemia has been found to be the best overall prognostic indicator of outcome.

Treatment

Give oxygen to all patients (even if they are not hypoxaemic), and if a pulse oximeter is available keep SpO_2 in the range 94–100%.

Correct reversible causes of acidosis, especially dehydration and severe anaemia.

- If Hb is ≥ 5 g/dL, give 10 mL/kg of 0.9% Ringer-lactate or Hartmann's solution IV as a bolus and then reassess.
- If haemoglobin level is < 5 grams/dL, give whole blood (10 mL/kg) over 30 minutes, and a further 10 mL/kg over 1–2 hours without diuretics. Check the respiratory rate and pulse rate every 15 minutes. If either of these shows any rise, transfuse more slowly to avoid precipitating pulmonary oedema (*see* Section 1.7).
- Monitor ECG for cardiac arrhythmias if possible.
- The use of sodium bicarbonate is controversial.

Respiratory distress due to pulmonary oedema

This is different to that due to acidosis, and there is usually more chest recession, hypoxaemia (cyanosis, SpO_2 < 94%), basal lung crepitations, enlarging liver, gallop rhythm, and raised jugular venous pressure. It may be due to fluid overload, often in the presence of severe anaemia. The most effective treatment is to tilt the bed of the patient head up so that the venous blood flow to the heart is reduced. If the bed cannot be tilted, sit the patient up, give furosemide 1 mg/kg for children and 40 mg IV for pregnant girls, and proceed with a careful transfusion of packed blood cells. Repeat furosemide as needed.

Respiratory distress due to pulmonary aspiration or pneumonia

Prevent aspiration pneumonia if possible, because it can be fatal. Place the comatose patient in the recovery position and ensure that the airway is open. If it is safe to intubate and maintain this, do so in order to protect the airway if the patient is unconscious (U on the APVU scale, or Glasgow Coma Scale score of < 9).

- Give oxygen if the SaO_2 is < 94% or, if pulse oximetry is not available, if there is cyanosis, severe lower chest wall indrawing or a respiratory rate of ≥ 70 breaths/minute. Keep SpO_2 94–100%. Give IM or IV antibiotics as described for pneumonia (*see* Section 5.3.A), and add in metronidazole 7.5 mg/kg 8 hourly (maximum individual dose 500 mg) until the patient can take these orally, for a total of 7 days.

Shock

Most children with malaria have warm peripheries. Shock is unusual in malaria (algid malaria). Some patients may have a cold clammy skin. Some of them may be in shock (increased heart rate, cold extremities, weak pulse, capillary refill time longer than 3 seconds, low blood pressure (late sign)). These features are not usually due to malaria alone.

If shock is present, consider septicaemia, do a blood culture and start a broad-spectrum antibiotic IV (penicillin and gentamicin **or** cefotaxime or ceftriaxone) in addition to antimalarial drugs.

Management (*see* Section 5.5) includes fluid replacement as follows:

- **Children:** Give Ringer-lactate or Hartmann's solution IV, 10 mL/kg as a rapid bolus. Reassess, and if the patient is no better, or improving but still in shock, consider further 10 mL/kg boluses.
- **Pregnant girls:** Give Ringer-lactate or Hartmann's solution IV, 500 mL as a rapid bolus, then reassess.

If there is no improvement in capillary refill or tachycardia, repeat the infusion once or twice more, as required.

Give broad-spectrum antibiotics to treat septicaemia and any associated infections.

Acute renal failure

Acute renal failure (ARF) is defined as an abrupt decline in the renal regulation of water, electrolytes and acid–base balance, and continues to be an important factor contributing to the morbidity and mortality of malaria patients (*see* Section 5.6.C). Oliguria or anuria is often associated with jaundice, anaemia and bleeding disorders.

Note that ARF is uncommon in children, and dehydration is a more common cause of poor urine output.

- The basic principles of management are avoidance of life-threatening complications, maintenance of fluid and electrolyte balance, and nutritional support.
- Urinary catheterisation can be helpful if it can be safely undertaken, so that urine output can be accurately measured. Alternatively, weigh nappies in young children.
- Acute renal failure is suspected when the **hourly** urine output is less than 1 mL/kg of body weight/hour). Blood levels of urea and creatinine are usually raised.
- Make sure that the patient is adequately hydrated, but avoid overload, which will precipitate pulmonary oedema if the kidneys cannot excrete excess water.
- If urine output continues to be low despite adequate hydration, peripheral perfusion and normal blood pressure, give furosemide 1 mg/kg and repeat as required.
- If renal failure is established, restrict fluid to insensible loss (30 mL/kg/day) plus urine output and other fluid losses (e.g. vomit, diarrhoea).
- Consider peritoneal dialysis (if available) or ideally haemodialysis.

Abnormal bleeding

- Transfuse with fresh blood.
- Give vitamin K, 250–300 microgram/kg (maximum 10 mg) IV.
- Avoid IM injections and non-steroidal anti-inflammatory drugs (NSAIDs).

Coexisting infections

Treat any associated pneumonia, dysentery, etc.

Summary of supportive care for the treatment of severe malaria in hospital

- If the patient is unconscious, maintain a clear airway. Nurse them in the recovery position to avoid aspiration pneumonia, and turn them 2-hourly.
- Do not allow the child to lie in a wet bed, and provide special care for pressure points. Turn the patient every 2 hours.
- Give oxygen for patients who are in respiratory distress or in shock.
- In children with no dehydration, ensure that they receive their daily fluid requirements, but take care not to exceed the recommended limits (*see* Section 9 Appendix). Be particularly careful when fluids are given IV.
- Treat convulsions and hypoglycaemia.
- If you cannot exclude meningitis, give an appropriate antibiotic intravenously.
- If there is deep or laboured breathing suggestive of acidosis, give one bolus of 10 mL/kg IV fluid (normal Ringer-lactate or Hartmann's) to correct hypovolaemia and reassess. A second bolus may be required.
- During rehydration, examine frequently for fluid overload (increased liver size is probably the best sign, as well as gallop rhythm, fine crackles at the lung bases, raised jugular venous pressure and eyelid oedema in infants).
- In infants, if possible always use an in-line infusion chamber for IV rehydration. If this is not available and supervision is poor, empty the IV fluid bag until only 200–300 mL is remaining then if it all goes in quickly it will be less harmful than if the whole bag is being infused.
- If necessary, use a nasogastric tube to rehydrate the patient.
- Avoid giving drugs like corticosteroids and other anti-inflammatory drugs, urea, invert glucose, low-molecular dextran, heparin, adrenaline (epinephrine), prostacyclin and cyclosporine, as they do not treat malaria and can be harmful.
- Give safe blood transfusion where necessary, with careful monitoring to prevent fluid overload. Packed cells should be used in children and pregnant girls where possible. If overload is suspected, give a single dose of furosemide.
- If the patient is unconscious and you cannot exclude meningitis or the child is in shock, administer a broad-spectrum antibiotic to manage septicaemia, pneumonia or meningitis, which are often associated with cerebral malaria.

Summary of monitoring

- Check the patient regularly, at least every 3 hours. A doctor (if available) should see the patient at least twice a day.
- The rate of IV infusion should be checked hourly.
- Patients with cold extremities, hypoglycaemia on admission, respiratory distress and/or deep coma are at highest risk of death. It is particularly important that these children are kept under very close observation.
- Monitor and report immediately any change in the level of consciousness, convulsions, or changes in the patient's behaviour.
- Monitor the temperature, pulse rate and respiratory rate (and if possible the blood pressure) every 6 hours for at least the first 48 hours.
- Fluid balance charts: unconscious patients may be catheterised in order to measure urine output and facilitate correct fluid balance, and to detect possible renal failure.
- Frequent measurement of blood glucose levels (every hour, especially when receiving quinine and/or where the level of consciousness does not improve).
- If the patient is conscious, regularly (4-hourly) determine

blood glucose levels to exclude hypoglycaemia if the patient is not eating well. This is especially important in young children and pregnant women, and in those patients who are receiving quinine therapy.
- Check haemoglobin levels and haematocrit daily.
- Check plasma urea and electrolytes where possible, and take blood gas and lactate measurements (if available).
- Check the rate of IV infusion regularly. If available, use a giving chamber with a volume of 100–150 mL. Be very careful about over-infusion of fluids from a 500-mL or 1-litre bottle or bag, especially if the child is not supervised all the time. Partially empty the IV bottle or bag. If the risk of over-infusion cannot be ruled out, rehydration using a nasogastric tube may be safer.
- Keep a careful record of fluid intake (including IV) and urine output (should be at least 1 mL/kg/hour).
- Undertake a daily slide to determine the level of parasitaemia and to monitor treatment efficacy.
- Regular haemoglobin measurement. The frequency will depend on the rate of red blood cell breakdown. This may be very rapid in cases of high parasite density.

On discharge from hospital

When the child or pregnant girl is due to leave hospital, talk with the relatives and carers to ensure that:
- the patient sleeps under a net (LLIN); if not, provide one
- the patient completes any outstanding treatment
- the carers and relatives recognise symptoms and where to get treatment for simple malaria in future
- the family knows to give extra meals to make up for the poor nutrition during the illness
- the family know when to bring the patient for further check-ups and arrange a follow-up appointment.

Examine for any neurological sequelae and advise the family on how to manage these and the possible prognosis. Arrange a physiotherapy session if necessary. Good follow-up is important.

Management of non-severe anaemia

If anaemia associated with malaria is not severe (defined as a haemoglobin level of 6–9.3 grams/dL), treat as follows. Give iron once daily in combination with folic acid (one tablet contains ferrous sulphate 200 mg, equivalent to 60 mg of elemental iron) plus 250 micrograms/kg/day of folic acid. Give 3–6 mg/kg (maximum 200 mg) of elemental iron in 2–3 divided doses and for folic acid give 250 microgram/kg once daily (usually one 5 mg tablet). Stress the importance of keeping the tablets out of reach of young children. Iron poisoning is very dangerous.

If the child is taking sulfadoxine-pyrimethamine for malaria, or co-trimoxazole for HIV prophylaxis, do not give folic acid until 2 weeks later (it interferes with antimalarial action).

TABLE 6.3.A.D.1 Dose of ferrous fumarate 140 mg/5 mL in children

Weight	Dose
3–6 kg	1 mL
6–10 kg	1.25 mL
10–15 kg	2.0 mL
15–20 kg	2.5 mL
20–30 kg	4 mL

An alternative for a young child is iron syrup (ferrous fumarate) 140 mg in 5 mL and equivalent to 45 mg of iron. Give once daily (*see* Table 6.3.A.d.1).

Plus separate folic acid 250 micrograms/kg/day.

Treat for 3 months where possible (1 month to correct anaemia and 1–3 months to build iron stores).

Patients with HIV infection

Patients with HIV infection who develop malaria should receive prompt effective antimalarial treatment regimens as recommended above.

However, treatment with an ACT involving sulfadoxine-pyrimethamine should not be given to HIV-infected patients receiving co-trimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis.

Treatment in HIV-infected patients on zidovudine (AZT) or efavirenz should, if possible, avoid amodiaquine-containing ACT regimens. Amodiaquine can cause anaemia in G6PD deficiency, and AZT may also cause anaemia.

Infection with *P. vivax*, *P. ovale* and *P. malariae*

Of the four species of *Plasmodium* that affect humans, only *P. vivax* and *P. ovale* form hypnozoites, parasite stages in the liver, which can result in multiple relapses of infection weeks to months after the primary infection. Thus a single infection causes repeated bouts of illness. Ideally, the objective of treating malaria caused by *P. vivax* and *P. ovale* is to cure (radical cure) both the blood stage and the liver stage infections, and thereby prevent recrudescence and relapse, respectively. **However, primaquine which is used to produce a radical cure is contraindicated in children under 4 years of age.**

Diagnosis

- Microscopy using a Giemsa-stained quality-assured thin film.
- pLDH tests can detect all species of malaria. Combination tests are now available that combine HRP2 and pLDH to detect both *P. falciparum* and non-*P. falciparum* malaria.

Treatment

Both *P. ovale* and *P. malariae* are regarded as very sensitive to chloroquine, although there is a single recent report of chloroquine resistance in *P. malariae*.

P. vivax is generally still sensitive to chloroquine, although resistance is prevalent and increasing in some areas (notably Indonesia, Peru and Oceania). Resistance to pyrimethamine has increased rapidly in some areas, and sulfadoxine/pyrimethamine is consequently ineffective. There are insufficient data on current susceptibility to proguanil and chlorproguanil, although resistance to proguanil was selected rapidly when it was first used in *P. vivax*-endemic areas.

In general, *P. vivax* is sensitive to all of the other antimalarial drugs, and slightly less sensitive to mefloquine (although mefloquine is still effective). In contrast to *P. falciparum*, asexual stages of *P. vivax* are susceptible to primaquine. Thus chloroquine plus primaquine can be considered as a combination treatment. The only drugs with significant activity against the hypnozoites are the 8-aminoquinolines (bulaquine, primaquine and tafenoquine).

Treatment of uncomplicated P. vivax

For chloroquine-sensitive *P. vivax* malaria (i.e. in most places where *P. vivax* is prevalent), oral chloroquine at a total dose of 25 mg base/kg body weight for a course of treatment is effective and well tolerated. Lower total doses are not recommended, as these might encourage the emergence of resistance. Chloroquine is given in an initial dose of 10 mg base/kg body weight followed by either 5 mg/kg body weight at 6 hours, 24 hours and 48 hours or, more commonly, by 10 mg/kg body weight on the second day and 5 mg/kg body weight on the third day.

Recent studies have also demonstrated the efficacy of the recommended ACTs in the treatment of *P. vivax* malaria. The exception to this is artesunate plus sulfadoxine-pyrimethamine.

For treatment of chloroquine-resistant *P. vivax* malaria, amodiaquine, mefloquine and quinine are effective. ACTs based on either amodiaquine, mefloquine or piperaquine, rather than monotherapy, are the recommended treatment of choice.

For the complete (radical) removal of *P. vivax* infection, primaquine is required, but is contraindicated in children under 4 years of age and in pregnant women and girls.

Treatment of uncomplicated malaria caused by P. ovale *and* P. malariae

Treat with chloroquine as described for *P. vivax* above.

Prevention of malaria

Most important is the prevention of mosquito bites. All children, all pregnant girls and all patients who have had a recent bout of malaria should be provided with an insecticide-impregnated bed net.

Drugs for prophylaxis depend on the region and sensitivity of the malarial parasite.

This is important for:

- children with sickle-cell disease: chloroquine 5 mg/kg weekly
- children or adults who return to an endemic area after an absence of over 1 year, even if they are originally from that region
- non-immune individuals: people from non-endemic areas.

Intermittent preventive treatment for malaria in infants (ITPi) and children (ITPc, now called seasonal malaria chemoprevention, SMC)

IPTi

- Malaria cases can be reduced by 30% in infants during the first 12 months of life using this safe, affordable and simple tool. It can be implemented via existing vaccination programmes run by the WHO.
- For infants, a treatment dose of sulfadoxine/pyrimethamine (SP) should be given three times at the time of each immunisation, beginning at 2 months (DTP2), 3 months (DTP3) and 9 months (measles and yellow fever). Each tablet of SP contains 500 mg sulfadoxine and 25 mg pyrimethamine, and for infants the following sizes for each dose are: a quarter tablet for children weighing less than 5 kg, and a half tablet for children weighing 5–10 kg.

SMC

- For children living in areas where transmission is highly seasonal (e.g. in Mali, Senegal, Niger and northern Nigeria), aged 1–6 years, a single dose of one tablet of SP plus three doses of one tablet/day for 3 days of amodiaquine (200 mg) is given once a month during the malaria transmission season.
- Tablets are crushed and suspended in water and given by spoon. Side effects are very rare. Minor gastrointestinal side effects may occur.
- For areas in which there is resistance to SP, piperaquine may be used instead of SP.

ITPi and SMC are recommended in addition to treated bed nets in areas of moderate to high levels of malaria transmission and low to moderate levels of parasite resistance to SP.

Preventive treatment for malaria in pregnant girls and women (see *Section 2.8.D)*

Follow-up care for anaemia

- If moderate or severe anaemia has been documented, give home treatment with a daily dose of iron/folate tablet or iron syrup for 3 months where possible (it takes 2–4 weeks to correct the anaemia and 1–3 months to build up iron stores).
- **However, if the child is taking sulfadoxine-pyrimethamine for malaria, do not give iron tablets that contain folate until a follow-up visit in 2 weeks. The folate may interfere with the action of this antimalarial drug.**
- If the child is over 1 year and has not had mebendazole/albendazole in the previous 6 months, give one dose of mebendazole (500 mg) for possible hookworm or whipworm infestation (*see* Section 6.3.C.a). Advise the mother about good feeding practices.
- Omit iron in any child with severe malnutrition in the acute phase.
- A study in Malawi showed that many children who were so anaemic as to require a blood transfusion died within 6 months of discharge from hospital. Prophylactic antimalarial drugs (coArtem) at 1 month and 2 months post discharge prevented many readmissions and deaths.

Follow-up care after malaria has been treated

- Ask the mother to return if the fever returns or persists after 2 days of treatment, or if the child's condition gets worse in any way.
- If this happens, reassess the child to exclude the possibility of other causes of fever.
- Check whether the child actually took the full course of treatment, and repeat a blood smear. If the treatment was not taken, repeat it. If it was taken but the blood smear is still positive (remember that an RDT can remain positive for up to 6 weeks after the initial infection), and the child is not seriously ill, re-treat with first-line drugs.
- If the child returns within 2 weeks, give a full course of oral quinine.
- If the child is severely ill, refer them to a hospital for inpatient treatment.

6.3.B Other protozoal infections

Introduction

The organisms collectively termed **protozoa** are not closely related to each other. They do have some similarities when viewed under a microscope, as they are largely unicellular and motile, although with exceptions.

Toxoplasmosis

Toxoplasmosis is caused by infection with a common parasite called *Toxoplasma gondii*. *T. gondii* can be found in:

- undercooked or raw meat
- cured meat
- unpasteurised goats' milk
- cat faeces.

It cannot be passed from person to person apart from mother to unborn child.

During acute toxoplasmosis, symptoms are often influenza-like (swollen lymph nodes, or muscle aches and pains that last for a month or more).

Swollen lymph nodes are commonly found in the neck or under the chin, followed by the axillae and the inguinal region. Swelling may occur at different times after the initial infection, persist, and/or recur for various times independently of antiparasitic treatment. It is usually found at single sites in adults, but in children multiple sites may be more common. Enlarged lymph nodes will resolve within 1–2 months in 60% of patients. However, 25% of patients take 2–4 months to return to normal, and a few take longer than this.

Young children and immunocompromised patients, such as those with HIV/AIDS, may develop severe toxoplasmosis. This can cause encephalitis or necrotising retinochoroiditis.

Infants can develop a congenital infection acquired *in utero*. The key features are fever, rash, petechiae, lymphadenopathy, hepatosplenomegaly, jaundice, hydrocephalus or microcephaly, microphthalmia, epilepsy and chorioretinitis.

Management

Congenital toxoplasmosis in newborns and immunocompromised children with HIV infection can be treated for a year with pyrimethamine (with additional folinic acid) plus sulfadiazine. This treatment requires expert management.

Amoebiasis

Infection by *Entamoeba histolytica* is acquired from human hosts via contaminated food, water or direct contact. Most infected children are asymptomatic, but some have systemic illness. This can last for many weeks. The disease presents with acute diarrhoea with colicky abdominal pains. A small proportion have bloody diarrhoea with a fever, and rarely intestinal perforation with peritonitis or haemorrhage may occur.

The diagnosis can be confirmed by observing the amoebae in a fresh stool or following a biopsy of the ulcers at sigmoidoscopy.

Amoebic liver abscesses occur in less than 1% of infected individuals. They present with fever, abdominal pain, and a tender liver sometimes with a palpable mass. The liver abscess often occurs without gastrointestinal symptoms and with negative stools. The diagnosis can be confirmed by ultrasound scan or **CT scan (if available)**.

Treatment is required for those with systemic illnesses, those with diarrhoea due to invasive ulceration and those with liver abscesses.

- Metronidazole is the drug of choice and is well absorbed orally: 7.5 mg/kg three times daily for 5–10 days (maximum daily dose 400 mg).
- If the abscess is very large and particularly if there is concern that it may rupture, it may require aspiration under careful ultrasound support.
- After the acute treatment of a liver abscess, diloxanide should be used immediately following the course of metronidazole in order to remove all amoebae from the bowel.
- The dose of diloxanide is:
  - 1 month to 12 years of age: 6.6 mg/kg three times daily for 10 days
  - > 12 years of age: 500 mg three times daily for 10 days.

Cryptosporidiosis

Cryptosporidium parvum can be acquired from infected human or animal hosts and from contaminated water and food.

It causes an acute gastroenteritis, which is self-limiting in most children. The enteritis is associated with watery diarrhoea, nausea and colicky abdominal pains. It lasts for approximately 2 weeks. In otherwise healthy children it does not usually require treatment with antimicrobial drugs unless it persists or is associated with systemic illness, in which case azithromycin may be effective.

In children with AIDS it can produce a protracted and severe illness involving major weight loss, in which case it can be treated with azithromycin. Avoid azithromycin in patients with liver disease.

The dose of azithromycin is:

- 6 months to 12 years of age: 10 mg/kg once daily for 3 days or longer in AIDS.

Giardiasis

Infection by *Giardia lamblia* can be acquired from infected human or animal hosts and from contaminated water and food. The organisms live in the duodenum.

The infection may be asymptomatic or it can produce an acute gastroenteritis with watery stools, colicky abdominal pains and nausea. It can also produce a chronic diarrhoeal illness with malabsorption and colicky abdominal pain lasting for many months.

Diagnosis is best made from examining a fresh stool. Sometimes more than one examination will be necessary.

- Metronidazole (at the doses described for amoebiasis above) is appropriate in the chronic form of the infection. The acute form usually resolves without treatment.

6.3.C Helminth infections

6.3.C.a Worms

BOX 6.3.C.A.1 Minimum standards
- Faecal microscopy and egg count.
- Anoscopy.
- Eosinophil count and chest X-ray if available.
- Mebendazole, albendazole and ivermectin.
- Topical thiabendazole.

Introduction

In low-resource countries, children presenting to medical facilities may harbour intestinal helminthiasis (worms) or their juvenile forms (larvae) in other organs. Often this situation may exist without the presence of any signs or symptoms. In such situations ill health or the risk of serious complications is directly related to the number of parasites in a child; although children bearing heavy loads of parasites are in a minority. These patients will often present for other reasons, without their heavy worm infections being recognised.

Parasitology of worms

There are three important groups of helminth infections:

1 **Cestodes:** Beef tapeworm (*Taenia saginata*) and pig tapeworm (*Taenia solium*).
2 **Nematodes:** Roundworms (*Ascaris* species), hookworms (*Ancylostoma duodenale*), whipworms (*Trichurius* species) and threadworms (*Enterobius* species).
   - *Ascaris lumbricoides* is the commonest human roundworm. Adult worms are whitish pink, several millimetres (mm) wide and up to 30 centimetres (cm) long, which may live for years in the small intestine. They are often seen in stool or vomit. Transmission is by ingestion of embryonated eggs from soil. Adult worms shed their eggs in faeces. The ill effects of ascariasis are largely indirect and rare (e.g. a worm in the common bile duct). The probability of this obstruction increases with worm load.
   - Hookworms are of two species, *Necator americanus* (the New World hookworm) and *Ancylostoma duodenale.* Both adult forms are hair-like, about 1 cm long, with cutting plates at the mouth end. *Ancylostoma* is generally the more virulent pathogen. Both species occur widely, with overlap, and the differences between them can be ignored by clinicians without a special interest in this subject. They have invasive larvae, and both skin penetration and ingestion of embyonated eggs are involved in transmission. Sustained blood loss in the small intestine leads to an accumulating risk of anaemia. In children, protein-losing enteropathy and systemic secondary effects of chronic inflammation are equally important.
   - *Trichuristrichiura* commonly known as the whipworm can be up to 4 cm long with thickness of a hair except at the tail end which is wider. Transmission is similar to *Ascaris* but maturation occurs only in the gut without tissue invasion beyond the mucosa. Its ill effects are related to worm load and may lead to a form of colitis with systemic secondary effects of chronic inflammation. This intensity of infection occurs only in a small minority of children.
   - *Enterobius vermicularis* is an intestinal helminth which is spread in the form of embryonated eggs by personal contact among children. It is largely harmless but can cause secondary infection in the vaginal introitus.
   - *Strongyloides stercoralis* is capable of independent existence in the soil. It is an opportunistic parasite of several mammals, including humans. Person-to-person spread occurs with probability related to intimacy of contact. Although it is acquired in childhood, its most devastating (often fatal) effects occur only when filariform larvae become disseminated through asexual reproduction in the host. This happens if host immunity breaks down, for example with severe malnutrition or malignancy in later life. Surprisingly, disseminated strongyloidiasis is not associated with HIV infection, although it is associated with another retrovirus, HTLV1.
3 **Trematodes** or flukes, which include blood flukes (e.g. schistosomiasis) (*see* Section 6.3.C.c) and biliary tract, lung and gut flukes.

Diagnosis

The main clues to heavy parasitosis are in growth, nutrition and in the case of hookworm, anaemia. Gastrointestinal symptoms also occur. Often a presumptive diagnosis is based on manifestations suggestive of worm infections. An increasing number of studies on the effects of helminth infections on cognitive function and general physical fitness have added to the case for community control of these infections as an important public health measure.

Investigations

Investigation for adult worms in the intestine

Except for *Enterobius*, this depends on the examination of stool. Full laboratory details are beyond the scope of this manual, but for *Ascaris*, hookworm and *Trichuris*, examination by the Kato (modified Kato or Kato-Katz) method is recommended. This requires only microscope slides, a standard hole in a flat spatula with which a 50 mg stool sample is squashed on to the slide, cellophane, glycerol and a stain such as malachite green. A microscopic count of eggs per gram of stool gives an indication of the intensity of infection.

Enterobius (thread worm) eggs are only occasionally seen in stool because they adhere to perianal skin where the female worm has deposited them. They can be picked up on sticky tape and transferred to a glass slide. Specific diagnosis of *Enterobius* is not really necessary in any case,

TABLE 6.3.C.A.1 Diagnosis of helminth infections due to the presence of adult worms

Symptom or sign	Likely species of adult worm in the viscera
Short stature, not growing	*Trichuris* or hookworm
Mild or moderate muscle wasting	*Trichuris* or hookworm
Anaemia, microcytic hypochromic	Hookworm or severe trichuriasis; not *Ascaris*
Hypoproteinaemia, possible oedema	Hookworm or severe trichuriasis or disseminated strongyloidiasis: not *Ascaris*
Pica, especially eating soil (geophagia)	Any or all helminths
Colicky abdominal pain	*Ascaris:* common but a weak correlation
Intestinal obstruction	*Ascaris:* a quite common surgical emergency
Jaundice and/or pancreatitis	*Ascaris:* uncommon
Laryngeal obstruction	*Ascaris:* rare
Vomiting up worms	*Ascaris:* common
Chronic diarrhoea	*Trichuris* or severe hookworm or strongyloidiasis
Defecating during sleep	*Trichuris*
Blood and mucus in stool	*Trichuris*
Rectal prolapse	*Trichuris*
Finger clubbing	Intense trichuriasis or hookworm; not *Ascaris*
Perianal itching	*Enterobius*
Vulvovaginitis	*Enterobius*

as it is reasonable to treat the patient and family when it is suspected, without proving the presence of the worm (see below).

The most effective way to establish that *Trichuris* infection is intense is to see the worms on prolapsed rectal mucosa or to perform anoscopy. An otoscope with a wide-aperture speculum can be used for anoscopy in young children. The worms are usually confined to the caecum, so if they have reached the lower rectal mucosa the infection must be intense.

Strongyloides is a rare cause of illness in young children, although it becomes more significant in adolescence in some regions. Microscopy has a low sensitivity, and the stool requires culture by special techniques. Serology is not widely available and also lacks specificity (*see* Section 6.3.C.h).

Investigation for migrating larvae

Eosinophilia is characteristic of this stage with 20–50% of the leucocytes being eosinophils in some cases. By contrast, eosinophilia is not a constant feature of established infection with adult worms and so is a useless diagnostic marker for intestinal infection.

The chest X-ray may show a flaring shadow spreading out from the hila.

Serology is diagnostically useful in visceral larva migrans (*Toxocara* infection), but is only undertaken in special centres or research laboratories.

Diagnosis of cutaneous larva migrans (dog hookworm infection picked up from skin–ground contact) is purely clinical. The key is to think of it when looking at a patch of itchy pyoderma; the red line has often disappeared under the scratching.

TABLE 6.3.C.A.2 Illness due to larvae rather than adult worms

Symptom or sign	Likely species of larvae in the viscera
Cough and wheeze	*Toxocara canis* or *T. cati* (dog or cat roundworm) Also *Ascaris* and hookworm
Hepatomegaly	*Toxocara*
Lymphadenopathy	*Toxocara*
Leucocytosis with extreme eosinophilia	*Toxocara*
Epilepsy or encephalopathy	*Toxocara* (rare)
Uveitis or proliferative retinitis	*Toxocara* (younger children escape in endemic areas: naive strangers are more susceptible)

It is not clear how much of the total burden of cough, wheezing and dyspnoea in a child population in an endemic zone is due to the pulmonary migration of helminth larvae. Factors that make the symptoms more severe are migration of children naive to *Ascaris* or hookworm infection into the endemic area, and zoonotic larvae (*Toxocara*) which cannot complete their migration but die in their human hosts.

Treatment

The broad-spectrum antihelmintics, mebendazole and albendazole, are drugs which combine great efficacy with an almost complete absence of side effects in ordinary use. They are the drugs of choice for ascariasis, hookworm infection, trichuriasis and enterobiaisis. Albendazole is as effective as thiabendazole for visceral larva migrans, and with fewer side effects. However, visceral larva migrans is a self-limiting condition where symptoms and signs resolve in 3 months. Thiabendazole is still useful for cutaneous larva migrans in a topical preparation (10% in aqueous cream; the pharmacist may be able to make this on site, see Regimens below). Ivermectin is recommended for strongyloidiasis, but albendazole remains useful and is preferable to thiabendazole because it is less toxic.

Mebendazole

This is most commonly available as 100 mg tablets, but is also produced as a 20 mg/5 mL liquid and a 500 mg tablet. The tablets are chewable and reasonably palatable. The 500 mg tablet is useful for mass campaigns against *Trichuris* or hookworm. It is not approved for use in children under 2 years of age, but clinical judgement should be used in a symptomatic child. **It is considered unsafe in pregnancy or lactation.**

Threadworms and pinworms

Oral dose:

- Children from 6 months up to 10 kg body weight: Give 50 mg as a single dose; if reinfection occurs a second dose may be needed after 2 weeks.
- Children over 1 year of age or more than 10 kg body weight: Give 100 mg as a single dose; if reinfection occurs a second dose may be needed after 2 weeks.

Whipworms, roundworms and hookworms
Oral dose:
- Children from 6 months up to 10 kg body weight: Give 50 mg twice daily for 3 days.
- Children over 1 year of age or more than 10 kg body weight: Give 100 mg twice daily for 3 days.

Capillariasis
Oral dose:
- Children over 2 years of age: Give 200 mg twice daily for 20 days.

Echinococcus (mebendazole is second-line therapy, albendazole is preferred)
Oral dose:
- Child over 2 years of age: Give 15 mg/kg/dose three times daily.

Toxocariasis: visceral larva migrans (mebendazole is second-line therapy, albendazole is preferred)
Oral dose:
- Children over 2 years of age: Give 100–200 mg twice daily for 5 days, although doses of up to 1 gram/day have been used for 21 days. Severe disease may warrant corticosteroid use.

Trichinosis (gastrointestinal phase of illness only)
Oral dose:
- Children over 2 years of age: 5 mg/kg (maximum 200 mg) twice daily with food for 7 days; severe infection may require concomitant corticosteroid use; late-phase antihelmintic therapy is not indicated.

Albendazole
This drug is closely related to mebendazole, with similar pharmokinetics. It has superior efficacy to mebendazole in systemically invasive conditions, and is more effective against migrating larvae. It is available as 200 mg tablets or 200 mg/5 mL liquid. Cautions are as for mebendazole, noting its greater systemic absorption.

Hookworms, roundworms, pinworms and threadworms (ancylostomiasis, necatoriasis, ascariasis and enterobiasis)
Oral dose:
- Children aged 12 months to 2 years: Give 200 mg as a single dose.
- Children over 2 years or 10 kg: Give 400 mg as a single dose before food. Treatment may be repeated in 3 weeks.

Echinococcus
Oral dose:
- 7.5 mg/kg twice daily (maximum dose 400 mg twice daily). Given continuously for up to 2 years.

Tapeworm (taeniasis) and strongyloidiasis
Oral dose:
- Children under 10 kg: Give 200 mg daily before food for 3 days.
- Children over 10 kg: Give 400 mg daily before food for 3 days. Treatment may be repeated in 3 weeks.

Neurocysticercosis
Oral dose:
- Children under 60 kg: Give 7.5 mg/kg (maximum dose 400 mg) twice daily after food for 7–30 days.

Whipworm (trichuriasis)
Oral dose:
- Children over 2 years of age: Give 200–400 mg as a single dose, or in heavier infections, 400 mg daily for 3 days. Treatment may be repeated in 3 weeks.

Filariasis for community eradication programmes in combination with diethylcarbamazine or ivermectin
Oral dose:
- Children under 10 kg: Give 200 mg once annually for 5 years.
- Children over 10 kg: Give 400 mg annually for 5 years.

Hairworm (trichostrongyliasis)
Oral dose:
- Child over 10 kg: Give 400 mg as a single dose.

Cutaneous larva migrans
Oral dose:
- Children over 10 kg: Give 400 mg as a single dose, or 400 mg daily for 3 days.

Visceral larva migrans (toxocariasis)
Oral dose:
- Child of all ages: Give 10 mg/kg daily (maximum 400 mg daily) for 5 days.

Trichinosis
Oral dose:
- Children over 10 kg: Give 400 mg daily for 8–14 days.

For topical treatment of cutaneous larva migrans, thiabendazole tablets can be crushed and mixed with aqueous cream or 1% hydrocortisone cream or ointment to a concentration of 10% thiabendazole.

In places or situations where only the older drugs are available
Details and dosages are not given here. The manufacturers' recommendations may be followed, but these drugs are inferior to mebendazole and albendazole, and should be replaced if possible.
- Piperazine is effective against *Ascaris* and *Enterobius.* It has no action on *Trichuris* or hookworm, and is toxic in children prone to epileptic seizures.
- Levamisole is effective against *Ascaris* and is fairly useful effective in hookworm infection (especially *Necator americanus*); to be used in mass control programmes.
- Thiabendazole has limited effectiveness in trichuriasis and is useful in strongyloidiasis, toxocariasis and cutaneous larva migrans.
- Pyrantel is effective against *Ascaris* and *Enterobius*, with some action against *Necator americanus* and less against *Ancylostoma duodenale*. Only if combined with oxantel does the preparation affect *Trichuris*.

Further reading
WHO's programme 'Action against worms' http://evidenceaction.org/deworming/

6.3.C.b Hydatid disease

BOX 6.3.C.B.1 Minimum standards
- Ultrasound/radiology.
- Albendazole.
- Percutaneous aspiration, injection with hypertonic saline and re-aspiration (PAIR).
- Surgical excision.

Introduction

The adult stage of the tapeworm *Echinococcus granulosus* lives in the gut of dogs and certain other carnivores. The usual intermediate hosts are herbivores. **Humans may become an accidental intermediate host for the cystic stage of the parasite following ingestion of eggs in dog faeces contaminating the fingers, food or water.** Because of the slow rate of growth of hydatid cysts, symptoms from infection in childhood often present in adulthood. Many cysts remain asymptomatic, eventually calcify and become sterile.

Epidemiology

The disease is widespread in sheep-farming countries and wherever there is intimate contact between humans and dogs or other canids, and where dogs scavenge dead animals or offal. There is a high incidence in the Turkana region of Kenya.

Clinical features

- Cysts may occur in virtually any organ.
- Many cysts are asymptomatic but may be palpable if they are large or superficial.
- Abdomen:
  - Palpable mass: liver (60% of all cysts), spleen, other intra-abdominal cysts.
  - Communication with the biliary tract: cholangitis, rigors, jaundice.
  - Abdominal pain.
  - Rupture from trauma.
- Chest:
  - Lungs (25% of cysts).
  - Pleuritic pain and cough.
  - Often asymptomatic, detected on chest X-ray.
- Other areas:
  - Brain: space-occupying lesions (3–5% in some countries).
  - Bone cysts: pathological fractures, respond poorly to chemotherapy.
  - Cyst rupture may cause anaphylaxis and/or spread by 'seeding' of daughter scolices (heads of immature worms).

Diagnosis

- Ultrasound is effective in detecting liver and abdominal cysts. The presence of a separated membrane or daughter cysts makes the diagnosis highly likely. The condition needs to be differentiated from simple hepatic cysts.
- Plain X-ray for lung or bone cysts. CT or MRI (if available) is also useful (e.g. for brain cysts).
- Eosinophilia is present in around 20% of cases. This may be due to cyst leakage or rupture.
- Serology: specific IgG ELISA AgB (antigen-B-rich fraction) (if available) is most sensitive. Serology lacks sensitivity for extra-hepatic cysts (note that false-positive results are obtained in cysticercosis).
- A urine antigen detection test appears promising.

Treatment

Calcified cysts require no treatment.

Medical treatment

- Albendazole is useful for patients with inoperable, widespread or numerous cysts, and for patients unfit for surgery.
- Continuous treatment is now recommended (for up to 2 years). Its duration depends on the lesion's response. The dose is 7.5 mg/kg orally twice daily. The maximum dose is 400 mg twice daily.
- The absorption of albendazole is enhanced if it is taken with fatty meals.
- Albendazole plus praziquantel has greater protoscolicidal activity. The combination is successful for inoperable spinal, pelvic, abdominal, thoracic or hepatic hydatid, and as an adjunct to surgery.
- Antihelmintics may reduce the need for surgery in uncomplicated pulmonary cysts.
- Patients undergoing surgery or PAIR should receive pre-operative albendazole (for 1–3 months) with or without praziquantel.

Percutaneous aspiration under ultrasound control

Puncture, aspiration, injection, re-aspiration (PAIR):
- The patient should be on albendazole for at least 4 weeks prior to PAIR.
- Following initial aspiration of the cyst, hypertonic saline is injected into the cyst and re-aspirated after 20 minutes.
- Percutaneous aspiration combined with an 8-week course of albendazole is more effective than either treatment alone.
- Laparoscopic treatment of liver and spleen hydatid is also effective.
- Contraindications to PAIR include cysts in the CNS or heart, and cysts communicating with the biliary tree, abdominal cavity, urinary tract or bronchi.

Surgery

Surgical removal is standard treatment if the lesion is accessible but is unsuitable for PAIR. The procedure is as follows:
- The patient should be on albendazole for at least 4 weeks prior to surgery.
- Pack around the cyst and avoid spillage of the cyst contents (there is a risk of anaphylaxis and seeding).
- Drain the cyst, replace fluid with hypertonic saline, drain again, and then remove the cyst capsule.

- High rates of recurrence and of surgical complications are recorded in inexpert hands.
- It is important to avoid hypertonic saline entering the bile ducts, as this may cause sclerosing cholangitis.

Prevention

- Ensure disposal of infected herbivore carcasses and offal.
- Treat dogs with praziquantel.
- Maintain strict hygiene, and protect food and water from contamination.

6.3.C.c Schistosomiasis

BOX 6.3.C.C.1 Minimum standards
- Public health measures to improve water and sanitation.
- Urine and faecal microscopy
- Praziquantel.

Introduction

Schistosomiasis occurs in areas of the world where there is a combination of warm fresh water containing specific snails, and urinary and/or faecal excretion of *Schistosoma* eggs by humans.

Parasite and life cycle

Eggs are passed from humans in stool or urine into freshwater containing snails, *Bulinus* (*S. haematobium*), *Biomphalaria* (*S. mansoni*) and *Oncomelania* (*S. japonicum*). Miracidia hatch from the eggs, penetrate the snail, and replicate into cercariae (larval forms) which are then released into the water.

The cercaria penetrates the skin (or pharyngeal mucosa) of humans, loses its tail and becomes a schistosomula, which is then transported to the lung capillaries. It reaches the left side of the heart and is distributed throughout the body. Those that reach the portal system develop into mature worms about 1 cm in length in the liver.

Adult males and females copulate and migrate in pairs to their preferred egg-laying sites, *S. haematobium* to the vesical veins and pelvic plexus, and *S. mansoni* to the superior and inferior mesenteric veins.

Female flukes produce eggs daily throughout their average 3- to 4-year lifespan. Most eggs pass through the vessel wall, and about 50% reach the lumen of the urinary tract or intestine and are excreted. Those that remain in the tissues provoke an immune reaction which causes the disease. Some eggs are transported to the liver and some reach the general circulation.

Pathogenesis

Pathogenesis can be divided into four stages.

1 **Dermatitis.** An itchy papular rash 'swimmers itch' lasting one to two days may develop as a result of humoral immune reaction to invading cercariae and schistosomulae. However, it is more likely to be due to avian schistosoma (non-pathogenic to man). Older children and adults develop a degree of resistance to this stage of invasion.
2 **Katayama fever** (2–8 weeks). A humoral reaction to adult worms and eggs results in an acute illness associated with formation of immune complexes. Symptoms include fever, rigors, malaise, diarrhoea, cough, hepatosplenomegaly and marked eosinophilia. It is a self-limiting disease.
3 **Established disease** (usually after 2 months). A T-cell delayed-hypersensitivity response to eggs deposited in tissue results in granuloma formation. If the worm load is reduced by drug therapy at this stage, granulomata may resolve, leaving little disease.
4 **Fibrotic complications.** Repeated infections without treatment eventually result in fibrosis, for example of the ureter and bladder (*S. haematobium*) and liver (*S. mansoni*). There is little response to drug therapy at this stage.

TABLE 6.3.C.C.1 Schistosomiasis: geographical areas (the commonest species and areas are shown in bold type)

Schistosoma *species*	Disease	Area
S. haematobium	Urinary tract	**Africa**, Middle East
S. mansoni	Intestines, liver	**Africa**, Middle East, **South America**
S. intercalatum	Intestines, liver	Central and West Africa, uncommon
S. japonicum	Intestines, liver	**China**, **Indonesia**, **Philippines**
S. mekongi	Intestines, liver	Laos, Kampuchea, small number of foci

Epidemiology

- Schistosomiasis affects at least 240 million people worldwide, and more than 700 million people live in endemic areas.
- Schistosomiasis is associated with communities living near swamps, rivers, irrigation canals and rice fields, who have poor hygiene and sanitary facilities and lack a ready supply of clean water.
- Infection is highest in children (5–14 years) who are an important reservoir of infection because of their indiscriminate excretion habits near and in water.
- Infections decrease after puberty, but adults are still at risk when farming or washing clothes.

Clinical features

TABLE 6.3.C.C.2 Symptoms and complications of *S. haematobium* and *S. mansoni*

Initial stage	*S. haematobium*	*S. mansoni*	Comments
Swimmers' itch	Terminal haematuria	Bloody diarrhoea Anaemia	*S. japonicum* is similar to *S. mansoni*
Katayama fever	Obstructive uropathy Calcification of bladder and lower ureters Bladder calculi	Hepatic fibrosis Portal hypertension Ascites Colonic polyposis Nephropathy	Hepatic fibrosis is most often seen with *S. mansoni* Katayama fever is more severe with *S. japonicum*

S. haematobium

This causes urinary schistosomiasis.

- Terminal haematuria, there may be dysuria.
- In a minority of children, frequent untreated infections eventually lead to structural disorder of the bladder and lower ureter, resulting in obstructive uropathy, hypertension and chronic renal failure.
- Obstruction can be demonstrated by ultrasonography and intravenous pyelogram. Adequate treatment in the early stages may be followed by resolution of ureteric lesions.

S. mansoni

This causes intestinal schistosomiasis along with other species, namely *S. intercalatum*, *S. japonicum* and *S. mekongi*.

- Bloody diarrhoea. In long-standing cases there is severe iron-deficient anaemia, and even heart failure (due to anaemia).
- Protein-losing enteropathy with hypoalbuminaemia may result from colonic granulomatous disease and polyps.
- The left lobe of the liver is enlarged more than the right lobe. Ascites may occur. Liver function is usually well preserved.
- Marked splenomegaly due to portal hypertension is associated with pancytopenia.
- Haematemesis from oesophageal varices is the final event which influences the prognosis.
- Ultrasonography is useful for grading the degree of peri-portal fibrosis and in differential diagnosis from other liver diseases.
- Acute and long-term management of oesophageal varices requires endoscopy and decisions regarding sclerotherapy (*see* Section 5.7.B on liver disease).
- Nephropathy due to immune complex disease may manifest with microscopic haematuria and proteinuria or nephrotic syndrome. Nephrotic syndrome has a poor prognosis, especially if associated with amyloid disease (*see* Section 5.6.A).

Salmonella infection

Schistosoma worms may harbour *Salmonella* species, including *S. typhi*, which cannot be eradicated until the schistosomiasis is treated. This phenomenon occurs in both *S. haematobium* and *S. mansoni* infections. *Salmonella* may cause a reversible nephritis in *S. mansoni* infection.

Complications common to S. haematobium *and* S. mansoni

- Spinal cord myelopathy (less common with *S. haematobium*).
- Brain granulomata (more common with *S. japonicum*, less common with *S. haematobium*).
- Pulmonary hypertension (less common with *S. haematobium*).
- Chronic *Salmonella* infection.

Diagnosis

Microscopy of urine or faeces

S. haematobium

A midday specimen is best. Urine should be sedimented or filtered. Viability of the eggs (and thus requirement for treatment) can be established by looking for miracidia, which hatch when eggs are put in boiled water that has been cooled.

S. mansoni

If stool smear is negative on microscopy, a concentration method must be undertaken. Miracidial hatching techniques are also available.

Rectal biopsy

Rectal biopsy to demonstrate the presence of eggs is undertaken if urine and faeces are negative.

Serology

Serology is of little value for diagnosis in indigenous patients, but may be useful in the non-immune (e.g. tourists to an endemic area). Antigen tests are being developed.

Treatment

Praziquantel is effective against all human *Schistosoma* species, and is the only available drug treatment. Treatment at least three times in childhood usually prevents adult disease.

Praziquantel is given at a dose of 40 mg/kg in two divided doses given 4–6 hours apart on one day. It can also be given as a single dose of 40 mg/kg. For heavy *S. mansoni* infection and for *S. japonicum* infection, 60 mg/kg is advised, given in two doses 4–6 hours apart. Repeat urine or stool examination should be done at 3–4 months.

Praziquantel is safe during pregnancy. The safety of praziquantel in children under 4 years of age has not been established, but this drug can be used to treat individually infected children.

Side effects include dizziness, drowsiness, skin reactions, fever, headache and vomiting.

Prevention

Control of schistosomiasis is very difficult. Measures include regular mass treatment of communities and improvement in water supply, sanitation and hygiene. Mollusciciding (use of chemicals to kill the snails) is usually impractical and too expensive for general use.

6.3.C.d Fascioliasis (liver fluke infections)

BOX 6.3.C.D.1 Minimum standards

- Vector control.
- Triclabendazole (preferred) or Bithional.

Introduction

This disease is caused by *Fasciola hepatica* and *Fasciola gigantica*, and occurs in sheep- and cattle-rearing areas worldwide, especially South America.

Freshwater snails act as the intermediate amplifying hosts, liberating free-swimming cercariae which encyst as metacercariae on water plants. Humans are infected following ingestion of metacercarial cysts on raw aquatic plants (e.g. watercress) or from contaminated water. Following ingestion, the larvae emerge in the duodenum, penetrate the intestinal wall, migrate via the peritoneal cavity to the liver, penetrate the liver capsule, and after 3–4 months mature into adults in the bile ducts.

Clinical features

Infections may be asymptomatic. Acute presentations occur 6–12 weeks after infection. Fluke migration may be associated with fever, malaise, abdominal pain, weight loss, urticaria, cough and wheeze. In chronic presentations, symptoms may be minimal or may be due to recurrent cholangitis, intermittent biliary obstruction or anaemia.

Ectopic flukes may cause granuloma or abscess formation in various organs, and also present as migrating skin nodules.

Investigations

- Eosinophilia is common.
- Liver ultrasound is often normal.
- CT of the liver (if available) may reveal hypodense lesions.
- Serology may be helpful in established *F. hepatica* infections, but is less reliable for *F. gigantica*. Fasciola excretory–secretory (FES) antigen detection in faeces is available for *F. hepatica*.
- In established infections, eggs may be found in faeces.

Treatment

Triclabendazole is the drug of choice for *F. hepatica* and *F. gigantica* infections. One dose of 10 mg/kg taken with food is usually effective, but should be repeated after 12 hours in severe infections. Expulsion of dead or damaged flukes may cause biliary colic 3–7 days after treatment; the colic responds well to antispasmodics. Triclabendazole resistance has been reported in Ireland, the UK and Australia.

Bithional, 30–50 mg/kg/day in three divided doses on alternate days for 10–15 days was the preferred treatment previously. Side effects include mild gastrointestinal upset and pruritus.

Nitazoxanide may be effective.

Praziquantel is unreliable in the treatment of fascioliasis.

Prevention and control

- Avoid potentially contaminated watercress and other aquatic plants.
- Treat herbivores.
- Undertake snail control.

6.3.C.e Dracunculiasis (guinea-worm disease)

BOX 6.3.C.E.1 Minimum standards

- Early identification of blister and worm emergence.
- Removal of worm and prevention of secondary infection.
- Filtering of water.
- Temephos to kill *Cyclops* species.

Introduction

Guinea-worm disease is transmitted exclusively by drinking stagnant water contaminated with tiny water fleas (*Cyclops* species) that carry infective guinea-worm larvae. Once ingested, the larvae mature into worms, growing up to 1 metre in length. Humans are the only known reservoirs for the disease.

About 1 year after infection, a very painful blister forms, 90% of the time on the lower leg, and one or more worms emerge accompanied by a burning sensation. To soothe the burning pain, patients often immerse the infected area in water. The worm then releases thousands of larvae into the water, contaminating the water and bringing the infective cycle full circle.

Epidemiology

The main source of infection is stagnant water sources such as ponds and sometimes shallow or step wells. 'Man-made' ponds are the main source of transmission.

Only four African countries (Chad, Ethiopia, Mali and

South Sudan) are known to be affected, with the majority of cases in South Sudan.

Guinea-worm disease is seasonal, occurring with two broad patterns found in endemic areas of Africa, depending on climatic factors. In the Sahelian zone, transmission generally occurs in the rainy season (from May to August). In the humid savanna and forest zone, the peak occurs in the dry season (from September to January).

A successful eradication programme for guinea-worm disease consists of several preventive strategies, such as ensuring wider access to safe drinking-water supplies, filtration of drinking water (with cloth filters) to prevent infection, intense surveillance and control to detect every case within 24 hours of the emergence of the worm(s), treatment of ponds with the larvicide temephos that kills the water fleas, and promoting health education and behaviour change.

Early case detection (when the patient feels the initial pain) is vital in order to contain the disease. There are thousands of village volunteers in the remaining endemic countries who are trained to find new cases, take care of them and report them to the area supervisor.

Clinical effects

Once a new case is identified, the wound must be disinfected and bandaged to help to prevent secondary infection. The worm should be gently pulled out a few inches every day until all of it has been removed. Many patients are unable to leave their beds for a month after the emergence of the worm.

Guinea-worm disease is not fatal, but infected people cannot work or attend school for months. Since the peak transmission period often coincides with the agricultural season, fields are left untended and food production declines. In Mali, guinea-worm disease is called 'the disease of the empty granary'. As adults lie sick, older children must take on the household chores and miss months of schooling. Younger children may miss vital vaccinations.

Prevention

- Effective surveillance to detect all cases within 24 hours of worm emergence.
- **Ensure access to safe drinking water, and convert unsafe sources to safe ones.**
- Construction of copings around well heads or installation of boreholes with hand pumps.
- **There must be regular and systematic filtering of drinking water derived from ponds and shallow unprotected wells, or from surface water.** Fine-meshed cloth or, better still, a filter made from a 0.15-mm nylon mesh, is all that is needed to filter out the *Cyclops* species from the drinking water.
- Treatment of unsafe water sources with temephos to kill the *Cyclops* species.
- Health education and social mobilisation to encourage affected communities to adopt healthy behaviour with regard to use of drinking water.

6.3.C.f Filariasis

BOX 6.3.C.F.1 Minimum standards
- Treatment of endemic communities.
- Control of mosquitoes (the vector).
- Diethylcarbamazine citrate (DEC), albendazole, doxycycline and ivermectin.

Introduction

This painful and profoundly disfiguring disease is usually acquired in childhood.

The disease is caused by three species of thread-like nematode worms, known as filariae, namely *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*. Around 90% of infections are caused by *Wuchereria bancrofti* and most of the remainder by *Brugia malayi*. About 120 million people are affected worldwide (of whom 60% live in South-East Asia and 30% live in Africa).

Life cycle of filariae

Filariae are transmitted by mosquitoes. When a mosquito with infective-stage larvae takes a blood meal, the parasites are deposited through the person's skin, from which they enter the body. These larvae then migrate to the lymphatic vessels and develop into adult worms over a period of 6–12 months, causing damage to and dilatation of the lymphatic vessels. The adult filariae live for several years in the human host. During this time they produce millions of immature microfilariae that circulate in the peripheral blood and are ingested by mosquitoes that bite the infected human. The larval forms further develop inside the mosquito before becoming infectious to humans. Thus a cycle of transmission is established.

Threadlike adult worms of *Wuchereria bancrofti* live in the lymphatics (groin, scrotum, arm). Male worms are about 3–4 cm in length, and female worms 8–10 cm. The male and female worms together form 'nests' in the lymphatic system. Females release thousands of microfilariae into the peripheral blood periodically every day, synchronising with the biting habits of the predominant local mosquito vector. Nocturnal periodicity is commonest, except in some Polynesian islands where microfilariae are more numerous by day.

Brugia malayi has two main forms: the nocturnal periodic form in swampy areas from India to Korea and Japan, and the nocturnal sub-periodic form in the damp forests of South-East Asia. The parasites of *B. malayi* are transmitted by various species of the genus *Mansonia*, and in some areas anopheline mosquitoes are responsible for transmitting infection. Brugian parasites are confined to areas of East and South Asia, notably India, Indonesia, Malaysia and the Philippines.

An estimated 120 million people in tropical and subtropical areas are infected, of whom almost 25 million men have genital disease (most commonly hydrocoele) and almost 15 million, mostly women, have lymphoedema or elephantiasis of the leg.

Diagnosis

Eosinophilia is common in the acute stages. Examination of thick smears of 20–60 microlitres of blood from a finger tip or filtration of 1 mL of intravenous blood and examination of the filtrate can reveal the microfilariae provided that the concentration is high (> 100 microfilariae/mL). Concentration techniques can improve sensitivity (e.g. Nuclepore filtration).

Samples should be appropriately timed (usually between 22.00 and 02.00 hours for *W. bancrofti*).

A variety of more sensitive diagnostic techniques are now available, including complement fixation tests for circulating *W. bancrofti* antigen (e.g. an ELISA 'TropBio-test') and a rapid finger-prick immunochromatographic card test (Amrad ICT, Binax). The rapid ICT has a high sensitivity and specificity and is currently the preferred diagnostic test for *W. bancrofti*. It is also used for monitoring the success of mass drug programmes. The test requires 100 microlitres of finger-prick blood drawn at any time, day or night.

Clinical features

The majority of infected people are asymptomatic, but virtually all have subclinical lymphatic damage, and up to 40% have kidney damage, with proteinuria and haematuria.

Inflammatory episodes associated with lymphatic filariasis involve:

- responses to the parasite itself
- the effects of secondary bacterial infection
- sometimes inflammatory mediators associated with endosymbiotic bacteria (*Wolbachia*).

Endosymbiotic bacteria infect most species of filarial nematodes that are pathogenic to humans, and contribute to the damage done by the filaria. Further characterisation of the *Wolbachia*–nematode relationship might allow the development of new therapeutic approaches to these parasitic diseases.

Acute episodes of local inflammation involving the skin, lymph nodes and lymphatic vessels often accompany chronic lymphoedema or elephantiasis (see below). Some of these episodes are caused by the body's immune response to the parasite, but many are the result of bacterial skin infections, linked to the partial loss of the body's normal defences as a result of underlying lymphatic damage. **Careful cleansing is extremely helpful in healing the infected areas and in both slowing and even reversing much of the damage that has already occurred.**

Acute symptoms may recur several times a year in three forms:

1 Acute filarial fever without lymphadenitis.
2 Acute filarial lymphangitis (AFL) follows the death of an adult worm, causing an inflammatory nodule or cord with lymphangitis spreading away from the affected node. This is usually mild, but may develop into an abscess.

Acute dermatolymphangioadenitis (ADLA) resembles cellulitis or erysipelas, and is often associated with secondary bacterial infection and impaired lymphatic flow, ascending lymphangitis and limb oedema. ADLA is more common than AFL, and is an important cause of lymphoedema and elephantiasis.

Chronic lymphatic filariasis may develop over months or years even without a history of acute symptoms. Lymphatic obstruction eventually leads to **elephantiasis**, most commonly affecting the legs, scrotum, arms and breast. Recurrent secondary bacterial skin infections (often streptococcal) cause acute pain and fever, and may be complicated by acute glomerulonephritis.

Other presentations of lymphatic filariasis include:

- hydrocoele, usually unilateral
- swelling of the scrotum
- acute epididymitis
- funiculitis (inflammation of the spermatic cord)
- monoarthritis
- glomerulonephritis
- chyluria, chylous diarrhoea, chylous ascites (due to rupture of dilated lymphatics). (Malabsorption of fat-soluble vitamins may complicate chylous diarrhoea.)

Brugian filariasis is usually less severe than Bancroftian filariasis.

The most severe symptoms generally appear in adults, and in males more often than in females. In endemic communities, around 10–50% of men suffer genital damage

TABLE 6.3.C.F.1 Recommended treatment strategies for mass drug distribution, individual drug administration, and morbidity control and treatment of lymphatic filariasis

Mass drug administration		Individual drug administration	Morbidity control and treatment
Africa	Rest of world		
IVM + ALB for at least 5 years	DEC + ALB for at least 5 years	(a) DEC (with or without ALB) 6 mg/kg single dose[1] (b) DEC 12-day course of 6 mg/kg per day in two or three divided doses **or** (c) doxycycline 200 mg/day for 4 weeks followed by one dose IV or IM	Lymphoedema: hygiene, physiotherapy, doxycycline 200 mg/day for 6 weeks Hydrocoele: surgical hydrocoelectomy, doxycycline 200 mg/day for 6 weeks Tropical pulmonary eosinophilia: doxycycline 200 mg/day for 4 weeks followed by one dose IV or IM

Based on Taylor M *et al.* (2010) *Lancet*, **376**, 1175–85.

[1] If the patient continues to live in an endemic area, or is less than 8 years of age (contraindication of doxycycline).

ALB, Albendazole; DEC, diethylcarbamazine (omit if there is onchocerciasis co-infection or a risk of serious adverse events with *Loa loa*); IVM, ivermectin (omit if there is a risk of serious adverse events with *Loa loa*).

Doxycycline: the doses above are suitable for children aged ≥ 8 years and weighing > 45 kg. Children aged ≥ 8 years but weighing < 45 kg should receive 4.4 mg/kg/day. Doxycycline should not be used for children < 8 years.

(hydrocoele and elephantiasis of the penis and scrotum). Elephantiasis of the entire leg or arm, the vulva and the breast may affect up to 10% of men and women.

In endemic areas, chronic and acute manifestations of filariasis tend to develop more often and sooner in refugees or newcomers than in local populations. Lymphoedema may develop within 6 months, and elephantiasis as soon as 1 year after arrival.

Tropical pulmonary eosinophilia (TPE)

A hypersensitivity response to microfilariae in the lungs can develop in some patients, causing cough and wheeze, especially at night. There may also be an enlarged liver, spleen and lymph nodes. Chest X-ray may show diffuse miliary shadows. Untreated TPE may progress to irreversible lung fibrosis. The condition is usually associated with high eosinophilia and high microfilaria titres. Microfilariae are usually absent from peripheral blood, but the rapid antigen test is usually positive.

Treatment and control of filariasis

A number of antihelmintic agents are effective, although care must be taken in the choice of antihelmintic depending on the risk of co-infection with onchocerciasis and/or *Loa loa*. Mass drug administration is an important strategy in community control. The treatment and control options are summarised in Table 6.3.C.F.1.

Treating endemic communities (*see* Table 6.3.C.F.1)
The goal is to eliminate microfilariae from the blood of infected individuals in order to interrupt the cycle of transmission by mosquitoes. A single dose of diethylcarbamazine citrate (DEC) has the same long-term (1-year) effect in decreasing levels of microfilaraemia as the formerly recommended 12-day regimen of DEC. More importantly, the use of single doses of two drugs administered together (optimally albendazole with DEC or ivermectin) is 99% effective in removing microfilariae from the blood for a full year after treatment. The following recommended drug regimens need to be administered once a year for at least 5 years, with coverage of at least 65% of the total at-risk population:

- 6 mg/kg of body weight diethylcarbamazine citrate (DEC) + 400 mg albendazole,

or

- 150 micrograms/kg of body weight ivermectin + 400 mg albendazole (in areas that are also endemic for onchocerciasis).

Treating individuals

Most problems result from bacterial and fungal 'superinfection' of tissues, linked to compromised lymphatic function caused by earlier filarial infection. Antibiotics against streptococcal and other bacterial infections are important. Surgical procedures are available to correct hydrocoele.

Because secondary bacterial infections play an important role in precipitating acute adeno-lymphangitis episodes and progression of lymphoedema, simple hygiene (either alone or in combination with antibiotic treatment) plays an important role in preventing episodes of acute disease and in the management of lymphoedema. Daily washing of affected limbs with soap and safe water to prevent secondary infection, combined with simple exercises, elevation of the limb, and treatment of cracks and entry points, provides significant relief from acute episodes and slows progression of the disease.

Vector control

Avoidance of mosquito bites through personal protection measures or community-level vector control is the best option for preventing lymphatic filariasis. If possible, malaria and lymphatic filariasis vector control should be integrated. Periodic examination of blood for infection and initiation of the above treatment is essential.

6.3.C.g Onchocerciasis

BOX 6.3.C.G.1 Minimum standards

- Rapid diagnostic tests.
- Ivermectin and doxycycline.

Introduction

Onchocerciasis is caused by the filarial worm *Onchocerca volvulus*, and is an important cause of blindness and skin disease in tropical Africa, Yemen and Central and South America. It is transmitted by the bite of blackflies (*Simulium* species).

Epidemiology

This infection mainly affects people living or working near fast-flowing rivers (*Simulium* breeding sites), but may be more widely distributed by flies carried on winds.

Pathology

Adult worms evade the host immune response and cause few symptoms. The main problems are the result of immunological reactions to dying and dead microfilariae and their endosymbiotic bacteria (*Wolbachia*), which release bacterial mediators that trigger the innate immune system. In addition, activated eosinophils release cellular proteins that cause connective tissue damage.

Onchocerciasis may increase the risk of HIV-1 seroconversion. Treatment of onchocerciasis is associated with reduced HIV-1 viral replication. Onchodermatitis is more severe in HIV-positive patients.

Clinical features

The incubation period is usually 15–18 months. Infected patients may be asymptomatic. Palpable firm painless subcutaneous nodules (intertwined adult worms), several centimetres in diameter, may be most obvious over bony prominences.

Skin disease

A variety of different skin manifestations are seen, usually with a significant degree of overlap:

- Acute papular onchodermatitis (APOD): an intensely itchy papular rash, sometimes with local oedema.
- Chronic papular onchodermatitis (CPOD): larger pruritic (itchy) hyperpigmented papules.
- Lichenified onchodermatitis (LOD): discrete or confluent pruritic hyperpigmented papulonodular plaques, often with lymphadenopathy.

Severe itching may give rise to excoriation and secondary bacterial infection. Healing is associated with progressive hyperpigmentation, blackening and thickening of the skin.

Unrelenting itching may result in chronic sleep disturbance, poor concentration and depression.

Heavy infections in childhood can impair growth. After some years, skin atrophy and depigmentation give a wrinkled prematurely aged appearance (presbydermia). Patchy depigmentation, especially of the legs, results in a 'leopard-skin' appearance.

Inguinal or femoral lymphadenopathy may give rise to the so-called 'hanging groin' appearance.

Eye disease

Early symptoms include itching, redness and excess lacrimation. Late disease leads to varying degrees of loss of vision, and eventually to blindness.

Anterior eye disease

- Punctate keratitis due to death of microfilariae in the cornea may appear as a reversible 'snow-flake' opacity.
- Pannus forms as blood vessels invade the cornea from the sides and below. The pannus may cover the pupil (sclerosing keratitis) and cause blindness.
- Iritis leads to a loss of the pigment frill and to synechiae that cause a deformed, often pear-shaped pupil. Secondary cataracts occasionally result.

Posterior eye disease

- Chorioretinitis with pigmentary changes.
- Optic atrophy.
- 'Tunnel vision' and various other forms of visual loss may become evident in young adults.

Diagnosis

- Skin snips in saline examined under the microscope for microfilariae.
- Slit-lamp examination for microfilariae in the anterior chamber of the eye.
- Rapid diagnostic tests. A new luciferase immunoprecipitation systems (LIPS) assay has 100% sensitivity and specificity for *O. volvulus* using a rapid 15-minute format (QLIPS).
- Biochemical methods: Recent advances include a serum antibody test card using recombinant antigen to detect *O. volvulus*-specific IgG4 in finger-prick whole-blood specimens, a triple-antigen indirect ELISA rapid-format card test, and a highly sensitive and specific urine antigen dipstick test.
- Surgery: Subcutaneous nodules can be removed to demonstrate adult worms, or aspirated with a needle to look for microfilariae.
- DEC patch test: Diethylcarbamazine (DEC), although no longer recommended for the treatment of onchocerciasis because of the risk of provoking a Mazzotti reaction (see below), may be used in the following manner in patients with repeatedly negative skin snips, where other diagnostic techniques are unavailable. A 1-cm square of filter paper soaked in a solution of DEC is applied to the skin of the patient. If positive, this will provoke intense localised itching and inflammation at the site of application. DEC patch testing of children aged 3–5 years is advocated as an effective low-cost method for monitoring the endemicity and transmission of onchocerciasis in Africa.
- **Warning: A DEC patch test may precipitate a full-blown Mazzotti reaction**. This consists of microfilaria death resulting in an intensely itchy papular rash, may be accompanied by fever, limb oedema, hypotension and worsening of eye damage, and may be fatal. It is commonly associated with the use of oral DEC, and is rarely caused by ivermectin.

Treatment

Ivermectin kills microfilariae by immobilising them so that they are carried away via the lymphatics.

Warning: Ivermectin may precipitate meningoencephalitis or renal failure in patients who have *Loa loa* with a high microfilariaemia (> 2500 microfilariae/mL).

It is therefore important to exclude *Loa loa* if there is any possibility of co-infection, before giving ivermectin.

Doxycycline kills the endosymbiotic *Wolbachia*, resulting in the slow, less pathogenic death of the microfilariae. The drug also blocks worm embryogenesis and has a significant macrofilaricidal effect. Contraindications to doxycycline include age less than 9 years, pregnancy and breastfeeding.

Treatment of individual patients

Provided that the patient does not have a high *Loa loa* microfilaraemia, and ivermectin (or doxycycline) is not otherwise contraindicated, the following options are available:

- If the patient will continue to live in an endemic area, or is less than 9 years old and weighs more than 15 kg, give **ivermectin** 150 micrograms/kg every 3–6 months.
- If interruption of worm embryogenesis and cessation of microfilariae production is desired, give **doxycycline** 200 mg/day for 4 weeks, or 100 mg/day for 6 weeks, followed by one dose of **ivermectin** after 4–6 months (children aged > 9 years).
- If a strong macrofilaricidal effect is desired, give **doxycycline** 200 mg/day for 6 weeks, followed by one dose of ivermectin after 4–6 months.

Patients with onchocerciasis who do have a high *Loa loa* microfilaraemia may be treated with **doxycycline** 200 mg daily for 6 weeks, unless contraindicated. If they are under 9 years of age, in which case doxycycline is contraindicated, *Loa loa* microfilaraemia must be reduced by treatment with **albendazole** prior to treatment with **ivermectin**.

Surgical removal of head nodules (nodulectomy) was advised in the past in an attempt to reduce the likelihood of eye disease. There is no guarantee that this will eliminate the risk of eye disease, because not all nodules are evident, and the remaining nodules continue to produce

microfilariae. Improved drug treatment has reduced the justification for nodulectomy.

Control

There has been rapid progress in the past 30 years, largely due to successful international public–private partnerships, sustained funding for regional programmes, and technical advances.

Initial efforts in vector control using the organophosphate larvicide **temephos** proved inadequate.

A major breakthrough came with Merck's donation of ivermectin. Thereafter larviciding was abandoned in favour of regular mass drug treatment.

The African Programme for Onchocerciasis Control (APOC) is a Community-Directed Treatment with Ivermectin (CDTI) programme that aims to treat over 90 million people annually in 19 countries, protecting an at-risk population of 115 million, and should prevent over 40 000 cases of blindness every year. High-risk foci of *Loa loa* are currently excluded from community ivermectin programmes.

The Onchocerciasis Elimination Programme for the Americas (OEPA) adopts a similar approach to APOC, except that ivermectin is administered twice a year until transmission has been interrupted. By the end of 2012, transmission of the infection, judged by surveys following WHO guidelines, had been interrupted or eliminated in four of the six endemic countries in the WHO Americas Region.

6.3.C.h Strongyloidiasis

BOX 6.3.C.H.1 Minimum standards

- Hygiene, sanitation and shoes are useful in prevention.
- Ivermectin is the treatment of choice.
- Albendazole.

Introduction

This parasite affects 50–100 million people worldwide, and occurs in warm, wet, tropical and subtropical regions where sanitation is poor. *Strongyloides stercoralis* is the main species infecting humans. However, *Strongyloides fülleborni*, which is principally a parasite of primates, also occurs in humans in Africa and Papua New Guinea.

Human infection is due to percutaneous penetration of filariform larvae in contaminated soil. Filariform larvae travel via the lungs to the small intestine, where they develop into adults and penetrate the duodenal and jejunal mucosa. Fertilised females produce eggs which hatch in the intestinal mucosa and release the first-stage rhabditiform larvae, which are excreted in faeces. In favourable conditions, the rhabditiform larvae transform into infectious filariform larvae within 48 hours, and remain viable in the soil for weeks.

An important feature of *Strongyloides* is auto-infection. This occurs when rhabditiform larvae transform into infectious dwarf filariform larvae in the gut lumen and penetrate the mucosa or the peri-anal skin. Infection may persist for decades without further exposure. Person-to-person transmission may also occur.

Clinical features

Initial skin penetration may cause itching, urticaria and sometimes a snake-like (serpiginous) rash. Migration through the lungs may cause cough, wheeze and evidence of pneumonitis. Invasion of the small bowel may cause abdominal pain, vomiting, malabsorption and paralytic ileus.

Chronic infection is often asymptomatic, but may cause intermittent abdominal pain, diarrhoea and urticaria. Malabsorption and a protein-losing enteropathy may occur. A transient, intensely itchy serpiginous rash, known as 'larva currens' or 'creeping eruption', may appear on the trunk, buttocks or elsewhere.

Episodic pneumonitis and, more rarely, a reactive arthritis may occur.

Strongyloides hyperinfection syndrome

One of the major dangers associated with *Strongyloides* infection occurs as a result of massive auto-infection. Risk factors include immunosuppression induced by various drugs, including corticosteroids, or associated with diseases such as malignancies (particularly leukaemia and lymphoma), severe malnutrition and severe infections, including advanced AIDS and human T-cell leukaemia virus type 1 (HTLV-1).

Hyperinfection syndrome may present with severe diarrhoea, often with blood in the stool. Bowel inflammation with micro-perforations may give rise to paralytic ileus, peritonitis and Gram-negative septicaemia. Proliferation and dissemination of larvae and enteropathogens may cause widespread pathology, including endocarditis, pneumonitis and meningitis.

All patients with a history of possible exposure to *Strongyloides* should be screened before being treated with any drugs that cause immunosuppression. Those at significant risk should be treated empirically even if investigations are negative.

Investigations

Eggs are rarely found in the stool, and larvae may be difficult to identify. Stool culture (e.g. on charcoal or agar) is recommended.

Larvae may be seen in duodenal aspirates or using the string capsule technique (Enterotest).

Larvae may also be found in sputum, CSF and urine in hyper-infection syndrome.

Serology is useful for immune-competent patients who are not normally resident in an endemic area. However, interpretation of a positive test may be a problem due to cross-reactions with filarial antigens.

Eosinophilia is common in immune-competent patients, but may be absent in hyperinfection syndrome.

Treatment

Ivermectin is the drug of choice for children over 5 years old

or weighing more than 15 kg. An oral dose of 200 micrograms/kg/day for 2 days gives excellent results.

Albendazole 400 mg every 12 hours for 7 days may also be effective, and can be used in children over 2 years of age.

Hyperinfection syndrome can be very difficult to manage. There may be problems with administration or absorption of oral medication, and no IV or IM preparations of ivermectin or albendazole are licensed for use in humans. However, parenteral ivermectin, available as a veterinary preparation, has been administered subcutaneously in the successful treatment of *Strongyloides* hyperinfection. Patients with hyper-infection syndrome also require treatment for Gram-negative septicaemia.

Prevention and control

- Improve hygiene and sanitation.
- Wear shoes.
- Avoid contact with contaminated soil.