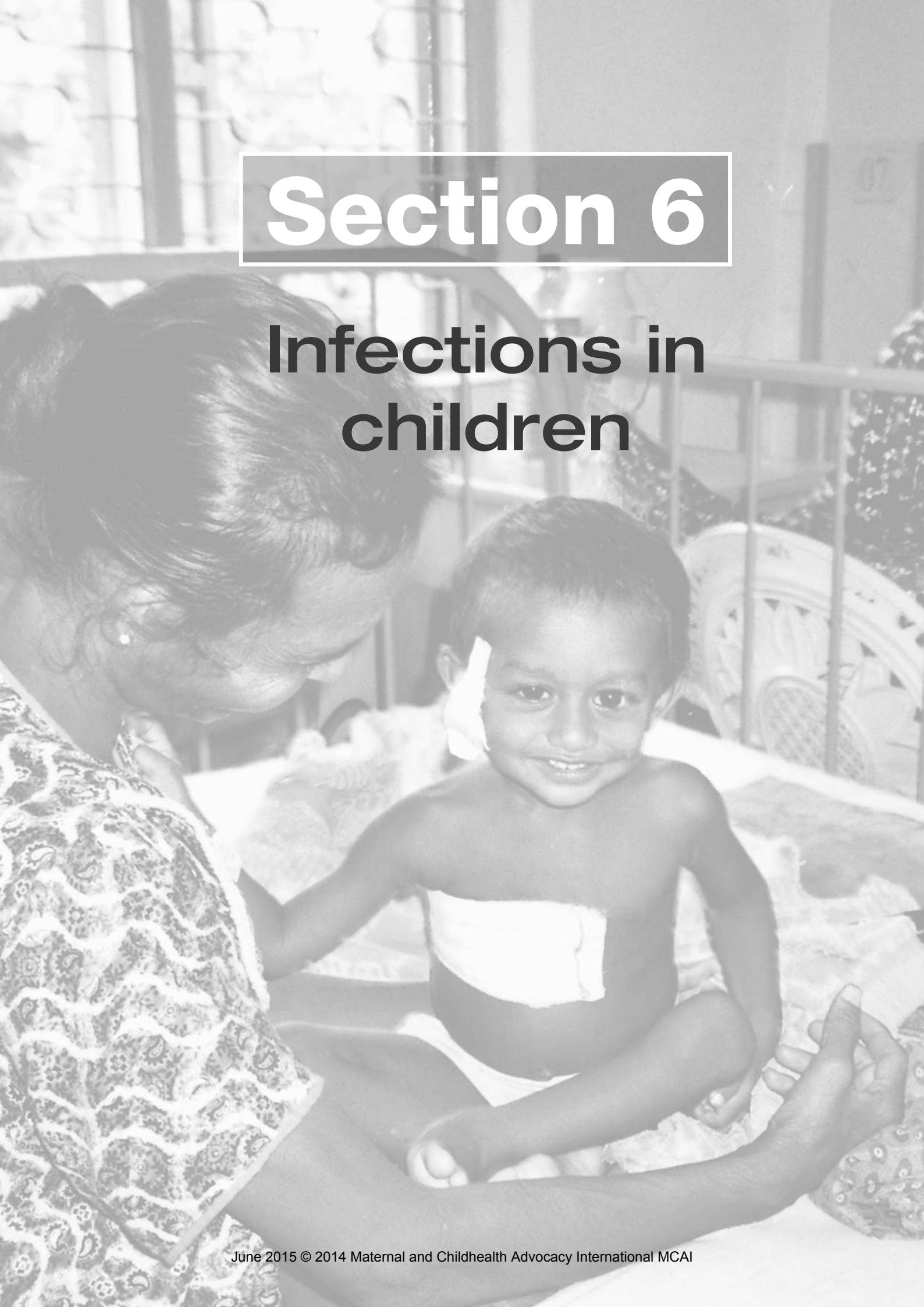


Section 6

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.

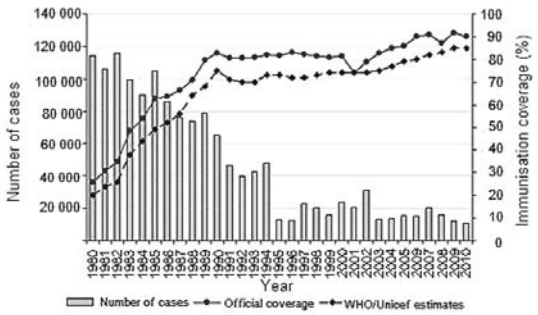


FIGURE 6.1.L.1 Total tetanus global annual reported cases and coverage, 1980–2010. Source: WHO/IVB Database, 2011.

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.

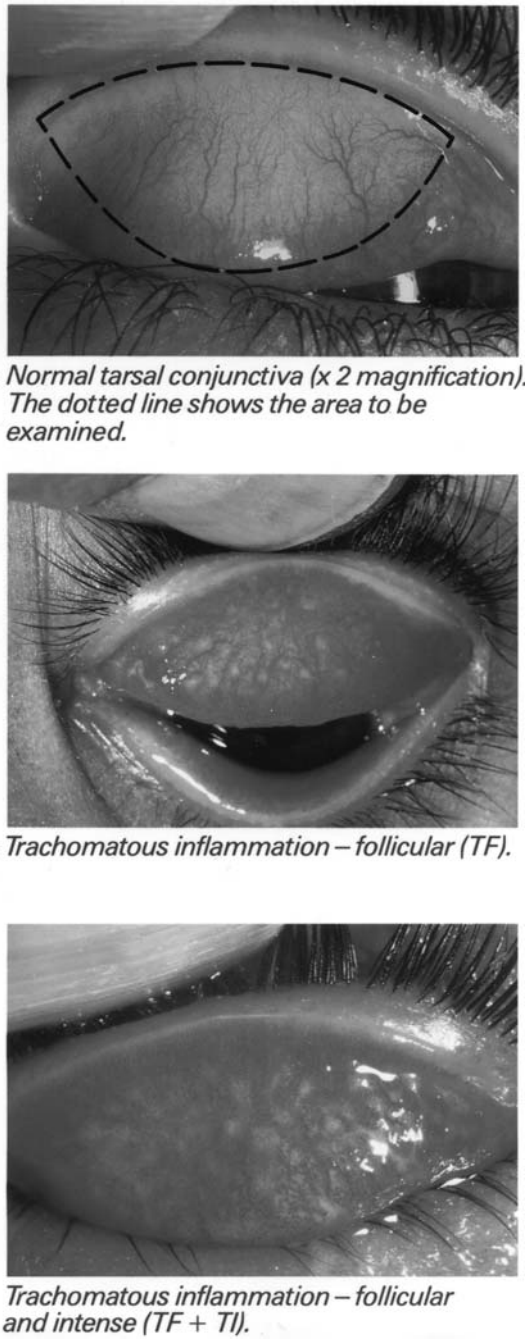
Treatment

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.

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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.

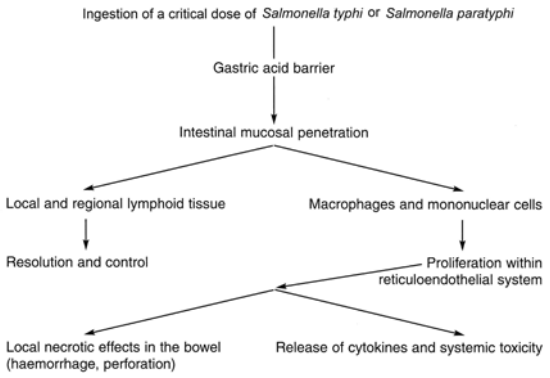

FIGURE 6.1.0.1 The pathogenesis of typhoid.

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.

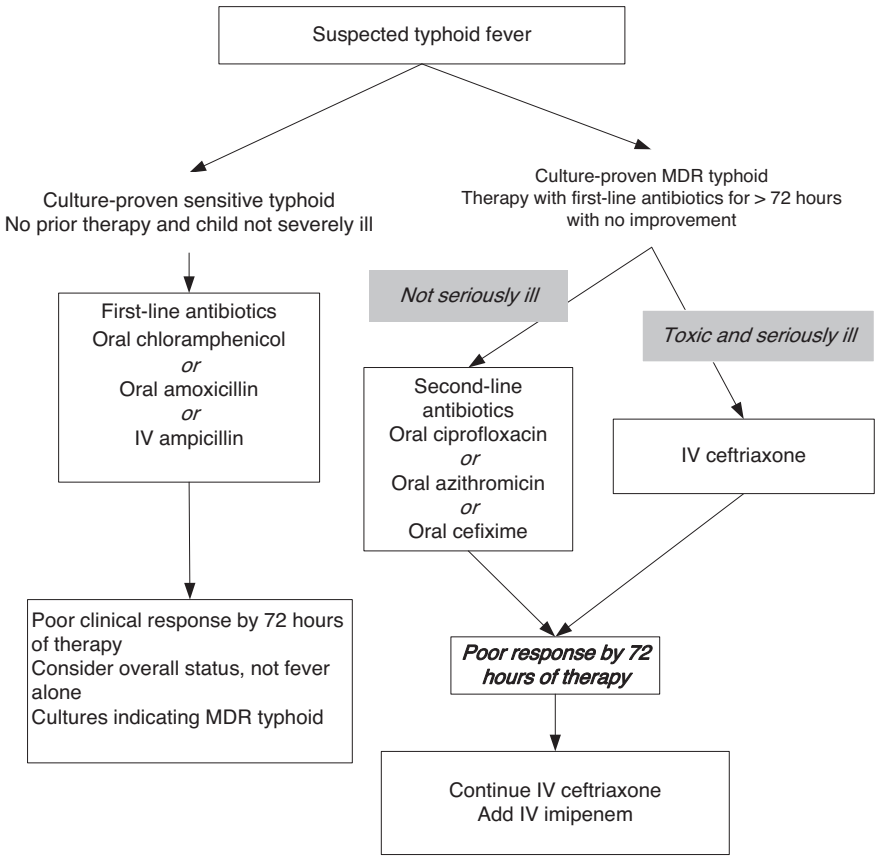

FIGURE 6.1.0.2 Algorithm for the treatment of typhoid. MDR, multi-drug-resistant.

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.