6.3 Other parasitic infections

6.3.A Systemic protozoal infections

6.3.A.a African trypanosomiasis

Introduction

Gambian trypanosomiasis, caused by *Trypanosoma brucei gambiense*, is a slowly progressive disease of West and Central Africa. Rhodesian trypanosomiasis, caused by *T. b. rhodesiense*, is a subacute infection found in East and Southern Africa. Trypanosomiasis of wild and domestic animals is often caused by other 'subspecies' of *T. brucei* which are indistinguishable morphologically from those that cause human infection.

Transmission
- By the bite of infected tsetse flies (*Glossina*).
- Riverine tsetse (*Glossina palpalis* group) are responsible for transmission of *T. b. gambiense*, chiefly from a human reservoir. Infection may be endemic or epidemic.
- Savannah tsetse flies (*Glossina morsitans* group) are mainly responsible for sporadic transmission of *T. b. rhodesiense* from animals to humans.
- Congenital transmission is also well recognised.

Clinical features

A painful bite lesion (the trypanosomal chancre) may form at the site of the infected bite and last for up to 3 weeks. Among indigenous people in endemic areas, this is more commonly seen in *T. b. rhodesiense* (19%) than in *T. b. gambiense* infections. However, a chancre may be seen in 25–40% of early presentations of *T. b. gambiense* among expatriates. Clinical staging is essential for planning treatment, and depends on evidence of CNS involvement based on lumbar puncture findings.

Haemolymphatic stage 1
- Symptoms of fever and malaise that last for about a week are associated with waves of parasitaemia.

- Lymph nodes (especially those at the back of the neck in Gambian disease) become enlarged.
- There may be short-lived oedematous swellings of the face or limbs, and sometimes a patchy circular erythematous rash or skin itching.
- Early symptoms are often milder in Gambian disease, and this stage may last for months to years.
- In Rhodesian disease, patients are usually more ill with tachycardia, high fever, hepatosplenomegaly, myocarditis, anaemia and sometimes jaundice.

Meningo-encephalitic stage 2
- Severe headache and altered behaviour are often seen.
- Patients may become apathetic, depressed or frankly psychotic.
- Sleep is disturbed, so that patients are often awake during the night and sleep by day; eventually deep coma results.
- Ataxia and cerebellar signs are frequent.
- Delayed response to pain after deep pressure, the appearance of primitive reflexes and altered tendon reflexes may be seen.
- Death often results from intercurrent infection.

Diagnosis
- In *T. b. rhodesiense* infections, trypanosomes can usually be observed in thick blood films. These are also useful for *T. b. gambiense* infections, but may be negative during periods of low parasitaemia.
- More sensitive methods of examining the blood include microhaematocrit centrifugation, use of the quantitative buffy coat (QBC) technique, and the mini-anion exchange column method.
- When there are enlarged lymph nodes, particularly posterior cervical nodes in *T. b. gambiense* infections (Winterbottom's sign), microscopy of a node aspirate may demonstrate trypanosomes.
- **Serological methods: The card agglutination test for trypanosomiasis (CATT) is useful only for population screening for *T. b. gambiense* infections. Positive results need to be confirmed by the finding of parasites. Other serological tests exist that may be useful for screening suspected cases of *T. b. gambiense*, but are rarely available in resource-limited settings.** Seropositives require parasitological confirmation. Negative serology does not exclude the diagnosis. Always search for

parasites. No serological screening tests are currently available for *T. b. rhodesiense*.

- Treatment depends on evaluation of the stage of infection, so lumbar puncture is essential. Criteria for stage 2 disease in a previously untreated patient include either the presence of trypanosomes in the CSF, or a raised CSF lymphocyte count (> 5 cells/mm³) in the absence of another cause. CSF protein levels are usually raised. CSF IgM (if available) may be useful as an early marker of CNS invasion.

Treatment

Drug resistance is becoming more widespread. Check local resistance patterns and treatment recommendations.

The drugs used for treatment are toxic. They should only be started after a parasitological diagnosis has been confirmed and, particularly in stage 2 *T. b. gambiense* disease, after the patient's general condition has been improved by attention to hydration, nutrition and intercurrent infections.

T. b. gambiense stage 1

- Give pentamidine isethionate 4 mg/kg IM daily for 7–10 days.
- Children should be given a meal or a sweet drink 1 hour prior to treatment (to reduce the risk of hypoglycaemia), and must lie down for an hour after an injection and have careful checks of pulse and blood pressure (there is a **risk of severe hypotension**).
- **Side effects:** hypoglycaemia (may occur up to 7 days after treatment), arrhythmias, bone-marrow suppression, electrolyte disturbances (low K^+, Ca^{2+}, Mg^{2+}). Monitoring is recommended if possible.

T. b. gambiense stage 2

- **Recommended treatment is nifurtimox–eflornithine combination treatment (NECT).**
- Give nifurtimox 5 mg/kg orally three times daily for 10 days plus eflornithine 200 mg/kg every 12 hours by IV infusion (over 2 hours) for 7 days.
- Second choice, if nifurtimox is not available and the patient is under 12 years of age, is to give eflornithine 150 mg/kg every 6 hours by IV infusion (over 2 hours) for 14 days. If the patient is over 12 years of age, give eflornithine 100 mg/kg every 6 hours by IV infusion (over 2 hours) for 14 days.
- There is a risk of infection and phlebitis at the IV site. Care is needed with regard to sterile procedures and securing the IV line. Change the IV site every 2 days.
- Side effects include **CNS abnormalities (due to nifurtimox), convulsions**, and bone-marrow suppression (due to eflornithine).
- **Relapse after NECT or eflornithine:** Give **melarsoprol**, 2.2 mg/kg/day slowly IV for 10 days. **Encephalopathy occurs in up to 15% of patients treated with melarsoprol, and is associated with a 50% case-fatality**

rate. Co-administration of prednisolone reduces the risk of encephalopathy to less than 5%. Prior to the first dose of melarsoprol, start prednisolone orally 1 mg/kg (maximum 40 mg/day) daily for 10 days, then taper and stop over 3 days.

- **Side effects include encephalopathy, peripheral neuropathy, skin reactions including Stevens–Johnson syndrome, and phlebitis.** Note that melarsoprol IV is very painful, particularly if extravasation occurs, and may cause tissue necrosis.

T. b. rhodesiense stage 1

- **Suramin:** initial test dose of 4–5 mg/kg slowly IV over 5 minutes on day 1, then 20 mg/kg slowly IV on days 3, 10, 17, 24 and 31. Maximum single dose 1 g/injection.
- The initial test dose is to reduce the risk of idiosyncratic anaphylactic reactions to suramin. Have IM adrenaline available (*see* Section 5.1.B).
- Test the urine for albumin before each dose, and modify the regime if more than a trace of protein is seen.
- This regime may also be used for **stage 1 *T. b. gambiense*** if pentamidine is unavailable.
- **Side effects include hypersensitivity, nephrotoxicity** (monitor urine albumin levels before each dose, and modify the regime if more than a trace of protein is seen) and peripheral neuropathy.

T. b. rhodesiense stage 2

- **Melarsoprol:** 3.6 mg/kg slowly IV for 3 or 4 days repeated three or four cycles with an interval of 7–10 days between treatment series.
- **Prednisolone:** 1 mg/kg (maximum 40 mg/day) orally daily throughout the course of melarsoprol, then gradually taper and stop. Note that the recommendation for use in *T. b. rhodesiense* stage 2 is largely based on evidence for use in *T. b. gambiense* stage 2.
- Side effects: see previous notes.

Follow-up

- **Notify all cases** so that effective surveillance and public health action is taken.
- All patients should have follow-up lumbar puncture for 2 years (*T. b. gambiense*, lumbar puncture 6-monthly; *T. b. rhodesiense*, 3-monthly for 1 year and then 6-monthly).
  If initially stage 1 but at follow-up:
  (i) CSF 6–19 white blood cells/mm³: repeat lumbar puncture in 1–2 months.
  (ii) CSF ≥ 20 white blood cells/mm³: treat as stage 2.

  If initially stage 2, CSF white cell count trend at follow-up is more important than the actual value.
- Drug resistance is increasing – if suspected seek expert advice.

6.3.A.b American trypanosomiasis (Chagas disease)

BOX 6.3.A.B.1   Minimum standards
- ■ Bed nets.
- ■ Vector control.
- ■ Benznidazole.
- ■ Nifurtimox.

Introduction

American trypanosomiasis is potentially life-threatening and is caused by the protozoan parasite, *Trypanosoma cruzi*.

An estimated 10 million people are infected worldwide, mostly in Latin America, where it is endemic. In 2008 it killed more than 10 000 people. It is increasingly being detected in the USA, Canada, many European and some Western Pacific countries.

In Latin America, *T. cruzi* is mainly transmitted by the infected faeces of blood-sucking triatomine bugs. These bugs typically live in the cracks of poorly constructed homes in rural or suburban areas. They become active at night when they feed on human blood by biting an exposed area of skin such as the face, where the bug defecates close to the bite. The parasites enter the body when the person instinctively smears the bug faeces into the bite, the eyes, the mouth, or any break in the skin.

T. cruzi can also be transmitted in the following ways:
- via food contaminated with the parasite through, for example, contact with triatomine bug faeces
- by blood transfusions from infected donors
- by transmission from an infected mother to her newborn during pregnancy or childbirth.

Clinical management

Signs and symptoms

The disease presents in two phases. The initial acute phase lasts for about 2 months after infection. During the acute phase, a high number of parasites circulate in the blood. In most cases, symptoms are absent or mild, but can include fever, headache, enlarged lymph glands, pallor, muscle pain, difficulty in breathing, swelling and abdominal or chest pain. In less than 50% of people bitten by a triatomine bug, the characteristic first visible signs can be a skin lesion or a purplish swelling of the lids of one eye.

During the chronic phase, the parasites congregate in the heart and digestive tract. Up to 30% of patients suffer from cardiac disorders, and up to 10% suffer from digestive (typically enlargement of the oesophagus or colon), neurological or mixed pathology. The infection can lead to sudden death or heart failure caused by progressive destruction of the heart muscle.

Treatment

Benznidazole and nifurtimox are both almost 100% effective in curing the disease if given soon after infection. However, the efficacy of both diminishes the longer a person has been infected. Treatment is also indicated for those in whom the infection has been reactivated (e.g. due to immunosuppression), for infants with congenital infection, and for patients during the early chronic phase. The potential benefits of medication in preventing or delaying the disease should be weighed against the long duration of treatment (up to 2 months) and possible adverse reactions (occurring in up to 40% of treated patients).

Benznidazole and nifurtimox should not be taken by pregnant women or by people with kidney or liver failure. Nifurtimox is also contraindicated in people with a history of neurological or psychiatric disorders. In addition, specific treatment for cardiac or digestive manifestations may be required.

Benznidazole 100 mg tablets

Acute or early chronic phase:
- Full term newborn infant give 5 mg/kg daily in 3 divided doses increasing after 3 days to 10 mg/kg daily if no leukopenia or thrombocytopenia occurs. Treat for 60 days.
- Infant or child, 40 kg body weight give 7.5 mg/kg daily in 2–3 divided doses for 60 days.
- Child > 40 kg give 5 mg/kg daily in 2–3 divided doses for 60 days.

Chronic phase:
Infant or child 5 mg/kg daily in 2–3 divided doses for 60 days.

Nifurtimox Tablets 30, 120 and 250 mg

Acute or early chronic phase:given after meals
- Neonate, infant or child < 40 kg give 15–20 mg/kg daily in 3 divided doses for 60 days
- Child > 40 kg 12.5–15 mg/kg daily in 3 divided doses for 60 days

Chronic phase:
Infant or child 8–10 mg/kg daily in 3 divided doses for 60 days.

Vector control and prevention

There is no vaccine for Chagas disease. Vector control is the most effective method of preventing this disease in Latin America. Blood screening is necessary to prevent infection through transfusion.

The WHO recommends:
- insecticide spraying of houses and surrounding areas
- house improvements to prevent vector infestation
- personal preventive measures such as bed nets
- good hygiene practices in food preparation, transportation, storage and consumption
- screening of blood donors
- screening of newborns from infected mothers, and of siblings of infected children to provide early diagnosis and treatment.

6.3.A.c Leishmaniasis

> **BOX 6.3.A.C Minimum standards**
> ■ Public health measures and vector control.
>
> **Leishmaniasis: visceral**
> ■ Bone-marrow, splenic and lymph-node aspirate.
> ■ Pentavalent antimonials.
> ■ Amphotericin B.
> ■ Paromomycin.
>
> **Leishmaniasis: cutaneous and mucocutaneous**
> ■ Pentavalent antimonials.
> ■ Topical 15% aminosidine plus 12% methyl benzethonium.
> ■ Ketoconazole.

Introduction

Leishmaniasis is caused by *Leishmania*, a protozoon whose reservoir is in animals, including rodents and dogs, and in some areas (e.g. India) in humans. The vector is the female sandfly.

There are three main clinical types of disease:
- cutaneous (CL)
- mucocutaneous (MCL)
- visceral leishmaniasis (VL) or kala-azar.

Parasite and life cycle
- About 21 of the 30 or more species of *Leishmania* infect humans. They are morphologically similar and can only be differentiated by isoenzyme analysis which identifies the zymodeme in the cultured parasite.
- In animals and humans, *Leishmania* lives in macrophages in the reticulo-endothelial system in the form of amastigotes (Leishman–Donovan bodies). When taken up by the biting sandfly it transforms into a promastigote, which has a flagellum.
- There are two main genera of sandfly responsible for transmission, *Phlebotomus* in the Old World and *Lutzomyia* in the New World (Central and South America). Sandflies breed in organic material in dark moist sites, such as cracks in masonry, termite hills, or leaves on the forest floor. The female obtains her blood meal at night by feeding on animals, and also on humans if they are living or working in the vicinity.

Epidemiology
The Old World comprises Africa, Asia and Europe (collectively known as Afro-Eurasia), plus the surrounding islands. It is used in the context of, and contrast with, the 'New World' (i.e. the Americas and sometimes Oceania). Old world CL and VL are found in the Mediterranean basin, the Middle East, the Sudan, Ethiopia, Kenya, Afghanistan, the Indian subcontinent, and southern regions of the former Soviet Union, and China. Where HIV infection and VL coexist, there are major problems in the treatment of VL. Drug resistance in VL is a serious concern in India and the Sudan. Bihar State has 90% of VL in India and 45% of world cases.

In the New World, CL and MCL are the main forms of infection. VL occurs mainly in North-East Brazil.

Currently, leishmaniasis occurs in four continents and is considered to be endemic in 88 countries, 72 of which are resource-limited:
- 90% of all visceral leishmaniasis cases occur in Bangladesh, Brazil, India, Nepal and Sudan
- 90% of mucocutaneous leishmaniasis cases occur in Bolivia, Brazil and Peru
- 90% of cutaneous leishmaniasis cases occur in Afghanistan, Brazil, Iran, Peru, Saudi Arabia and Syria.

Leishmaniasis is a disease of poverty associated with malnutrition, displacement, poor housing and migration of non-immune people to endemic areas. It is linked with deforestation and urbanisation.

Immunology
- A strong cell-mediated immune (CMI) response is required for control of and recovery from disease. Polyclonal stimulation of B cells results in high levels of IgG.
- Subclinical infection is common. CL usually heals spontaneously, but untreated MCL will progress, and VL will result in death. Development of VL indicates that the host's CMI is unable to control the infection, and if untreated, progressive immunosuppression will develop.
- Death is usually due to a secondary infection (e.g. respiratory tract or gut infection).

Cutaneous and mucocutaneous leishmaniasis

Cutaneous leishmaniasis
The species responsible are *L. tropica*, *L. major*, *L. aethiopica* in the Old World, and *L. mexicana* and *L. amazonensis* in the New World. Single or multiple nodules develop on exposed areas, especially the face or extremities, and usually ulcerate. Most heal spontaneously within months to a year or so, leaving scars.

Mucutaneous leishmaniasis
The species responsible is *L. braziliensis*. A nodule develops initially, as in CL, but at about the time of healing, metastatic lesions occur on mucosal surfaces, such as the nasal mucosa and oropharynx. If these are left untreated, progressive destruction of local tissue occurs.

Diagnosis
- Slit skin smear or aspiration should be undertaken from the raised margin of the lesion (not the base of the ulcer). Material is spread on a slide, dried, fixed in methanol and stained with Giemsa or Leishman.
- If a biopsy is undertaken (e.g. in MCL), impression smears should be done before fixing.
- If available, the specimen should be cultured.

Management
Most CL lesions are self-limiting. Treatment is indicated for

multiple, large and disfiguring lesions and all MCL. Clean the lesion, and give antibiotics if necessary.

Standard treatment for CL and MCL is with pentavalent antimonials (Sb): **sodium stibogluconate** (Pentostam, 100 mg Sb/mL) or **meglumine antimoniate** (Glucantime, 85 mg Sb/mL). **It is essential to remember that the doses of these two drugs are different, because they contain different concentrations of antimony (Sb).** Give 20 mg Sb/kg/day IV or IM in a single dose for 20–28 days depending on the species of *Leishmania* (e.g. MCL requires 28 days or more). The IV infusion is stopped if coughing or substernal pain occurs. Urinary excretion of Sb is rapid (its half-life is 2 hours), although slow accumulation occurs.

For *L. major*, weekly or twice weekly intra-lesional injections of Sb (which are painful) may be administered (1 mL/lesion at four sites per ulcer) to adolescents or adults, using a 1-mL syringe and a fine (24-gauge) needle, for 4–8 weeks. A topical ointment containing 15% aminosidine and 12% methylbenzethonium chloride applied twice daily for 10–20 days may be tried. Efficacy is variable, but it may be combined with intra-lesional Sb injections.

Oral fluconazole, 3 mg/kg once daily (maximum 100 mg) for up to 6 weeks, may be effective, but there is a **danger of liver dysfunction**.

In areas where there is antimonial resistance, pentamidine (IM 2 mg/kg every second day for seven injections), amphotericin B and oral miltefosine may be required (see management of VL below).

All three of these drugs have potentially serious side effects.

Visceral leishmaniasis (kala azar)

Epidemics occur in situations of famine, complex emergencies and mass movements of populations. It has a high fatality rate if untreated. It is estimated that there are 360 000 new cases every year globally, of which more than 60% occur in Northern India (Bihar).

The species responsible are *L. donovani* and *L. infantum* in the Old World, and *L. chagasi* in the New World.

- The major presenting features include the triad of prolonged fever, anaemia and moderate to marked splenomegaly. In the early stages the child is often only mildly unwell and may have a reasonable appetite. In a minority of cases, the onset may be acute, with a high temperature, toxaemia and mild splenomegaly.
- Pancytopenia is the main laboratory finding.

Diagnosis

- In children, the diagnosis is usually confirmed by demonstrating amastigotes on bone-marrow aspirate.
- Splenic aspirates have a higher sensitivity, and this procedure is safe in skilled hands so long as the platelet count is above 40×10^9/litre and coagulation is normal.
- Repeat bone-marrow or splenic aspiration to monitor progress if required.
- If there is lymphadenopathy, diagnosis may be attempted by fine-needle aspiration.
- **Serological antibody tests such as ELISA have a high sensitivity, and are particularly helpful if a parasitological diagnosis cannot be obtained.**
- If a microscopic diagnosis cannot be made, **the polymerase chain reaction (PCR) should be undertaken. The value of the PCR is being evaluated**.

Differential diagnosis

- Differential diagnosis of marked hepatosplenomegaly, anaemia and pancytopenia includes hyper-reactive splenomegaly (tropical splenomegaly) syndrome and schistosomiasis, as well as myeloid leukaemia and myelofibrosis.
- In acute-onset disease, malaria, disseminated tuberculosis, typhoid, brucellosis, African trypanosomiasis, relapsing fever and leukaemia should be considered.
- **HIV infection greatly increases the risk of visceral leishmaniasis, and thus co-infection is common.**

TABLE 6.3.A.C.1 Clinical features of visceral leishmaniasis

Incubation period: 2–4 months (weeks to two years)
Fever: intermittent at first
Anaemia: bone-marrow depression, hypersplenism
Splenomegaly: progressive enlargement
Hepatomegaly
Weight loss
Epistaxis: haemorrhage from other sites may occur in advanced disease
Diarrhoea: invasion of gut by amastigotes, secondary infection
Cough
Oedema: hypoalbuminaemia
Hair and skin signs of malnutrition in chronic forms
Lymphadenopathy: in some African countries

TABLE 6.3.A.C.2 Clinical pathology of visceral leishmaniasis

Haemoglobin: low; normochromic, normocytic film
White blood cells: low, $2–3 \times 10^9$/litre Eosinophils low
Platelets: low, $< 100 \times 10^9$/litre
Reticulocytes: low
Serum albumin: low
Serum globulin: elevated
Liver transaminases and serum bilirubin: normal

Management of visceral leishmaniasis

Consider HIV co-infection and secondary disorders such as malaria, respiratory and gut infections, and tuberculosis. Blood transfusion for anaemia is seldom required, as the child has usually adapted to the low haemoglobin level. Give haematinics and vitamin supplements during nutritional rehabilitation and convalescence.

Liposomal amphotericin B used to be expensive, but following a campaign the WHO has brought about a 90% reduction in price, and consequently this is now the treatment of choice.

The alternative treatment is with antimoniates (Sb), for which again the WHO has obtained a substantial reduction in cost. Meglumine antimoniate and sodium stibogluconate are available. The duration of Sb treatment is usually 4 weeks, but prolonged treatment (up to 6 weeks) may be necessary in resistant cases (*see* Table 6.3.A.c.3).

For relapse, a second course can be given after a few weeks. Serious toxicity is rare in children, but if a prolonged course of high dosage is required, or toxicity is suspected, liver function tests and an ECG looking for conduction

disorders should be undertaken. Serious toxicity may require dimercaprol to chelate and remove the antimony.

In areas where there is resistance to Sb, such as Bihar state in India, and the Sudan, alternative drugs are required as follows: amphotericin B by slow infusion; paromomycin (aminoglycoside, identical to aminosidine); or oral miltefosine. Combinations of drugs (e.g. paromomycin and Sb) may be more effective. In patients with HIV/VL co-infection, management is difficult because of frequent relapse when treatment is stopped. HAART combined with maintenance anti-leishmanial therapy is important.

TABLE 6.3.A.C.3 Drugs used in the treatment of visceral leishmaniasis

Drug	Doses	Contraindications and cautions	Side effects
Liposomal amphotericin B	4 mg/kg IV over 30–60 minutes once daily by IV infusion on days 1, 2, 3, 5 and 10	An initial test dose of 100 micrograms/kg (maximum 1 mg) is infused over 15 minutes. Observe for 1 hour to ensure that anaphylaxis does not occur, then proceed	May produce hypotension, fever, vomiting, headache, and muscle and joint pain. Less commonly, chest pain, hypoxia, severe abdominal pain, flushing, urticaria, and flank or leg pain
Sodium stibogluconate (100 mg Sb/mL) or meglumine antimoniate (81 mg Sb/mL)	20 mg/kg (minimum 200 mg) IV infusion or deep IM injection over over 5–10 minutes once daily for 28 days Prolonged treatment for 6 weeks in resistant cases	Pre-existing severe cardiac, liver, renal, pancreatic or haematological abnormalities Not to be given during pregnancy Filter solution through 5-micron filter immediately before infusion	Vomiting, abdominal pain, myalgia and arthralgia, headache, metallic taste. Rarely sudden death with prolonged QT interval; therefore monitor ECG and stop infusion if QT exceeds 0.5 seconds
Conventional amphotericin B	Slow IV infusion, 1 mg/kg every second day for 15 days, or daily for 20 days. (daily dose must never exceed 1.5 mg/kg)	An initial test dose of 100 micrograms/kg (maximum 1 mg) is infused over 15 minutes. Observe for 1 hour to ensure that anaphylaxis does not occur, then proceed	May produce hypotension, fever, vomiting, headache, and muscle and joint pain
Paromomycin	Daily IV or IM injections 16–20 mg/kg/day for 21 days	Do not give at the same time as gentamicin or other aminoglycosides. Avoid if there is renal impairment	Vomiting, diarrhoea, abdominal pain, fever and ototoxicity
Miltefosine	2.5 mg/kg/day orally for 28 days	Not in pregnancy	Nausea and vomiting

A limited stock of the above drugs is kept by the WHO in Geneva for rapid response to an epidemic.

A study looking at the effectiveness of a single-dose treatment (by IV infusion) using liposomal amphotericin B is currently in progress in India.

Follow-up and prognosis

Symptomatic improvement usually occurs within a few days, and a haematological response occurs within 2 weeks. Splenomegaly slowly regresses, but may take a year or more to resolve. Prolonged follow-up (at least 1 year) is necessary to detect relapse. Relapse is treated with a repeat prolonged course of antimonials (up to 8 weeks). Unresponsiveness will require alternative drugs such as liposomal amphotericin B (if available), aminosidine, standard amphotericin B or pentamidine. Trials of miltefosine are in progress.

Prevention and control

Prevention is similar to that of malaria, and includes insect repellents and the use of fine-mesh bed nets impregnated with permethrin. Control includes spraying of sandfly resting sites and human dwellings, destruction of animal reservoirs and treatment of cases.

Further reading

Murray HW, Berman JD, Davies CR *et al*. (2005) Advances in leishmaniasis. *Lancet*, **366**, 1561–77.
World Health Organization (2014) *Leishmaniasis*. www.who.int/leishmaniasis/en/

6.3.A.d Malaria

BOX 6.3.A.D.1 Minimum standards for an effective malaria control programme

1 Prevention:
- Impregnated bed nets (ITNs), preferably long-lasting insecticidal nets (LLINs).
- Where appropriate, intermittent preventive treatment in infants (IPTi) and seasonal malaria chemoprevention (SMC) for older children.
- Other methods of vector control, such as indoor residual spraying (IRS), personal protection (e.g. mosquito coils, impregnated clothing, repellents, etc.).

2 A well-informed population to improve early care seeking and adherence to treatment and preventive regimes.

3 Good case management:
- Early accurate diagnosis: all patients should have a biological test before treatment:
  — Quality-assured thick blood film and/or rapid diagnostic test (RDT).
  — Haemoglobin measurement to detect and treat malaria anaemia (e.g. using a haemocue machine).
  — In severe disease, facilities to measure blood glucose levels and provide safe blood transfusion.
- Effective treatment:
  — Treatment for simple malaria.
    » Artemisinin combination therapy (ACT) (following the national protocol for recommended ACT).
  — Treatment for severe disease.
    » IV or IM artesunate (IM artemether, rectal artesunate, or IV or IM quinine if artesunate is not available).
  — Pre-referral treatment.
    » Rectal artesunate (if artesunate is not available, rectal quinine) or if injections are safe IV or IM artesunate or IM artemether, or IM quinine.

4 Accessible, acceptable and affordable care:
- Consider training community health workers in remote areas to diagnose and treat malaria.
- Make treatment free for pregnant girls and children under five.
- Set up a good referral system from community and first-level health facilities to facilities with means to treat severe cases, including transport and facilities to access resources to pay for treatment if needed.

BOX 6.3.A.D.2 Minimum standards for hospital treatment of severe malaria

- A triage system.
- RDTs and microscopy for initial diagnosis, plus laboratory facilities to determine levels of parasitaemia.
- Antimalarial drugs for IV, IM and oral treatment.
- Oxygen.
- Antibiotics and anticonvulsants.
- Safe blood transfusion services.
- Nasogastric feeding.
- Good nursing care (monitoring of vital signs and fluid balance, nasogastric feeding).

Malaria is estimated to cause at least 650 000 deaths each year, mostly among African children.

- Unlike anywhere else in the world, children aged 6–24 months in Africa are most at risk of the worst forms of malaria. Every 30 seconds an African child dies of malaria.

There are five *Plasmodium* species known to be infective to humans, namely *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*.

P. falciparum causes severe disease and is the most prevalent form in sub-Saharan Africa (most sub-Saharan Africans are protected against *P. vivax* due to lacking a protein in their red blood cells (the Duffy antigen)). *P. falciparum* differs from the other species in that infected erythrocytes adhere to capillary epithelium, thus disappearing from the circulation and evading destruction by the spleen.

P. vivax and *P. ovale* can cause recurrent malaria attacks due to the formation of a dormant form existing as hypnozoites in the liver, which are periodically released into the blood. Drugs to eliminate the hypnozoites from the liver are limited (primaquine).

P. malariae can cause long-term problems, including kidney failure, and *P. knowlesi* is a newly emerging form which has caused severe disease in Asia (Papua New Guinea and Thailand).

Life cycle

The infected *Anopheles* female mosquito injects sporozoites into the bloodstream of an individual. Sporozoites circulate for less than 30 minutes before being phagocytosed or entering liver parenchymal cells. The blood and liver phase prior to re-entry into the circulation is called the pre-erythrocytic phase, and it varies in length according to the species. At the end of this phase, merozoites invade the red blood cells and begin the erythrocytic phase. Parasites rapidly multiply within the red blood cells, which finally burst, releasing more merozoites into the bloodstream to invade further red blood cells.

Periodic bouts of fever are associated with the release of the merozoites. After some time, sexual forms of the parasites (gametocytes) are formed which are then ingested by a female mosquito to complete the cycle in humans. In the mosquito stomach, the gametocytes merge and eventually form sporozoites which migrate to the salivary

Introduction

Malaria is an extremely important public health burden in Africa, disproportionately affecting the youngest and most vulnerable. Children under 5 years and pregnant women, especially in the first pregnancy, suffer from severe forms of the disease. In Asia, the disease is more common in men and older children.

- Nearly 80% of the world's malaria burden is in Africa.

glands, where they are injected into the bloodstream by the mosquito as it takes a blood meal to support its own reproductive effort.

In two species (*P. vivax* and *P. ovale*) some hepatic-stage parasites remain within the liver cells with the formation of the dormant phase, called hypnozoites. For various reasons (perhaps including waning immunity), at a later date the dormant phases activate and reseed blood. This leads to manifestations of malaria not from a new infection but from the latent exo-erythrocytic phase.

P. falciparum differs from the other species in that infected erythrocytes adhere to capillary epithelium, thus disappearing from the circulation and evading destruction by the spleen.

P. falciparum is the most likely species to cause life-threatening disease, and is a major cause of mortality in children.

Plasmodium falciparum
Clinical features
- Typical symptoms include high-grade fever alternating with cold spells, rigors, chills and sweating. There are usually associated myalgias and arthralgias.
- However, features in children under 5 years of age may be non-specific, with fever, vomiting, diarrhoea and abdominal pain being the main symptoms.
- In older immune individuals the only symptoms may be fever with headache and joint pains.
- All fevers in children from a malaria-endemic area are therefore due to malaria until proven otherwise.

Diagnosis
Microscopy
- Blood smear for malaria remains the gold standard: a thick film for diagnosis, and a thin film to confirm the type of malarial parasite. Typically species-specific ring forms inside red blood cells are seen, but there may also be gametocytes.
- The level of parasitaemia is usually scored as 1–5+. If the malarial smear is 3+ or more, there is a high level parasitaemia. In areas where parasitic density is measured the smear is reported as parasites/mm^3.
- Malaria microscopy in district hospitals can be of very poor quality. A quality assurance programme should be in place that includes the following:
  — a properly trained and regularly updated microscopist
  — adequate time to look at slides, particularly for low-level parasitaemia
  — the correct stains and good-quality slides
  — a binocular microscope that is properly serviced and maintained
  — a system of internal and preferably external cross-checking of a sample of slides, especially the low parasitaemias and negative slides.
  — If possible examination requires a reliable electricity supply or good lighting near a window in the day time. Many modern microscopes have an inbuilt LED light.

Rapid diagnostic tests
Antigen-capture test kits use a rapid simple dipstick test from a finger-prick blood sample to give a result in 10–20 minutes. RDTs should be used in circumstances where microscope facilities and/or diagnostic expertise are limited.

There are two main forms of rapid test.

Histidine-rich protein 2 (HRP2) tests
These only detect *P. falciparum*. HRP2 tests have a sensitivity of 97–100% (i.e. there are very few false-negative results). These tests can lack specificity (which may be as low as 59% in some studies), so there can be a high frequency of false-positive results, especially in a high transmission zone where malaria infection is frequent (children can have as many as six attacks a year). HRP2 remains in the bloodstream for at least 2 weeks after all viable parasites have been killed, and often for considerably longer (6–8 weeks), so patients returning with fever within 4 weeks after treatment cannot be diagnosed using an HRP2-based RDT. However, a presumptive diagnosis that fever equals malaria has an even lower specificity.

HRP2 tests are very heat stable, but are sensitive to humidity. They have a shelf-life of 2 years, and their use can be taught to healthcare workers, even at village level, in a few hours. They are especially suitable for use in sub-Saharan Africa, where other species of malaria are rare.

Parasite lactate dehydrogenase (pLDH) tests
The parasite lactate dehydrogenase (pLDH) antigen is produced by all four *Plasmodium* species. The pLDH-based tests detect the antigen using a panel of monoclonal antibodies. They can have high sensitivity for *P. falciparum*, and are more specific than HRP2. They return to negative in 3–14 days (the majority do so within 7 days).

Some pLDH tests are able to differentiate between *P. falciparum* and other *Plasmodium* species, and between viable and non-viable parasites, thereby enabling their use for monitoring therapy and for detecting new infections within 2 weeks of successful treatment.

The tests currently on the market are available in two forms. The first has a pan-pLDH antibody that can detect any species of malaria. When positive, it produces a single test line. The second produces two test lines, a pan-specific line and a line that detects *P. falciparum*. In theory, there are monoclonal antibodies that can individually detect all of the different species, but these have not yet been validated.

pLDH tests are not as heat stable as HRP2 tests. Although pLDH has a high sensitivity for *P. falciparum*, its sensitivity for *P. vivax* appears to be less satisfactory if the patient has a low parasitaemia. pLDH tests are more expensive than HRP2 tests, and are not therefore recommended in sub-Saharan Africa, where 97% of infections are due to *P. falciparum.*

Advantages of RDTs over microscopy
- The result is available within 15–20 minutes and one person can set up a new test every 1 or 2 minutes. In contrast, there are more steps involved in microscopy (i.e. slide preparation, drying, staining, and drying stained slides), and a negative slide requires 6 minutes of reading time (a microscopy report can be delayed up to an hour from collecting the blood).
- Training takes 2 hours with minimally educated workers.
- Many more tests can be done in one clinic or outreach session.

A quality control/quality assurance system for RDTs should be in place at the level of importation where the Compliance

with last Malarial Treatment (CMT) is based, and at project level after transportation, to ensure that tests remain in good condition (lot testing). Monitoring of the conditions to which the tests are subjected during transportation may account for problems with their function at project level.

Field teams need to monitor the performance of healthcare staff regularly to ensure that tests are performed properly.

Other diagnostic tests that should be available in malaria programmes

- Haemacue to determine haemoglobin levels.
- Tests to deliver safe transfusion: two instant HIV tests, syphilis, hepatitis B and hepatitis C screen.
- Tests for G6PD deficiency if primaquine is to be used for radical treatment to eliminate hypnozoites and/or gametocytes of *P. falciparum*.
- Polymerase chain reaction (PCR) tests. These can be used to detect very low levels of parasitaemia. Work is progressing to develop a bedside PCR detection machine. PCRs are very important in elimination scenarios to detect very low parasitaemias, and in drug efficacy studies.

Case definitions of malaria

Suspected malaria: a patient with a fever or history of fever in the last 48 hours who lives in or has come from a malaria-endemic area.

Uncomplicated (simple malaria): a patient with a fever or history of fever in the last 48 hours who has a positive biological test and no symptoms of severe disease.

Complicated malaria: a patient with the signs and symptoms of simple malaria who is unable to take oral drugs.

Non-severe malaria may be associated with a variety of other symptoms, including cough, vomiting, diarrhoea, abdominal pain, myalgia, headache, sweating and rigors.

Severe malaria

A patient with one or more of the following signs or symptoms, with biologically confirmed *P. falciparum* infection (and occasionally *P. vivax*) and parasitaemia:

- prostration (inability to sit, or to drink or breastfeed)
- impaired consciousness (cerebral malaria)
- respiratory distress
- multiple convulsions
- circulatory collapse
- severe anaemia (haemoglobin concentration < 5 grams/dL or haematocrit of < 15%) may be the presenting symptom, especially in children and pregnant women, and can rapidly lead to death.

Other conditions that may be associated with severe malaria

Hyperparasitaemia may be associated with severe malaria, but is not pathognomonic of severe disease in itself. It has been associated with a higher risk of mortality and needs to be rigorously treated, preferably in the first instance with parenteral medications. If there are no other signs of severity, the patient may not need hospital admission.

Hypoglycaemia often causes unconsciousness or death if not detected and treated rigorously. It is especially dangerous in children, malnourished patients and pregnant women, and is exacerbated by quinine treatment.

Pulmonary oedema is a grave and often fatal complication of malaria. It can occur spontaneously (particularly during pregnancy), but it is often a result of fluid overload during treatment.

Metabolic (lactic) acidosis: see section on severe malaria below.

Abnormal bleeding is associated with thrombocytopaenia, and leads to bleeding of gums and epistaxis, and sometimes more severe internal bleeding.

Jaundice is more common in adults than in children. Mild jaundice only reflects haemolysis, whereas very high bilirubin levels suggest hepatic dysfunction.

Haemoglobinuria is common, but its more extreme form, blackwater fever, is rare. It is associated with quinine therapy.

Oliguria/anuria can be a sign of renal dysfunction, but make sure that the patient is adequately rehydrated before commencing therapy for renal failure. **Fluid balance charts should be instituted and monitored closely for all patients with severe malaria.**

Uncomplicated/simple malaria

There is a fever and a positive blood smear. There is no evidence of altered consciousness, hypoglycaemia, severe anaemia, jaundice or respiratory difficulties.

Management
Management of children who have always lived in an endemic area

- There is no need to admit the child to hospital (unless they are under 4 months of age or less than 5 kg in weight, or pregnant).
- A diagnostic test should be done before treatment (microscopy if available and quality assured, or an RDT). This will confirm malaria and also ensure that patients who do not have malaria receive appropriate treatment. **Note that malaria is frequently accompanied by other serious infections, such as pneumonia.** Signs of bacterial or viral infections should be looked for and treated appropriately even if the malaria diagnostic test is positive.
- Give first-line antimalarial treatment (ACTs) as recommended in local national guidelines.
- Ensure that tablets or syrup are swallowed and not vomited.
- Give the first dose under direct observation and advise the carer on how to administer the drug to young children by dissolving tablets in breast milk or syrup and giving this slowly with a syringe.
- If the child vomits within the first 30 minutes, repeat the full dose. If they vomit after 1 hour give a half dose. Advise the carer to return if further doses are vomited. Remember to advise the carer to give the dose with food if artemether/lumefantrine is used, to improve absorption of the lipophilic lumefantrine.
- Encourage oral fluid intake and continued feeding with light nutritious foods plus catch-up meals when the child recovers. Measures to lower the body temperature may be necessary (tepid sponging and paracetamol).
- Test for iron deficiency, and if the patient is pale and anaemic (based on palmar and conjunctival examination and/or haemoglobin test), give haematinics (iron

and folic acid, **but** if sulfadoxine-pyrimethamine has been used for malaria treatment, do not give folic acid for 2 weeks).

Management of children visiting or returning from an endemic area for the first time

Hospital admission for management of *P. falciparum* is always advisable.

Treat with an ACT

The WHO recommends the use of **fixed-dose combinations (FDCs)** if available, or pre-packaged drugs if FDCs are not available. **The WHO discourages the use of monotherapies, to reduce the risk of resistance developing.** In particular, the use of artesunate monotherapy, which is commonly available on the private market, is strongly discouraged.

ACTs recommended by the WHO

- Artesunate/amodiaquine (AS/AQ FDC).
- Artesunate + mefloquine (AS+MQ or AS/MQ FDC).
- Artesunate + sulphadoxine/pyrimethamine (AS + SP).
- Artemether + lumefantrine (AM/LM FDC).
- DHA/piperaquine (Duo-Cotecxin, Eurartesim) FDC.
- Artesunate/pyronaridine (Pyramax) FDC.

Non-ACTS

- Malarone (atovaquone/proguanil) FDC: this is very expensive and usually only used where there is artemisinin resistance, or for prophylaxis in western travellers.
- Quinine tablets in IV, IM and rectal forms: for true treatment failures.
- Chloroquine: only for non-*P. falciparum* malaria.
- Primaquine and its derivatives (tafenoquine): for radical treatment of *P. vivax* (and *P. falciparum* in elimination areas).

Paediatric formulations

- AS/AQ infant dose is dispersible, and suitable for children who weigh 4.5–8 kg.
- Paediatric Coartem® (AM/LM) is dispersible and available as cherry-flavoured tablets for children who weigh 5–25 kg.
- Artequin (Mepha) FDC AS/MQ is available as mango-flavoured pellets/granules that can be swallowed directly without water. It is not WHO prequalified.
- AS/MG FDC produced in Brazil for Drugs for Neglected Diseases (DNDi).

Drugs frequently available but not WHO prequalified

- ASMQ Artequin (also in paediatric granules).
- Artemisinin/piperaquine (Artequick).
- Artemisinin and naphthoquine.

Drugs in development

- Artemisone (partner drug not yet decided).
- Synthetic AS called OZ (Sanofi Aventis).
- Semi-synthetic artemisinin (One World Health).

Advice for carers

Discuss preventive efforts with carers (e.g. bed net at night, ideally impregnated with insecticide). Give LLIN if possible.

Tell the mother to return after 2 days if fever persists, and earlier if the child deteriorates.

If the child is repeatedly vomiting and the area is remote and admission to hospital difficult, give rectal artesunate until the vomiting settles. Then give a full 3-day course of ACT.

Management of severe malaria

Severe malaria is a complex multi-system disease that constitutes a medical emergency.

Mortality approaches 100% without treatment, and death often occurs within the first few hours. Prompt initiation of antimalarial treatment in peripheral healthcare facilities and comprehensive management in hospital are necessary to prevent deaths.

Neurological sequelae of cerebral malaria affect about 10% of African children who survive cerebral malaria. These sequelae are severe and permanent in up to 19 000 children annually, and include spastic paresis and epilepsy.

Care should be provided within 15 minutes of arrival at a healthcare facility. Triage systems should be in place in health centres and hospitals to pick up severely ill patients, referral should be rapid, and emergency facilities must be instituted in hospitals, with a high standard of medical and nursing care available 24 hours a day.

Any seriously ill or unconscious patient in a malaria-endemic area must be tested for malaria by RDT (remember that parasites may not be present in the peripheral blood of a patient with cerebral malaria). Malaria should be assumed in any child with severe anaemia, convulsions, hyperpyrexia and/or hypoglycaemia either in hospital or in a peripheral healthcare facility.

Even if a diagnostic test is not available, **the patient should be given an antimalarial drug (IV, IM or rectally, depending on the skill of the staff in the facility) before transfer to the hospital.** This can be repeated if transfer is impossible or is delayed for more than 12 hours. A note of what has been given should be sent with the patient as soon as transfer can be arranged.

If any doubt exists, it is safer to treat than not to treat before transfer.

Immediate measures (in hospital)

- Vital signs: temperature, pulse, blood pressure, and respiratory rate and depth.
- State of hydration.
- Estimate or ideally measure body weight. Estimate of weight by age in well-nourished children:
  — For an infant up to 1 year of age, birth weight doubles by 5 months and triples by 1 year.
  — For children over 1 year, use the following formula: weight (kg) = 2 (age in years + 4).

Be careful in HIV-endemic areas where body weights are often very different from those derived by this formula. Weigh the child if at all possible.

- Level of consciousness (AVPU or Glasgow or Adelaide coma scales) (*see* Section 5.16.A).
- The depth of coma may be assessed rapidly in children using the coma scale for children or by observing the response to standard vocal or painful stimuli (rub your knuckles on the child's sternum; if there is no response, apply firm pressure on the thumbnail bed with a horizontal pencil).
- RDT and malaria smear (thick and thin film) for diagnosis and for continued monitoring of the progress of the

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disease. **Do not wait for a malaria smear result before initiating treatment, as it can take up to an hour. If the RDT is positive, commence treatment immediately.**

- Perform lumbar puncture if the patient is unconscious to eliminate meningitis if there are no contraindications. **Contraindications include papilloedema or suspicion of raised intracranial pressure (irregular breathing and pupillary responses, posturing), bleeding problems or respiratory difficulty such that flexing the back would compromise respiration. In such a situation, give IV antibiotics to treat meningitis as well as malaria.**
- Measurement of glucose (finger prick), haemoglobin and haematocrit (packed cell volume, PCV).
- Group and cross-match blood and search for a suitable donor.

Parenteral IV or IM treatment

In Africa and many other regions, sodium artesunate or quinine are the drugs of choice for severe malaria. In South-East Asia and the Amazon Basin, quinine is no longer always effective and should be accompanied by doxycycline in adults or clindamycin in children. Large trials in mainly Asian Adults (SEAQUMAT study) and in African Children (AQUAMAT study) have proved that parenteral artesunate reduces mortality by over 30% and should be used in preference to quinine.

Initially give treatment intravenously, if possible; otherwise use the IM route. Change to oral therapy as soon as possible.

Especially in the malaria-endemic areas of Africa, the following initial antimalarial medicines are recommended. Artesunate has been shown to reduce mortality compared with quinine, but it is important to use whichever drug is available locally.

- artesunate IV or IM
- artemether IM (its absorption may be erratic in children in shock).
- quinine (IV infusion or divided IM injection)

First-line antimalarial drugs
Sodium artesunate IV or IM

Give 2.4 mg/kg IV (by slow injection) or IM on admission (time 0), followed by 2.4 mg/kg IV or IM at 12 hours and again at 24 hours, and then once daily for a minimum of 3 days until the child can take oral treatment with an ACT.

OR second choice
Artemether IM

Give 3.2 mg/kg IM as loading dose, then 1.6 mg/kg IM once daily (every 24 hours) for a minimum of three days until oral treatment can be taken. Use a 1 mL tuberculin syringe to give the small injection volume (note: absorption may be erratic and therefore only use if quinine and artesunate are not available) and if shocked do not use this drug as absorption is too unreliable.

Intravenous IV quinine (quinine dihydrochloride)

This is the second choice, to be used if sodium artesunate is not available. Give 20 mg/kg quinine dihydrochloride (maximum 1.4 grams) in 5% glucose at a concentration of 1 mg of quinine to 1 mL of 5% glucose over 2–4 hours (never more rapidly than over 2 hours). If possible use an in-line infusion chamber (100–150 mL) to ensure that the loading dose does not go in too quickly. Alternatively, ensure that the IV giving bag contains only the amount needed for each dose. There is a major risk of cardiac side effects if it is infused too quickly.

Subsequently give 10 mg/kg in 10 mL/kg fluid (5% glucose) IV every 12 hours for 24 hours, or longer if the child remains unconscious. These latter doses **must** be given over at least 2 hours.

Never give quinine as an IV bolus. The infusion rate must not exceed a total of 5 mg quinine salt/kg/hour.

If safe control over the rate of infusion of IV quinine is not possible (e.g. there are insufficient or only untrained nursing staff available), give a loading dose intramuscularly (with initial doses of 10 mg/kg quinine salt IM at 0 and 4 hours and then 12-hourly).

For IM injections, dilute the quinine solution to allow better absorption and less pain.

As soon as the child is able to take medication orally, switch to quinine tablets 10 mg/kg every 8 hours for a total of 7 days, or the locally available first-line ACT treatment for malaria.

Side effects:
- Common: cinchonism (tinnitus, hearing loss, nausea and vomiting, uneasiness, restlessness, dizziness, blurring of vision).
- Uncommon: hypoglycaemia, although this is a common complication of severe malaria.
- Serious cardiovascular problems (QT prolongation on the ECG) and neurological toxicity are rare.
- If overdosed by mistake with quinine tablets, give activated charcoal orally or by nasogastric tube as a suspension in water (1 gram/kg).

Chloroquine IV

This drug should never be used to treat severe falciparum malaria but only cases of non-resistant vivax or ovale malaria. Give 5 mg base/kg every 6 hours for a total of 25 mg base/kg (five doses) as an infusion in 5% glucose (give over 2 to 4 hours).

Antimalarial treatment after IV or IM regimes have ended

Following parenteral administration, usually for a minimum of 24 hours or until the child can take oral drugs, the treatment of severe malaria must be completed by giving a full course of one of the artemisinin-based combination therapies (ACT) described below. In some parts of the world, oral quinine combined with clindamycin to complete 7 days of treatment is used

The following ACTs are recommended:
- artemether plus lumefantrine
- artesunate plus amodiaquine
- artesunate plus sulfadoxine-pyrimethamine
- dihydroartemisinin plus piperaquine
- artemether plus clindamycin
- artesunate plus mefloquine.

The choice of ACT in a particular country or region will be based on the level of resistance of the partner medicine in the combination.

In areas of multi-drug resistance (e.g. East Asia), artesunate plus mefloquine, or artemether plus lumefantrine, or dihydroartemisinin plus piperaquine are recommended. In

areas without multi-drug resistance (mainly Africa), any of the ACTs, including those containing amodiaquine, may still be effective. Every country has a national malaria policy in which the first-line therapy is described and should be used.

If possible avoid using mefloquine if the patient has presented with an impaired conscious level.

Treatment for HIV-infected patients with P. falciparum *malaria*

- Patients with HIV infection who develop malaria should receive prompt effective antimalarial treatment regimens as recommended above.
- **Treatment with ACT involving sulfadoxine-pyrimethamine should not be given to HIV-infected patients who are receiving co-trimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis.**
- Treatment of HIV-infected patients who are on zidovudine or efavirenz should, if possible, avoid amodiaquine-containing ACT regimens.

Treatment of P. falciparum *malaria in malnourished patients*

Although there are many reasons why antimalarial pharmacokinetics may differ between malnourished patients and those who are well nourished, there is insufficient evidence to change current mg/kg body weight dosing recommendations.

Always check local guidelines on drug sensitivities.

With all antimalarial drugs, change to an oral therapy when the child can tolerate it.

Additional treatment where needed

- Insert a nasogastric tube to minimise the risk of aspiration pneumonia if the patient's level of consciousness is low. **This can also be used to give food to prevent hypoglycaemia if the child is unconscious for a long period and is unable to eat. Alternatively, sucrose (sugar) can be placed under the tongue.**
- Insert an IV cannula and restore the circulating volume.
  - **Fluids should be given with caution** and the need for them assessed on an individual basis after ascertaining the nutritional status and degree of dehydration present.
  - In general, **children with metabolic acidosis who have not previously received parenteral fluids are dehydrated and should be managed accordingly**.
- Give oxygen if SpO_2 is < 94% (to keep SpO_2 in the range 94–100%) or if there is respiratory distress and no pulse oximeter available.
- Treat severe anaemia with a safe blood transfusion if the child is showing signs of decompensation.
- Give anticonvulsants (diazepam is preferred) if the patient is convulsing (see below) to prevent long-term neurological damage (*see* Section 5.16.E). Convulsions associated with cerebral malaria should be distinguished from febrile convulsions common in children under 4 years of age. The child usually recovers rapidly, within a few minutes, from a febrile convulsion. Convulsions in malaria are common before or after the onset of coma. They are significantly associated with morbidity and sequelae. They may present in a very subtle way. Important signs include intermittent nystagmus, salivation, minor twitching of a single digit or a corner of the mouth, and an irregular breathing pattern.

Prophylactic anticonvulsants have been recommended in the past, but recent evidence suggests that **phenobarbital may be harmful in this situation**.

- Paracetamol, 15 mg/kg of body weight 4-hourly, may also be given orally or rectally as an antipyretic.
- Use tepid sponging and fanning to try to keep the rectal temperature below 39°C. Relatives are usually happy to do this when instructed.
- High-dose IV or IM antibiotics should be given routinely to an unconscious or shocked patient.
- Avoid using harmful ancillary drugs.

The patient will need intensive nursing care at least until they regain consciousness. They may urgently need glucose or a blood transfusion if hypoglycaemia or haemolysis is severe.

Management of associated causes of mortality in severe malaria

Some children with *P. falciparum* malaria go on to develop altered consciousness, severe anaemia, acidosis, or any combination of these. Where transmission of *P. falciparum* is endemic, malaria is the commonest cause of coma in children, especially in those aged 1–5 years.

Cerebral malaria (coma, confusion and convulsions)

Coma develops rapidly, often within 1 or 2 days of onset of fever, and sometimes within hours. Convulsions are usual and may be repeated. Clinical features suggest a metabolic encephalopathy, with raised intracranial pressure. Opisthotonos, decorticate or decerebrate posturing, hypotonia and conjugate eye movements are common. Oculovestibular reflexes and pupillary responses are usually intact. Papilloedema is found in a small minority of cases. A unique retinopathy with patchy retinal whitening and pallor of vessels is found. In fatal cases, brain swelling is commonly present at autopsy, but cerebral herniation is not usually found even in patients who have undergone lumbar puncture.

Hypoglycaemia, acidosis, hyperpyrexia and convulsions (sometimes undetectable without EEG) are common accompaniments of cerebral malaria, and require appropriate management (see below).

No physical signs are diagnostic of coma due to malaria, and incidental parasitaemia is common in endemic areas, so other causes of coma, especially hypoglycaemia and meningitis, must always be carefully sought, and if necessary treated on the basis of presumptive diagnosis.

Even with optimal treatment, the case fatality rate is 15–30%, and about 10% of survivors have residual neurological sequelae (hemiparesis, spasticity, cerebellar ataxia) that may partially or completely resolve over time.

Investigations

- Blood glucose levels (e.g. by blood glucose stick test).
- Lumbar puncture if meningitis is suspected; contraindications include papilloedema or suspicion of raised intracranial pressure (irregular breathing and abnormal pupillary responses, posturing), or respiratory difficulty such that flexing the back would compromise respiration. **In such a situation, give IV antibiotics to treat meningitis as well as malaria.**

Management

Coma

Ensure that the airway is open at all times and that the patient is breathing adequately. Give oxygen by face mask with a reservoir or nasal cannulae (to keep SpO_2 in the range 94–98% if a pulse oximeter is available). If the child stops breathing, give assisted ventilation with a bag-mask of suitable size (500 mL or 1600 mL).

Ensure that a bag-mask is available at all times.

Nurse the patient in the recovery position to avoid aspiration of secretions or vomit.

Exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis).

- Treat convulsions (*see* Section 5.16.A on coma and Section 5.16.E on convulsions).
- Treat hypoglycaemia.

Convulsions

Convulsions are common before and after the onset of coma.

- Ensure that the airway is open, and give oxygen by face mask with a reservoir or nasal cannulae.
- If the child stops breathing, give assisted ventilation with a bag-mask of suitable size (500 mL or 1600 mL).
- Examine all children with convulsions for hyperpyrexia and hypoglycaemia. Treat hypoglycaemia with IV or oral glucose if identified on blood testing, but also treat as for hypoglycaemia if blood glucose levels cannot be measured and the child is drowsy, unconscious or fitting (see below).
- Give anticonvulsant treatment with rectal diazepam or paraldehyde or IM paraldehyde.
- If the patient has a fever of ≥ 39°C (≥ 102.2°F), give paracetamol rectally (if available).
- Treat seizures lasting for more than 5 minutes with drugs. **Ensure that a bag-mask is available at all times in case of apnoea following the use of diazepam. Apnoea is usually short-lived and improves quickly with ventilation via bag and mask.**

Note that seizure activity needs to be looked for carefully, as it may appear as just a twitching of the thumb or mouth.

- Give IV diazepam:
  - **Children**: 300 microgram/kg of body weight as an IV infusion over 2 minutes or 400–500 microgram/kg of body weight intra-rectally. This dose can be repeated after 10–15 minutes if still fitting.
  - **Pregnant girls**: 10 mg rectally or by slow IV injection. This dose can be repeated after 10–15 minutes if still fitting.
  - Do not exceed 10 mg per dose.
- Alternatively, paraldehyde 0.1 mL/kg of body weight may be given by deep IM injection or 0.8 mL/kg of body weight (maximum 20 mL) intra-rectally using a sterile glass syringe (a disposable plastic syringe may be used provided that the injection is given immediately after the paraldehyde is drawn up, and the syringe is never reused).

Hypoglycaemia

Hypoglycaemia is common and is due to poor intake, increased metabolic needs of the patient and parasites and impaired hepatic gluconeogenesis. It is easily overlooked because clinical signs may mimic those of cerebral malaria.

Check for hypoglycaemia in **all** patients who are unconscious, in shock or deteriorating. Also regularly (every hour in the first instance) check pregnant girls, children under 5 years, and the malnourished, and all patients receiving quinine.

Hypoglycaemia is defined as blood glucose levels < 2.5 mmol/litre (< 45 mg/dl).

Prevent hypoglycaemia with a maintenance quantity of 5% glucose in 0.9% Ringer-lactate or Hartmann's solution (50 mL of 50% glucose in a 500-mL bag). If the child develops hypoglycaemia despite this, give maintenance as 10% glucose in 0.9% Ringer-lactate or Hartmann's solution (100 mL of 50% glucose in a 500-mL bag). Do not exceed maintenance fluid requirements for the child's weight (*see* Section 9 Appendix). If the child develops signs of fluid overload, stop the infusion; repeat the 10% glucose boluses (5 mL/kg) if there is hypoglycaemia identified by making regular checks of blood glucose levels.

If IV access is not possible and the child is hypoglycaemic, place an intra-osseous needle (*see* Section 8.4.B).

Treat hypoglycaemia or suspected hypoglycaemia with an IV glucose infusion or bolus:

- **Children:** 1 mL/kg of 50% dextrose, diluted with four times the volume of infusion fluid (usually Ringer-lactate or Hartmann's solution) infused over 5 minutes **or** 5 mL/kg of 10% glucose as a bolus.
- **Pregnant girls:** 50 mL of 50% dextrose diluted with an equal volume of infusion fluid (usually Ringer-lactate or Hartmann's solution) over 15 minutes (irritating to veins).

Re-test 15 minutes after completion of the infusion, and repeat the infusion if blood glucose remains low. Repeat until blood glucose recovers, then infuse with 5–10% glucose in Ringer-lactate or Hartmann's solution (according to hypoglycaemia risk) to prevent recurrence. Ensure regular feeding when oral intake can be sustained. Fluids used to treat hypoglycaemia must be included in daily fluid requirements.

If blood glucose levels cannot be measured and hypoglycaemia is a possibility, always give IV glucose as described above.

If the child is still unable to swallow after 48 hours, start nasogastric feeds. If a gag reflex is present and the child is able to swallow, feed them as soon as this is possible. For young children breastfeed every 3 hours if possible, or give milk feeds of 15 mL/kg 3-hourly if the child can swallow. If they are not able to feed without risk of aspiration, give milk, especially breast milk, by nasogastric tube or sugar sublingually (*see* Section 5.8.B). Continue to monitor the blood glucose levels, and treat accordingly (as described above) if these are found to be < 2.5 mmol/litre or < 45 mg/dL.

Hypoglycaemia is a major cause of death in severe malaria patients, especially in young children and pregnant girls. Remember that quinine will potentiate hypoglycaemia. Young children should receive regular feeding, including by nasogastric tube, if they are unable to take oral foods.

Severe anaemia

This is indicated by severe palmar pallor, often with a fast pulse rate, difficult breathing, confusion or restlessness. Signs of heart failure such as gallop rhythm, enlarged liver

and, rarely, pulmonary oedema (fast breathing, fine basal crackles on auscultation) may be present (see above).

Severe haemolytic anaemia is defined as < 5 grams of haemoglobin/dL or haematocrit < 15%.

Severe anaemia may be the presenting feature in malaria. Patients with severe anaemia, especially pregnant girls, should be tested for malaria.

Give a safe blood transfusion as soon as possible to:

- all children or pregnant girls with a haematocrit ≤ 12% or Hb of ≤ 4 g/dL
- less severely anaemic children (haematocrit > 12–15%; Hb 4–5 g/dL) with any of the following:
  — clinically detectable dehydration (as well as rehydrating orally if possible)
  — shock
  — impaired consciousness
  — deep and laboured breathing
  — heart failure
  — very high levels of parasitaemia (> 10% of red blood cells parasitised).

Give packed cells (10–20 mL/kg body weight for children and 500 mL for pregnant girls), if available, over three to four hours in preference to whole blood. Allow red blood cells to settle at the bottom of the bag, and stop the infusion when the cells have been used.

If not available, give fresh whole blood (20 mL/kg body weight) over 3–4 hours.

A diuretic is not usually indicated (unless pulmonary oedema or fluid overload is developing), because many of these children have a low blood volume (hypovolaemia).

Check the respiratory rate and pulse rate every 15 minutes. If one of them rises, transfuse more slowly. If there is any evidence of fluid overload due to the blood transfusion, give IV furosemide (1–2 mg/kg body weight) up to a maximum total of 20 mg for children, and give 40 mg IV for pregnant girls.

After the transfusion, if the haemoglobin level remains low, repeat the transfusion.

In severely malnourished children, fluid overload is a common and serious complication. Give whole blood (10 mL/kg body weight rather than 20 mL/kg) once, and only repeat the transfusion if there are no signs of overload.

Perform microscopy following transfusion, and repeat or extend antimalarial treatment if parasitaemia is increasing.

Respiratory distress due to acidosis

This presents with deep laboured breathing while the chest is clear on auscultation, sometimes accompanied by lower chest wall indrawing. It is caused by systemic metabolic acidosis (frequently lactic acidosis) and may develop in a fully conscious child, but more often in children with cerebral malaria or severe anaemia. Always exclude other causes, such as pneumonia or pulmonary oedema.

Metabolic acidosis in severe malaria has been attributed to the combined effects of several factors that reduce oxygen delivery to tissues:

- Increased production of lactic acid by parasites (through direct stimulation by cytokines).
- Decreased clearance by the liver.
- Marked reductions in the deformability of uninfected red blood cells may compromise blood flow through tissues.
- Dehydration and hypovolaemia can exacerbate microvascular obstruction by reducing perfusion pressure.

- Destruction of red blood cells and anaemia further compromise oxygen delivery.
- Mean venous blood lactate concentrations have been found to be almost twice as high in fatal cases as in survivors, and to correlate with levels of tumour necrosis factor and interleukin 1-alpha. The lactate concentrations fell rapidly in survivors but fell only slightly, or rose, in fatal cases. Sustained hyperlactataemia has been found to be the best overall prognostic indicator of outcome.

Treatment

Give oxygen to all patients (even if they are not hypoxaemic), and if a pulse oximeter is available keep SpO$_2$ in the range 94–100%.

Correct reversible causes of acidosis, especially dehydration and severe anaemia.

- If Hb is ≥ 5 g/dL, give 10 mL/kg of 0.9% Ringer-lactate or Hartmann's solution IV as a bolus and then reassess.
- If haemoglobin level is < 5 grams/dL, give whole blood (10 mL/kg) over 30 minutes, and a further 10 mL/kg over 1–2 hours without diuretics. Check the respiratory rate and pulse rate every 15 minutes. If either of these shows any rise, transfuse more slowly to avoid precipitating pulmonary oedema (*see* Section 1.7).
- Monitor ECG for cardiac arrhythmias if possible.
- The use of sodium bicarbonate is controversial.

Respiratory distress due to pulmonary oedema

This is different to that due to acidosis, and there is usually more chest recession, hypoxaemia (cyanosis, SpO$_2$ < 94%), basal lung crepitations, enlarging liver, gallop rhythm, and raised jugular venous pressure. It may be due to fluid overload, often in the presence of severe anaemia. The most effective treatment is to tilt the bed of the patient head up so that the venous blood flow to the heart is reduced. If the bed cannot be tilted, sit the patient up, give furosemide 1 mg/kg for children and 40 mg IV for pregnant girls, and proceed with a careful transfusion of packed blood cells. Repeat furosemide as needed.

Respiratory distress due to pulmonary aspiration or pneumonia

Prevent aspiration pneumonia if possible, because it can be fatal. Place the comatose patient in the recovery position and ensure that the airway is open. If it is safe to intubate and maintain this, do so in order to protect the airway if the patient is unconscious (U on the APVU scale, or Glasgow Coma Scale score of < 9).

- Give oxygen if the SaO$_2$ is < 94% or, if pulse oximetry is not available, if there is cyanosis, severe lower chest wall indrawing or a respiratory rate of ≥ 70 breaths/minute. Keep SpO$_2$ 94–100%. Give IM or IV antibiotics as described for pneumonia (*see* Section 5.3.A), and add in metronidazole 7.5 mg/kg 8 hourly (maximum individual dose 500 mg) until the patient can take these orally, for a total of 7 days.

Shock

Most children with malaria have warm peripheries. Shock is unusual in malaria (algid malaria). Some patients may have a cold clammy skin. Some of them may be in shock (increased heart rate, cold extremities, weak pulse, capillary refill time longer than 3 seconds, low blood pressure (late sign)). These features are not usually due to malaria alone.

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If shock is present, consider septicaemia, do a blood culture and start a broad-spectrum antibiotic IV (penicillin and gentamicin **or** cefotaxime or ceftriaxone) in addition to antimalarial drugs.

Management (*see* Section 5.5) includes fluid replacement as follows:

- **Children:** Give Ringer-lactate or Hartmann's solution IV, 10 mL/kg as a rapid bolus. Reassess, and if the patient is no better, or improving but still in shock, consider further 10 mL/kg boluses.
- **Pregnant girls:** Give Ringer-lactate or Hartmann's solution IV, 500 mL as a rapid bolus, then reassess.

If there is no improvement in capillary refill or tachycardia, repeat the infusion once or twice more, as required.

Give broad-spectrum antibiotics to treat septicaemia and any associated infections.

Acute renal failure

Acute renal failure (ARF) is defined as an abrupt decline in the renal regulation of water, electrolytes and acid–base balance, and continues to be an important factor contributing to the morbidity and mortality of malaria patients (*see* Section 5.6.C). Oliguria or anuria is often associated with jaundice, anaemia and bleeding disorders.

Note that ARF is uncommon in children, and dehydration is a more common cause of poor urine output.

- The basic principles of management are avoidance of life-threatening complications, maintenance of fluid and electrolyte balance, and nutritional support.
- Urinary catheterisation can be helpful if it can be safely undertaken, so that urine output can be accurately measured. Alternatively, weigh nappies in young children.
- Acute renal failure is suspected when the **hourly** urine output is less than 1 mL/kg of body weight/hour). Blood levels of urea and creatinine are usually raised.
- Make sure that the patient is adequately hydrated, but avoid overload, which will precipitate pulmonary oedema if the kidneys cannot excrete excess water.
- If urine output continues to be low despite adequate hydration, peripheral perfusion and normal blood pressure, give furosemide 1 mg/kg and repeat as required.
- If renal failure is established, restrict fluid to insensible loss (30 mL/kg/day) plus urine output and other fluid losses (e.g. vomit, diarrhoea).
- Consider peritoneal dialysis (if available) or ideally haemodialysis.

Abnormal bleeding
- Transfuse with fresh blood.
- Give vitamin K, 250–300 microgram/kg (maximum 10 mg) IV.
- Avoid IM injections and non-steroidal anti-inflammatory drugs (NSAIDs).

Coexisting infections
Treat any associated pneumonia, dysentery, etc.

Summary of supportive care for the treatment of severe malaria in hospital
- If the patient is unconscious, maintain a clear airway. Nurse them in the recovery position to avoid aspiration pneumonia, and turn them 2-hourly.
- Do not allow the child to lie in a wet bed, and provide special care for pressure points. Turn the patient every 2 hours.
- Give oxygen for patients who are in respiratory distress or in shock.
- In children with no dehydration, ensure that they receive their daily fluid requirements, but take care not to exceed the recommended limits (*see* Section 9 Appendix). Be particularly careful when fluids are given IV.
- Treat convulsions and hypoglycaemia.
- If you cannot exclude meningitis, give an appropriate antibiotic intravenously.
- If there is deep or laboured breathing suggestive of acidosis, give one bolus of 10 mL/kg IV fluid (normal Ringer-lactate or Hartmann's) to correct hypovolaemia and reassess. A second bolus may be required.
- During rehydration, examine frequently for fluid overload (increased liver size is probably the best sign, as well as gallop rhythm, fine crackles at the lung bases, raised jugular venous pressure and eyelid oedema in infants).
- In infants, if possible always use an in-line infusion chamber for IV rehydration. If this is not available and supervision is poor, empty the IV fluid bag until only 200–300 mL is remaining then if it all goes in quickly it will be less harmful than if the whole bag is being infused.
- If necessary, use a nasogastric tube to rehydrate the patient.
- Avoid giving drugs like corticosteroids and other anti-inflammatory drugs, urea, invert glucose, low-molecular dextran, heparin, adrenaline (epinephrine), prostacyclin and cyclosporine, as they do not treat malaria and can be harmful.
- Give safe blood transfusion where necessary, with careful monitoring to prevent fluid overload. Packed cells should be used in children and pregnant girls where possible. If overload is suspected, give a single dose of furosemide.
- If the patient is unconscious and you cannot exclude meningitis or the child is in shock, administer a broad-spectrum antibiotic to manage septicaemia, pneumonia or meningitis, which are often associated with cerebral malaria.

Summary of monitoring
- Check the patient regularly, at least every 3 hours. A doctor (if available) should see the patient at least twice a day.
- The rate of IV infusion should be checked hourly.
- Patients with cold extremities, hypoglycaemia on admission, respiratory distress and/or deep coma are at highest risk of death. It is particularly important that these children are kept under very close observation.
- Monitor and report immediately any change in the level of consciousness, convulsions, or changes in the patient's behaviour.
- Monitor the temperature, pulse rate and respiratory rate (and if possible the blood pressure) every 6 hours for at least the first 48 hours.
- Fluid balance charts: unconscious patients may be catheterised in order to measure urine output and facilitate correct fluid balance, and to detect possible renal failure.
- Frequent measurement of blood glucose levels (every hour, especially when receiving quinine and/or where the level of consciousness does not improve).
- If the patient is conscious, regularly (4-hourly) determine

blood glucose levels to exclude hypoglycaemia if the patient is not eating well. This is especially important in young children and pregnant women, and in those patients who are receiving quinine therapy.

- Check haemoglobin levels and haematocrit daily.
- Check plasma urea and electrolytes where possible, and take blood gas and lactate measurements (if available).
- Check the rate of IV infusion regularly. If available, use a giving chamber with a volume of 100–150 mL. Be very careful about over-infusion of fluids from a 500-mL or 1-litre bottle or bag, especially if the child is not supervised all the time. Partially empty the IV bottle or bag. If the risk of over-infusion cannot be ruled out, rehydration using a nasogastric tube may be safer.
- Keep a careful record of fluid intake (including IV) and urine output (should be at least 1 mL/kg/hour).
- Undertake a daily slide to determine the level of parasitaemia and to monitor treatment efficacy.
- Regular haemoglobin measurement. The frequency will depend on the rate of red blood cell breakdown. This may be very rapid in cases of high parasite density.

On discharge from hospital
When the child or pregnant girl is due to leave hospital, talk with the relatives and carers to ensure that:

- the patient sleeps under a net (LLIN); if not, provide one
- the patient completes any outstanding treatment
- the carers and relatives recognise symptoms and where to get treatment for simple malaria in future
- the family knows to give extra meals to make up for the poor nutrition during the illness
- the family know when to bring the patient for further check-ups and arrange a follow-up appointment.

Examine for any neurological sequelae and advise the family on how to manage these and the possible prognosis. Arrange a physiotherapy session if necessary. Good follow-up is important.

Management of non-severe anaemia
If anaemia associated with malaria is not severe (defined as a haemoglobin level of 6–9.3 grams/dL), treat as follows. Give iron once daily in combination with folic acid (one tablet contains ferrous sulphate 200 mg, equivalent to 60 mg of elemental iron) plus 250 micrograms/kg/day of folic acid. Give 3–6 mg/kg (maximum 200 mg) of elemental iron in 2–3 divided doses and for folic acid give 250 microgram/kg once daily (usually one 5 mg tablet). Stress the importance of keeping the tablets out of reach of young children. Iron poisoning is very dangerous.

If the child is taking sulfadoxine-pyrimethamine for malaria, or co-trimoxazole for HIV prophylaxis, do not give folic acid until 2 weeks later (it interferes with antimalarial action).

TABLE 6.3.A.D.1 Dose of ferrous fumarate 140 mg/5 mL in children

Weight	Dose
3–6 kg	1 mL
6–10 kg	1.25 mL
10–15 kg	2.0 mL
15–20 kg	2.5 mL
20–30 kg	4 mL

An alternative for a young child is iron syrup (ferrous fumarate) 140 mg in 5 mL and equivalent to 45 mg of iron. Give once daily (*see* Table 6.3.A.d.1).

Plus separate folic acid 250 micrograms/kg/day.

Treat for 3 months where possible (1 month to correct anaemia and 1–3 months to build iron stores).

Patients with HIV infection
Patients with HIV infection who develop malaria should receive prompt effective antimalarial treatment regimens as recommended above.

However, treatment with an ACT involving sulfadoxine-pyrimethamine should not be given to HIV-infected patients receiving co-trimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis.

Treatment in HIV-infected patients on zidovudine (AZT) or efavirenz should, if possible, avoid amodiaquine-containing ACT regimens. Amodiaquine can cause anaemia in G6PD deficiency, and AZT may also cause anaemia.

Infection with *P. vivax*, *P. ovale* and *P. malariae*
Of the four species of *Plasmodium* that affect humans, only *P. vivax* and *P. ovale* form hypnozoites, parasite stages in the liver, which can result in multiple relapses of infection weeks to months after the primary infection. Thus a single infection causes repeated bouts of illness. Ideally, the objective of treating malaria caused by *P. vivax* and *P. ovale* is to cure (radical cure) both the blood stage and the liver stage infections, and thereby prevent recrudescence and relapse, respectively. **However, primaquine which is used to produce a radical cure is contraindicated in children under 4 years of age.**

Diagnosis
- Microscopy using a Giemsa-stained quality-assured thin film.
- pLDH tests can detect all species of malaria. Combination tests are now available that combine HRP2 and pLDH to detect both *P. falciparum* and non-*P. falciparum* malaria.

Treatment
Both *P. ovale* and *P. malariae* are regarded as very sensitive to chloroquine, although there is a single recent report of chloroquine resistance in *P. malariae*.

P. vivax is generally still sensitive to chloroquine, although resistance is prevalent and increasing in some areas (notably Indonesia, Peru and Oceania). Resistance to pyrimethamine has increased rapidly in some areas, and sulfadoxine/pyrimethamine is consequently ineffective. There are insufficient data on current susceptibility to proguanil and chlorproguanil, although resistance to proguanil was selected rapidly when it was first used in *P. vivax*-endemic areas.

In general, *P. vivax* is sensitive to all of the other antimalarial drugs, and slightly less sensitive to mefloquine (although mefloquine is still effective). In contrast to *P. falciparum*, asexual stages of *P. vivax* are susceptible to primaquine. Thus chloroquine plus primaquine can be considered as a combination treatment. The only drugs with significant activity against the hypnozoites are the 8-aminoquinolines (bulaquine, primaquine and tafenoquine).

Treatment of uncomplicated *P. vivax*

For chloroquine-sensitive *P. vivax* malaria (i.e. in most places where *P. vivax* is prevalent), oral chloroquine at a total dose of 25 mg base/kg body weight for a course of treatment is effective and well tolerated. Lower total doses are not recommended, as these might encourage the emergence of resistance. Chloroquine is given in an initial dose of 10 mg base/kg body weight followed by either 5 mg/kg body weight at 6 hours, 24 hours and 48 hours or, more commonly, by 10 mg/kg body weight on the second day and 5 mg/kg body weight on the third day.

Recent studies have also demonstrated the efficacy of the recommended ACTs in the treatment of *P. vivax* malaria. The exception to this is artesunate plus sulfadoxine-pyrimethamine.

For treatment of chloroquine-resistant *P. vivax* malaria, amodiaquine, mefloquine and quinine are effective. ACTs based on either amodiaquine, mefloquine or piperaquine, rather than monotherapy, are the recommended treatment of choice.

For the complete (radical) removal of *P. vivax* infection, primaquine is required, but is contraindicated in children under 4 years of age and in pregnant women and girls.

Treatment of uncomplicated malaria caused by *P. ovale* and *P. malariae*

Treat with chloroquine as described for *P. vivax* above.

Prevention of malaria

Most important is the prevention of mosquito bites. All children, all pregnant girls and all patients who have had a recent bout of malaria should be provided with an insecticide-impregnated bed net.

Drugs for prophylaxis depend on the region and sensitivity of the malarial parasite.

This is important for:

- children with sickle-cell disease: chloroquine 5 mg/kg weekly
- children or adults who return to an endemic area after an absence of over 1 year, even if they are originally from that region
- non-immune individuals: people from non-endemic areas.

Intermittent preventive treatment for malaria in infants (ITPi) and children (ITPc, now called seasonal malaria chemoprevention, SMC)
IPTi

- Malaria cases can be reduced by 30% in infants during the first 12 months of life using this safe, affordable and simple tool. It can be implemented via existing vaccination programmes run by the WHO.
- For infants, a treatment dose of sulfadoxine/pyrimethamine (SP) should be given three times at the time of each immunisation, beginning at 2 months (DTP2), 3 months (DTP3) and 9 months (measles and yellow fever). Each tablet of SP contains 500 mg sulfadoxine and 25 mg pyrimethamine, and for infants the following sizes for each dose are: a quarter tablet for children weighing less than 5 kg, and a half tablet for children weighing 5–10 kg.

SMC

- For children living in areas where transmission is highly seasonal (e.g. in Mali, Senegal, Niger and northern Nigeria), aged 1–6 years, a single dose of one tablet of SP plus three doses of one tablet/day for 3 days of amodiaquine (200 mg) is given once a month during the malaria transmission season.
- Tablets are crushed and suspended in water and given by spoon. Side effects are very rare. Minor gastrointestinal side effects may occur.
- For areas in which there is resistance to SP, piperaquine may be used instead of SP.

ITPi and SMC are recommended in addition to treated bed nets in areas of moderate to high levels of malaria transmission and low to moderate levels of parasite resistance to SP.

Preventive treatment for malaria in pregnant girls and women (see Section 2.8.D)
Follow-up care for anaemia

- If moderate or severe anaemia has been documented, give home treatment with a daily dose of iron/folate tablet or iron syrup for 3 months where possible (it takes 2–4 weeks to correct the anaemia and 1–3 months to build up iron stores).
- **However, if the child is taking sulfadoxine-pyrimethamine for malaria, do not give iron tablets that contain folate until a follow-up visit in 2 weeks. The folate may interfere with the action of this antimalarial drug.**
- If the child is over 1 year and has not had mebendazole/albendazole in the previous 6 months, give one dose of mebendazole (500 mg) for possible hookworm or whipworm infestation (*see* Section 6.3.C.a). Advise the mother about good feeding practices.
- Omit iron in any child with severe malnutrition in the acute phase.
- A study in Malawi showed that many children who were so anaemic as to require a blood transfusion died within 6 months of discharge from hospital. Prophylactic antimalarial drugs (coArtem) at 1 month and 2 months post discharge prevented many readmissions and deaths.

Follow-up care after malaria has been treated

- Ask the mother to return if the fever returns or persists after 2 days of treatment, or if the child's condition gets worse in any way.
- If this happens, reassess the child to exclude the possibility of other causes of fever.
- Check whether the child actually took the full course of treatment, and repeat a blood smear. If the treatment was not taken, repeat it. If it was taken but the blood smear is still positive (remember that an RDT can remain positive for up to 6 weeks after the initial infection), and the child is not seriously ill, re-treat with first-line drugs.
- If the child returns within 2 weeks, give a full course of oral quinine.
- If the child is severely ill, refer them to a hospital for inpatient treatment.

6.3.B Other protozoal infections

Introduction

The organisms collectively termed **protozoa** are not closely related to each other. They do have some similarities when viewed under a microscope, as they are largely unicellular and motile, although with exceptions.

Toxoplasmosis

Toxoplasmosis is caused by infection with a common parasite called *Toxoplasma gondii*. *T. gondii* can be found in:

- undercooked or raw meat
- cured meat
- unpasteurised goats' milk
- cat faeces.

It cannot be passed from person to person apart from mother to unborn child.

During acute toxoplasmosis, symptoms are often influenza-like (swollen lymph nodes, or muscle aches and pains that last for a month or more).

Swollen lymph nodes are commonly found in the neck or under the chin, followed by the axillae and the inguinal region. Swelling may occur at different times after the initial infection, persist, and/or recur for various times independently of antiparasitic treatment. It is usually found at single sites in adults, but in children multiple sites may be more common. Enlarged lymph nodes will resolve within 1–2 months in 60% of patients. However, 25% of patients take 2–4 months to return to normal, and a few take longer than this.

Young children and immunocompromised patients, such as those with HIV/AIDS, may develop severe toxoplasmosis. This can cause encephalitis or necrotising retinochoroiditis.

Infants can develop a congenital infection acquired *in utero*. The key features are fever, rash, petechiae, lymphadenopathy, hepatosplenomegaly, jaundice, hydrocephalus or microcephaly, microphthalmia, epilepsy and chorioretinitis.

Management

Congenital toxoplasmosis in newborns and immunocompromised children with HIV infection can be treated for a year with pyrimethamine (with additional folinic acid) plus sulfadiazine. This treatment requires expert management.

Amoebiasis

Infection by *Entamoeba histolytica* is acquired from human hosts via contaminated food, water or direct contact. Most infected children are asymptomatic, but some have systemic illness. This can last for many weeks. The disease presents with acute diarrhoea with colicky abdominal pains. A small proportion have bloody diarrhoea with a fever, and rarely intestinal perforation with peritonitis or haemorrhage may occur.

The diagnosis can be confirmed by observing the amoebae in a fresh stool or following a biopsy of the ulcers at sigmoidoscopy.

Amoebic liver abscesses occur in less than 1% of infected individuals. They present with fever, abdominal pain, and a tender liver sometimes with a palpable mass. The liver abscess often occurs without gastrointestinal symptoms and with negative stools. The diagnosis can be confirmed by ultrasound scan or **CT scan (if available)**.

Treatment is required for those with systemic illnesses, those with diarrhoea due to invasive ulceration and those with liver abscesses.

- Metronidazole is the drug of choice and is well absorbed orally: 7.5 mg/kg three times daily for 5–10 days (maximum daily dose 400 mg).
- If the abscess is very large and particularly if there is concern that it may rupture, it may require aspiration under careful ultrasound support.
- After the acute treatment of a liver abscess, diloxanide should be used immediately following the course of metronidazole in order to remove all amoebae from the bowel.
- The dose of diloxanide is:
  - 1 month to 12 years of age: 6.6 mg/kg three times daily for 10 days
  - > 12 years of age: 500 mg three times daily for 10 days.

Cryptosporidiosis

Cryptosporidium parvum can be acquired from infected human or animal hosts and from contaminated water and food.

It causes an acute gastroenteritis, which is self-limiting in most children. The enteritis is associated with watery diarrhoea, nausea and colicky abdominal pains. It lasts for approximately 2 weeks. In otherwise healthy children it does not usually require treatment with antimicrobial drugs unless it persists or is associated with systemic illness, in which case azithromycin may be effective.

In children with AIDS it can produce a protracted and severe illness involving major weight loss, in which case it can be treated with azithromycin. Avoid azithromycin in patients with liver disease.

The dose of azithromycin is:

- 6 months to 12 years of age: 10 mg/kg once daily for 3 days or longer in AIDS.

Giardiasis

Infection by *Giardia lamblia* can be acquired from infected human or animal hosts and from contaminated water and food. The organisms live in the duodenum.

The infection may be asymptomatic or it can produce an acute gastroenteritis with watery stools, colicky abdominal pains and nausea. It can also produce a chronic diarrhoeal illness with malabsorption and colicky abdominal pain lasting for many months.

Diagnosis is best made from examining a fresh stool. Sometimes more than one examination will be necessary.

- Metronidazole (at the doses described for amoebiasis above) is appropriate in the chronic form of the infection. The acute form usually resolves without treatment.

6.3.C Helminth infections

6.3.C.a Worms

BOX 6.3.C.A.1 Minimum standards
- ■ Faecal microscopy and egg count.
- ■ Anoscopy.
- ■ Eosinophil count and chest X-ray if available.
- ■ Mebendazole, albendazole and ivermectin.
- ■ Topical thiabendazole.

Introduction

In low-resource countries, children presenting to medical facilities may harbour intestinal helminthiasis (worms) or their juvenile forms (larvae) in other organs. Often this situation may exist without the presence of any signs or symptoms. In such situations ill health or the risk of serious complications is directly related to the number of parasites in a child; although children bearing heavy loads of parasites are in a minority. These patients will often present for other reasons, without their heavy worm infections being recognised.

Parasitology of worms

There are three important groups of helminth infections:
1 **Cestodes:** Beef tapeworm (*Taenia saginata*) and pig tapeworm (*Taenia solium*).
2 **Nematodes:** Roundworms (*Ascaris* species), hookworms (*Ancylostoma duodenale*), whipworms (*Trichurius* species) and threadworms (*Enterobius* species).
   - ● *Ascaris lumbricoides* is the commonest human roundworm. Adult worms are whitish pink, several millimetres (mm) wide and up to 30 centimetres (cm) long, which may live for years in the small intestine. They are often seen in stool or vomit. Transmission is by ingestion of embryonated eggs from soil. Adult worms shed their eggs in faeces. The ill effects of ascariasis are largely indirect and rare (e.g. a worm in the common bile duct). The probability of this obstruction increases with worm load.
   - ● Hookworms are of two species, *Necator americanus* (the New World hookworm) and *Ancylostoma duodenale.* Both adult forms are hair-like, about 1 cm long, with cutting plates at the mouth end. *Ancylostoma* is generally the more virulent pathogen. Both species occur widely, with overlap, and the differences between them can be ignored by clinicians without a special interest in this subject. They have invasive larvae, and both skin penetration and ingestion of embyonated eggs are involved in transmission. Sustained blood loss in the small intestine leads to an accumulating risk of anaemia. In children, protein-losing enteropathy and systemic secondary effects of chronic inflammation are equally important.
   - ● *Trichuristrichiura* commonly known as the whipworm can be up to 4 cm long with thickness of a hair except at the tail end which is wider. Transmission is similar to *Ascaris* but maturation occurs only in the gut without tissue invasion beyond the mucosa. Its ill effects are related to worm load and may lead to a form of colitis with systemic secondary effects of chronic inflammation. This intensity of infection occurs only in a small minority of children.
   - ● *Enterobius vermicularis* is an intestinal helminth which is spread in the form of embryonated eggs by personal contact among children. It is largely harmless but can cause secondary infection in the vaginal introitus.
   - ● *Strongyloides stercoralis* is capable of independent existence in the soil. It is an opportunistic parasite of several mammals, including humans. Person-to-person spread occurs with probability related to intimacy of contact. Although it is acquired in childhood, its most devastating (often fatal) effects occur only when filariform larvae become disseminated through asexual reproduction in the host. This happens if host immunity breaks down, for example with severe malnutrition or malignancy in later life. Surprisingly, disseminated strongyloidiasis is not associated with HIV infection, although it is associated with another retrovirus, HTLV1.
3 **Trematodes** or flukes, which include blood flukes (e.g. schistosomiasis) (*see* Section 6.3.C.c) and biliary tract, lung and gut flukes.

Diagnosis

The main clues to heavy parasitosis are in growth, nutrition and in the case of hookworm, anaemia. Gastrointestinal symptoms also occur. Often a presumptive diagnosis is based on manifestations suggestive of worm infections. An increasing number of studies on the effects of helminth infections on cognitive function and general physical fitness have added to the case for community control of these infections as an important public health measure.

Investigations
Investigation for adult worms in the intestine
Except for *Enterobius*, this depends on the examination of stool. Full laboratory details are beyond the scope of this manual, but for *Ascaris*, hookworm and *Trichuris*, examination by the Kato (modified Kato or Kato-Katz) method is recommended. This requires only microscope slides, a standard hole in a flat spatula with which a 50 mg stool sample is squashed on to the slide, cellophane, glycerol and a stain such as malachite green. A microscopic count of eggs per gram of stool gives an indication of the intensity of infection.

Enterobius (thread worm) eggs are only occasionally seen in stool because they adhere to perianal skin where the female worm has deposited them. They can be picked up on sticky tape and transferred to a glass slide. Specific diagnosis of *Enterobius* is not really necessary in any case,

TABLE 6.3.C.A.1 Diagnosis of helminth infections due to the presence of adult worms

Symptom or sign	Likely species of adult worm in the viscera
Short stature, not growing	*Trichuris* or hookworm
Mild or moderate muscle wasting	*Trichuris* or hookworm
Anaemia, microcytic hypochromic	Hookworm or severe trichuriasis; not *Ascaris*
Hypoproteinaemia, possible oedema	Hookworm or severe trichuriasis or disseminated strongyloidiasis: not *Ascaris*
Pica, especially eating soil (geophagia)	Any or all helminths
Colicky abdominal pain	*Ascaris:* common but a weak correlation
Intestinal obstruction	*Ascaris:* a quite common surgical emergency
Jaundice and/or pancreatitis	*Ascaris:* uncommon
Laryngeal obstruction	*Ascaris:* rare
Vomiting up worms	*Ascaris:* common
Chronic diarrhoea	*Trichuris* or severe hookworm or strongyloidiasis
Defecating during sleep	*Trichuris*
Blood and mucus in stool	*Trichuris*
Rectal prolapse	*Trichuris*
Finger clubbing	Intense trichuriasis or hookworm; not *Ascaris*
Perianal itching	*Enterobius*
Vulvovaginitis	*Enterobius*

TABLE 6.3.C.A.2 Illness due to larvae rather than adult worms

Symptom or sign	Likely species of larvae in the viscera
Cough and wheeze	*Toxocara canis* or *T. cati* (dog or cat roundworm) Also *Ascaris* and hookworm
Hepatomegaly	*Toxocara*
Lymphadenopathy	*Toxocara*
Leucocytosis with extreme eosinophilia	*Toxocara*
Epilepsy or encephalopathy	*Toxocara* (rare)
Uveitis or proliferative retinitis	*Toxocara* (younger children escape in endemic areas: naive strangers are more susceptible)

as it is reasonable to treat the patient and family when it is suspected, without proving the presence of the worm (see below).

The most effective way to establish that *Trichuris* infection is intense is to see the worms on prolapsed rectal mucosa or to perform anoscopy. An otoscope with a wide-aperture speculum can be used for anoscopy in young children. The worms are usually confined to the caecum, so if they have reached the lower rectal mucosa the infection must be intense.

Strongyloides is a rare cause of illness in young children, although it becomes more significant in adolescence in some regions. Microscopy has a low sensitivity, and the stool requires culture by special techniques. Serology is not widely available and also lacks specificity (*see* Section 6.3.C.h).

Investigation for migrating larvae

Eosinophilia is characteristic of this stage with 20–50% of the leucocytes being eosinophils in some cases. By contrast, eosinophilia is not a constant feature of established infection with adult worms and so is a useless diagnostic marker for intestinal infection.

The chest X-ray may show a flaring shadow spreading out from the hila.

Serology is diagnostically useful in visceral larva migrans (*Toxocara* infection), but is only undertaken in special centres or research laboratories.

Diagnosis of cutaneous larva migrans (dog hookworm infection picked up from skin–ground contact) is purely clinical. The key is to think of it when looking at a patch of itchy pyoderma; the red line has often disappeared under the scratching.

It is not clear how much of the total burden of cough, wheezing and dyspnoea in a child population in an endemic zone is due to the pulmonary migration of helminth larvae. Factors that make the symptoms more severe are migration of children naive to *Ascaris* or hookworm infection into the endemic area, and zoonotic larvae (*Toxocara*) which cannot complete their migration but die in their human hosts.

Treatment

The broad-spectrum antihelmintics, mebendazole and albendazole, are drugs which combine great efficacy with an almost complete absence of side effects in ordinary use. They are the drugs of choice for ascariasis, hookworm infection, trichuriasis and enterobiaisis. Albendazole is as effective as thiabendazole for visceral larva migrans, and with fewer side effects. However, visceral larva migrans is a self-limiting condition where symptoms and signs resolve in 3 months. Thiabendazole is still useful for cutaneous larva migrans in a topical preparation (10% in aqueous cream; the pharmacist may be able to make this on site, see Regimens below). Ivermectin is recommended for strongyloidiasis, but albendazole remains useful and is preferable to thiabendazole because it is less toxic.

Mebendazole

This is most commonly available as 100 mg tablets, but is also produced as a 20 mg/5 mL liquid and a 500 mg tablet. The tablets are chewable and reasonably palatable. The 500 mg tablet is useful for mass campaigns against *Trichuris* or hookworm. It is not approved for use in children under 2 years of age, but clinical judgement should be used in a symptomatic child. **It is considered unsafe in pregnancy or lactation.**

Threadworms and pinworms

Oral dose:

- Children from 6 months up to 10 kg body weight: Give 50 mg as a single dose; if reinfection occurs a second dose may be needed after 2 weeks.
- Children over 1 year of age or more than 10 kg body weight: Give 100 mg as a single dose; if reinfection occurs a second dose may be needed after 2 weeks.

Whipworms, roundworms and hookworms

Oral dose:

- Children from 6 months up to 10 kg body weight: Give 50 mg twice daily for 3 days.
- Children over 1 year of age or more than 10 kg body weight: Give 100 mg twice daily for 3 days.

Capillariasis

Oral dose:

- Children over 2 years of age: Give 200 mg twice daily for 20 days.

Echinococcus (mebendazole is second-line therapy, albendazole is preferred)

Oral dose:

- Child over 2 years of age: Give 15 mg/kg/dose three times daily.

Toxocariasis: visceral larva migrans (mebendazole is second-line therapy, albendazole is preferred)

Oral dose:

- Children over 2 years of age: Give 100–200 mg twice daily for 5 days, although doses of up to 1 gram/day have been used for 21 days. Severe disease may warrant corticosteroid use.

Trichinosis (gastrointestinal phase of illness only)

Oral dose:

- Children over 2 years of age: 5 mg/kg (maximum 200 mg) twice daily with food for 7 days; severe infection may require concomitant corticosteroid use; late-phase antihelmintic therapy is not indicated.

Albendazole

This drug is closely related to mebendazole, with similar pharmokinetics. It has superior efficacy to mebendazole in systemically invasive conditions, and is more effective against migrating larvae. It is available as 200 mg tablets or 200 mg/5 mL liquid. Cautions are as for mebendazole, noting its greater systemic absorption.

Hookworms, roundworms, pinworms and threadworms (ancylostomiasis, necatoriasis, ascariasis and enterobiasis)

Oral dose:

- Children aged 12 months to 2 years: Give 200 mg as a single dose.
- Children over 2 years or 10 kg: Give 400 mg as a single dose before food. Treatment may be repeated in 3 weeks.

Echinococcus

Oral dose:

- 7.5 mg/kg twice daily (maximum dose 400 mg twice daily). Given continuously for up to 2 years.

Tapeworm (taeniasis) and strongyloidiasis

Oral dose:

- Children under 10 kg: Give 200 mg daily before food for 3 days.
- Children over 10 kg: Give 400 mg daily before food for 3 days. Treatment may be repeated in 3 weeks.

Neurocysticercosis

Oral dose:

- Children under 60 kg: Give 7.5 mg/kg (maximum dose 400 mg) twice daily after food for 7–30 days.

Whipworm (trichuriasis)

Oral dose:

- Children over 2 years of age: Give 200–400 mg as a single dose, or in heavier infections, 400 mg daily for 3 days. Treatment may be repeated in 3 weeks.

Filariasis for community eradication programmes in combination with diethylcarbamazine or ivermectin

Oral dose:

- Children under 10 kg: Give 200 mg once annually for 5 years.
- Children over 10 kg: Give 400 mg annually for 5 years.

Hairworm (trichostrongyliasis)

Oral dose:

- Child over 10 kg: Give 400 mg as a single dose.

Cutaneous larva migrans

Oral dose:

- Children over 10 kg: Give 400 mg as a single dose, or 400 mg daily for 3 days.

Visceral larva migrans (toxocariasis)

Oral dose:

- Child of all ages: Give 10 mg/kg daily (maximum 400 mg daily) for 5 days.

Trichinosis

Oral dose:

- Children over 10 kg: Give 400 mg daily for 8–14 days.

For topical treatment of cutaneous larva migrans, thiabendazole tablets can be crushed and mixed with aqueous cream or 1% hydrocortisone cream or ointment to a concentration of 10% thiabendazole.

In places or situations where only the older drugs are available

Details and dosages are not given here. The manufacturers' recommendations may be followed, but these drugs are inferior to mebendazole and albendazole, and should be replaced if possible.

- Piperazine is effective against *Ascaris* and *Enterobius*. It has no action on *Trichuris* or hookworm, and is toxic in children prone to epileptic seizures.
- Levamisole is effective against *Ascaris* and is fairly useful effective in hookworm infection (especially *Necator americanus*); to be used in mass control programmes.
- Thiabendazole has limited effectiveness in trichuriasis and is useful in strongyloidiasis, toxocariasis and cutaneous larva migrans.
- Pyrantel is effective against *Ascaris* and *Enterobius*, with some action against *Necator americanus* and less against *Ancylostoma duodenale*. Only if combined with oxantel does the preparation affect *Trichuris*.

Further reading

WHO's programme 'Action against worms' http://evidence action.org/deworming/

6.3.C.b Hydatid disease

BOX 6.3.C.B.1 Minimum standards
- Ultrasound/radiology.
- Albendazole.
- Percutaneous aspiration, injection with hypertonic saline and re-aspiration (PAIR).
- Surgical excision.

Introduction

The adult stage of the tapeworm *Echinococcus granulosus* lives in the gut of dogs and certain other carnivores. The usual intermediate hosts are herbivores. **Humans may become an accidental intermediate host for the cystic stage of the parasite following ingestion of eggs in dog faeces contaminating the fingers, food or water.** Because of the slow rate of growth of hydatid cysts, symptoms from infection in childhood often present in adulthood. Many cysts remain asymptomatic, eventually calcify and become sterile.

Epidemiology

The disease is widespread in sheep-farming countries and wherever there is intimate contact between humans and dogs or other canids, and where dogs scavenge dead animals or offal. There is a high incidence in the Turkana region of Kenya.

Clinical features

- Cysts may occur in virtually any organ.
- Many cysts are asymptomatic but may be palpable if they are large or superficial.
- Abdomen:
  − Palpable mass: liver (60% of all cysts), spleen, other intra-abdominal cysts.
  − Communication with the biliary tract: cholangitis, rigors, jaundice.
  − Abdominal pain.
  − Rupture from trauma.
- Chest:
  − Lungs (25% of cysts).
  − Pleuritic pain and cough.
  − Often asymptomatic, detected on chest X-ray.
- Other areas:
  − Brain: space-occupying lesions (3–5% in some countries).
  − Bone cysts: pathological fractures, respond poorly to chemotherapy.
  − Cyst rupture may cause anaphylaxis and/or spread by 'seeding' of daughter scolices (heads of immature worms).

Diagnosis

- Ultrasound is effective in detecting liver and abdominal cysts. The presence of a separated membrane or daughter cysts makes the diagnosis highly likely. The condition needs to be differentiated from simple hepatic cysts.
- Plain X-ray for lung or bone cysts. CT or MRI (if available) is also useful (e.g. for brain cysts).
- Eosinophilia is present in around 20% of cases. This may be due to cyst leakage or rupture.
- Serology: specific IgG ELISA AgB (antigen-B-rich fraction) (if available) is most sensitive. Serology lacks sensitivity for extra-hepatic cysts (note that false-positive results are obtained in cysticercosis).
- A urine antigen detection test appears promising.

Treatment

Calcified cysts require no treatment.

Medical treatment

- Albendazole is useful for patients with inoperable, widespread or numerous cysts, and for patients unfit for surgery.
- Continuous treatment is now recommended (for up to 2 years). Its duration depends on the lesion's response. The dose is 7.5 mg/kg orally twice daily. The maximum dose is 400 mg twice daily.
- The absorption of albendazole is enhanced if it is taken with fatty meals.
- Albendazole plus praziquantel has greater protoscolicidal activity. The combination is successful for inoperable spinal, pelvic, abdominal, thoracic or hepatic hydatid, and as an adjunct to surgery.
- Antihelmintics may reduce the need for surgery in uncomplicated pulmonary cysts.
- Patients undergoing surgery or PAIR should receive pre-operative albendazole (for 1–3 months) with or without praziquantel.

Percutaneous aspiration under ultrasound control

Puncture, aspiration, injection, re-aspiration (PAIR):
- The patient should be on albendazole for at least 4 weeks prior to PAIR.
- Following initial aspiration of the cyst, hypertonic saline is injected into the cyst and re-aspirated after 20 minutes.
- Percutaneous aspiration combined with an 8-week course of albendazole is more effective than either treatment alone.
- Laparoscopic treatment of liver and spleen hydatid is also effective.
- Contraindications to PAIR include cysts in the CNS or heart, and cysts communicating with the biliary tree, abdominal cavity, urinary tract or bronchi.

Surgery

Surgical removal is standard treatment if the lesion is accessible but is unsuitable for PAIR. The procedure is as follows:
- The patient should be on albendazole for at least 4 weeks prior to surgery.
- Pack around the cyst and avoid spillage of the cyst contents (there is a risk of anaphylaxis and seeding).
- Drain the cyst, replace fluid with hypertonic saline, drain again, and then remove the cyst capsule.

- High rates of recurrence and of surgical complications are recorded in inexpert hands.
- It is important to avoid hypertonic saline entering the bile ducts, as this may cause sclerosing cholangitis.

6.3.C.c Schistosomiasis

BOX 6.3.C.C.1 Minimum standards
- ■ Public health measures to improve water and sanitation.
- ■ Urine and faecal microscopy
- ■ Praziquantel.

Introduction

Schistosomiasis occurs in areas of the world where there is a combination of warm fresh water containing specific snails, and urinary and/or faecal excretion of *Schistosoma* eggs by humans.

Parasite and life cycle

Eggs are passed from humans in stool or urine into freshwater containing snails, *Bulinus* (*S. haematobium*), *Biomphalaria* (*S. mansoni*) and *Oncomelania* (*S. japonicum*). Miracidia hatch from the eggs, penetrate the snail, and replicate into cercariae (larval forms) which are then released into the water.

The cercaria penetrates the skin (or pharyngeal mucosa) of humans, loses its tail and becomes a schistosomula, which is then transported to the lung capillaries. It reaches the left side of the heart and is distributed throughout the body. Those that reach the portal system develop into mature worms about 1 cm in length in the liver.

Adult males and females copulate and migrate in pairs to their preferred egg-laying sites, *S. haematobium* to the vesical veins and pelvic plexus, and *S. mansoni* to the superior and inferior mesenteric veins.

Female flukes produce eggs daily throughout their average 3- to 4-year lifespan. Most eggs pass through the vessel wall, and about 50% reach the lumen of the urinary tract or intestine and are excreted. Those that remain in the tissues provoke an immune reaction which causes the disease. Some eggs are transported to the liver and some reach the general circulation.

Pathogenesis

Pathogenesis can be divided into four stages.
1 **Dermatitis.** An itchy papular rash 'swimmers itch' lasting one to two days may develop as a result of humoral immune reaction to invading cercariae and schistosomulae. However, it is more likely to be due to avian schistosoma (non-pathogenic to man). Older children and adults develop a degree of resistance to this stage of invasion.

Prevention

- Ensure disposal of infected herbivore carcasses and offal.
- Treat dogs with praziquantel.
- Maintain strict hygiene, and protect food and water from contamination.

2 **Katayama fever** (2–8 weeks). A humoral reaction to adult worms and eggs results in an acute illness associated with formation of immune complexes. Symptoms include fever, rigors, malaise, diarrhoea, cough, hepatosplenomegaly and marked eosinophilia. It is a self-limiting disease.

3 **Established disease** (usually after 2 months). A T-cell delayed-hypersensitivity response to eggs deposited in tissue results in granuloma formation. If the worm load is reduced by drug therapy at this stage, granulomata may resolve, leaving little disease.

4 **Fibrotic complications.** Repeated infections without treatment eventually result in fibrosis, for example of the ureter and bladder (*S. haematobium*) and liver (*S. mansoni*). There is little response to drug therapy at this stage.

TABLE 6.3.C.C.1 Schistosomiasis: geographical areas (the commonest species and areas are shown in bold type)

Schistosoma *species*	Disease	Area
S. haematobium	Urinary tract	**Africa**, Middle East
S. mansoni	Intestines, liver	**Africa**, Middle East, **South America**
S. intercalatum	Intestines, liver	Central and West Africa, uncommon
S. japonicum	Intestines, liver	**China**, **Indonesia**, **Philippines**
S. mekongi	Intestines, liver	Laos, Kampuchea, small number of foci

Epidemiology

- Schistosomiasis affects at least 240 million people worldwide, and more than 700 million people live in endemic areas.
- Schistosomiasis is associated with communities living near swamps, rivers, irrigation canals and rice fields, who have poor hygiene and sanitary facilities and lack a ready supply of clean water.
- Infection is highest in children (5–14 years) who are an important reservoir of infection because of their indiscriminate excretion habits near and in water.
- Infections decrease after puberty, but adults are still at risk when farming or washing clothes.

Clinical features

TABLE 6.3.C.C.2 Symptoms and complications of *S. haematobium* and *S. mansoni*

Initial stage	S. haematobium	S. mansoni	Comments
Swimmers' itch	Terminal haematuria	Bloody diarrhoea Anaemia	*S. japonicum* is similar to *S. mansoni*
Katayama fever	Obstructive uropathy Calcification of bladder and lower ureters Bladder calculi	Hepatic fibrosis Portal hypertension Ascites Colonic polyposis Nephropathy	Hepatic fibrosis is most often seen with *S. mansoni* Katayama fever is more severe with *S. japonicum*

S. haematobium

This causes urinary schistosomiasis.

- Terminal haematuria, there may be dysuria.
- In a minority of children, frequent untreated infections eventually lead to structural disorder of the bladder and lower ureter, resulting in obstructive uropathy, hypertension and chronic renal failure.
- Obstruction can be demonstrated by ultrasonography and intravenous pyelogram. Adequate treatment in the early stages may be followed by resolution of ureteric lesions.

S. mansoni

This causes intestinal schistosomiasis along with other species, namely *S. intercalatum*, *S. japonicum* and *S. mekongi*.

- Bloody diarrhoea. In long-standing cases there is severe iron-deficient anaemia, and even heart failure (due to anaemia).
- Protein-losing enteropathy with hypoalbuminaemia may result from colonic granulomatous disease and polyps.
- The left lobe of the liver is enlarged more than the right lobe. Ascites may occur. Liver function is usually well preserved.
- Marked splenomegaly due to portal hypertension is associated with pancytopenia.
- Haematemesis from oesophageal varices is the final event which influences the prognosis.
- Ultrasonography is useful for grading the degree of peri-portal fibrosis and in differential diagnosis from other liver diseases.
- Acute and long-term management of oesophageal varices requires endoscopy and decisions regarding sclerotherapy (*see* Section 5.7.B on liver disease).
- Nephropathy due to immune complex disease may manifest with microscopic haematuria and proteinuria or nephrotic syndrome. Nephrotic syndrome has a poor prognosis, especially if associated with amyloid disease (*see* Section 5.6.A).

Salmonella infection

Schistosoma worms may harbour *Salmonella* species, including *S. typhi*, which cannot be eradicated until the schistosomiasis is treated. This phenomenon occurs in both *S. haematobium* and *S. mansoni* infections. *Salmonella* may cause a reversible nephritis in *S. mansoni* infection.

Complications common to S. haematobium *and* S. mansoni

- Spinal cord myelopathy (less common with *S. haematobium*).
- Brain granulomata (more common with *S. japonicum*, less common with *S. haematobium*).
- Pulmonary hypertension (less common with *S. haematobium*).
- Chronic *Salmonella* infection.

Diagnosis
Microscopy of urine or faeces
S. haematobium

A midday specimen is best. Urine should be sedimented or filtered. Viability of the eggs (and thus requirement for treatment) can be established by looking for miracidia, which hatch when eggs are put in boiled water that has been cooled.

S. mansoni

If stool smear is negative on microscopy, a concentration method must be undertaken. Miracidial hatching techniques are also available.

Rectal biopsy

Rectal biopsy to demonstrate the presence of eggs is undertaken if urine and faeces are negative.

Serology

Serology is of little value for diagnosis in indigenous patients, but may be useful in the non-immune (e.g. tourists to an endemic area). Antigen tests are being developed.

Treatment

Praziquantel is effective against all human *Schistosoma* species, and is the only available drug treatment. Treatment at least three times in childhood usually prevents adult disease.

Praziquantel is given at a dose of 40 mg/kg in two divided doses given 4–6 hours apart on one day. It can also be given as a single dose of 40 mg/kg. For heavy *S. mansoni* infection and for *S. japonicum* infection, 60 mg/kg is advised, given in two doses 4–6 hours apart. Repeat urine or stool examination should be done at 3–4 months.

Praziquantel is safe during pregnancy. The safety of praziquantel in children under 4 years of age has not been established, but this drug can be used to treat individually infected children.

Side effects include dizziness, drowsiness, skin reactions, fever, headache and vomiting.

Prevention

Control of schistosomiasis is very difficult. Measures include regular mass treatment of communities and improvement in water supply, sanitation and hygiene. Mollusciciding (use of chemicals to kill the snails) is usually impractical and too expensive for general use.

6.3.C.d Fascioliasis (liver fluke infections)

> **BOX 6.3.C.D.1 Minimum standards**
> ■ Vector control.
> ■ Triclabendazole (preferred) or Bithional.

Introduction

This disease is caused by *Fasciola hepatica* and *Fasciola gigantica*, and occurs in sheep- and cattle-rearing areas worldwide, especially South America.

Freshwater snails act as the intermediate amplifying hosts, liberating free-swimming cercariae which encyst as metacercariae on water plants. Humans are infected following ingestion of metacercarial cysts on raw aquatic plants (e.g. watercress) or from contaminated water. Following ingestion, the larvae emerge in the duodenum, penetrate the intestinal wall, migrate via the peritoneal cavity to the liver, penetrate the liver capsule, and after 3–4 months mature into adults in the bile ducts.

Clinical features

Infections may be asymptomatic. Acute presentations occur 6–12 weeks after infection. Fluke migration may be associated with fever, malaise, abdominal pain, weight loss, urticaria, cough and wheeze. In chronic presentations, symptoms may be minimal or may be due to recurrent cholangitis, intermittent biliary obstruction or anaemia.

Ectopic flukes may cause granuloma or abscess formation in various organs, and also present as migrating skin nodules.

Investigations

- Eosinophilia is common.
- Liver ultrasound is often normal.
- CT of the liver (if available) may reveal hypodense lesions.
- Serology may be helpful in established *F. hepatica* infections, but is less reliable for *F. gigantica*. Fasciola excretory–secretory (FES) antigen detection in faeces is available for *F. hepatica*.
- In established infections, eggs may be found in faeces.

Treatment

Triclabendazole is the drug of choice for *F. hepatica* and *F. gigantica* infections. One dose of 10 mg/kg taken with food is usually effective, but should be repeated after 12 hours in severe infections. Expulsion of dead or damaged flukes may cause biliary colic 3–7 days after treatment; the colic responds well to antispasmodics. Triclabendazole resistance has been reported in Ireland, the UK and Australia.

Bithional, 30–50 mg/kg/day in three divided doses on alternate days for 10–15 days was the preferred treatment previously. Side effects include mild gastrointestinal upset and pruritus.

Nitazoxanide may be effective.

Praziquantel is unreliable in the treatment of fascioliasis.

Prevention and control

- Avoid potentially contaminated watercress and other aquatic plants.
- Treat herbivores.
- Undertake snail control.

6.3.C.e Dracunculiasis (guinea-worm disease)

> **BOX 6.3.C.E.1 Minimum standards**
> ■ Early identification of blister and worm emergence.
> ■ Removal of worm and prevention of secondary infection.
> ■ Filtering of water.
> ■ Temephos to kill *Cyclops* species.

Introduction

Guinea-worm disease is transmitted exclusively by drinking stagnant water contaminated with tiny water fleas (*Cyclops* species) that carry infective guinea-worm larvae. Once ingested, the larvae mature into worms, growing up to 1 metre in length. Humans are the only known reservoirs for the disease.

About 1 year after infection, a very painful blister forms, 90% of the time on the lower leg, and one or more worms emerge accompanied by a burning sensation. To soothe the burning pain, patients often immerse the infected area in water. The worm then releases thousands of larvae into the water, contaminating the water and bringing the infective cycle full circle.

Epidemiology

The main source of infection is stagnant water sources such as ponds and sometimes shallow or step wells. 'Man-made' ponds are the main source of transmission.

Only four African countries (Chad, Ethiopia, Mali and

South Sudan) are known to be affected, with the majority of cases in South Sudan.

Guinea-worm disease is seasonal, occurring with two broad patterns found in endemic areas of Africa, depending on climatic factors. In the Sahelian zone, transmission generally occurs in the rainy season (from May to August). In the humid savanna and forest zone, the peak occurs in the dry season (from September to January).

A successful eradication programme for guinea-worm disease consists of several preventive strategies, such as ensuring wider access to safe drinking-water supplies, filtration of drinking water (with cloth filters) to prevent infection, intense surveillance and control to detect every case within 24 hours of the emergence of the worm(s), treatment of ponds with the larvicide temephos that kills the water fleas, and promoting health education and behaviour change.

Early case detection (when the patient feels the initial pain) is vital in order to contain the disease. There are thousands of village volunteers in the remaining endemic countries who are trained to find new cases, take care of them and report them to the area supervisor.

Clinical effects

Once a new case is identified, the wound must be disinfected and bandaged to help to prevent secondary infection. The worm should be gently pulled out a few inches every day until all of it has been removed. Many patients are unable to leave their beds for a month after the emergence of the worm.

Guinea-worm disease is not fatal, but infected people cannot work or attend school for months. Since the peak transmission period often coincides with the agricultural season, fields are left untended and food production declines. In Mali, guinea-worm disease is called 'the disease of the empty granary'. As adults lie sick, older children must take on the household chores and miss months of schooling. Younger children may miss vital vaccinations.

Prevention

- Effective surveillance to detect all cases within 24 hours of worm emergence.
- **Ensure access to safe drinking water, and convert unsafe sources to safe ones.**
- Construction of copings around well heads or installation of boreholes with hand pumps.
- **There must be regular and systematic filtering of drinking water derived from ponds and shallow unprotected wells, or from surface water.** Fine-meshed cloth or, better still, a filter made from a 0.15-mm nylon mesh, is all that is needed to filter out the *Cyclops* species from the drinking water.
- Treatment of unsafe water sources with temephos to kill the *Cyclops* species.
- Health education and social mobilisation to encourage affected communities to adopt healthy behaviour with regard to use of drinking water.

6.3.C.f Filariasis

BOX 6.3.C.F.1 Minimum standards
- ■ Treatment of endemic communities.
- ■ Control of mosquitoes (the vector).
- ■ Diethylcarbamazine citrate (DEC), albendazole, doxycycline and ivermectin.

Introduction

This painful and profoundly disfiguring disease is usually acquired in childhood.

The disease is caused by three species of thread-like nematode worms, known as filariae, namely *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*. Around 90% of infections are caused by *Wuchereria bancrofti* and most of the remainder by *Brugia malayi*. About 120 million people are affected worldwide (of whom 60% live in South-East Asia and 30% live in Africa).

Life cycle of filariae

Filariae are transmitted by mosquitoes. When a mosquito with infective-stage larvae takes a blood meal, the parasites are deposited through the person's skin, from which they enter the body. These larvae then migrate to the lymphatic vessels and develop into adult worms over a period of 6–12 months, causing damage to and dilatation of the lymphatic vessels. The adult filariae live for several years in the human host. During this time they produce millions of immature microfilariae that circulate in the peripheral blood and are ingested by mosquitoes that bite the infected human. The larval forms further develop inside the mosquito before becoming infectious to humans. Thus a cycle of transmission is established.

Threadlike adult worms of *Wuchereria bancrofti* live in the lymphatics (groin, scrotum, arm). Male worms are about 3–4 cm in length, and female worms 8–10 cm. The male and female worms together form 'nests' in the lymphatic system. Females release thousands of microfilariae into the peripheral blood periodically every day, synchronising with the biting habits of the predominant local mosquito vector. Nocturnal periodicity is commonest, except in some Polynesian islands where microfilariae are more numerous by day.

Brugia malayi has two main forms: the nocturnal periodic form in swampy areas from India to Korea and Japan, and the nocturnal sub-periodic form in the damp forests of South-East Asia. The parasites of *B. malayi* are transmitted by various species of the genus *Mansonia*, and in some areas anopheline mosquitoes are responsible for transmitting infection. Brugian parasites are confined to areas of East and South Asia, notably India, Indonesia, Malaysia and the Philippines.

An estimated 120 million people in tropical and sub-tropical areas are infected, of whom almost 25 million men have genital disease (most commonly hydrocoele) and almost 15 million, mostly women, have lymphoedema or elephantiasis of the leg.

Diagnosis

Eosinophilia is common in the acute stages. Examination of thick smears of 20–60 microlitres of blood from a finger tip or filtration of 1 mL of intravenous blood and examination of the filtrate can reveal the microfilariae provided that the concentration is high (> 100 microfilariae/mL). Concentration techniques can improve sensitivity (e.g. Nuclepore filtration).

Samples should be appropriately timed (usually between 22.00 and 02.00 hours for *W. bancrofti*).

A variety of more sensitive diagnostic techniques are now available, including complement fixation tests for circulating *W. bancrofti* antigen (e.g. an ELISA 'TropBio-test') and a rapid finger-prick immunochromatographic card test (Amrad ICT, Binax). The rapid ICT has a high sensitivity and specificity and is currently the preferred diagnostic test for *W. bancrofti*. It is also used for monitoring the success of mass drug programmes. The test requires 100 microlitres of finger-prick blood drawn at any time, day or night.

Clinical features

The majority of infected people are asymptomatic, but virtually all have subclinical lymphatic damage, and up to 40% have kidney damage, with proteinuria and haematuria.

Inflammatory episodes associated with lymphatic filariasis involve:

- responses to the parasite itself
- the effects of secondary bacterial infection
- sometimes inflammatory mediators associated with endosymbiotic bacteria (*Wolbachia*).

Endosymbiotic bacteria infect most species of filarial nematodes that are pathogenic to humans, and contribute to the damage done by the filaria. Further characterisation of the *Wolbachia*–nematode relationship might allow the development of new therapeutic approaches to these parasitic diseases.

Acute episodes of local inflammation involving the skin, lymph nodes and lymphatic vessels often accompany chronic lymphoedema or elephantiasis (see below). Some of these episodes are caused by the body's immune response to the parasite, but many are the result of bacterial skin infections, linked to the partial loss of the body's normal defences as a result of underlying lymphatic damage. **Careful cleansing is extremely helpful in healing the infected areas and in both slowing and even reversing much of the damage that has already occurred.**

Acute symptoms may recur several times a year in three forms:

1. Acute filarial fever without lymphadenitis.
2. Acute filarial lymphangitis (AFL) follows the death of an adult worm, causing an inflammatory nodule or cord with lymphangitis spreading away from the affected node. This is usually mild, but may develop into an abscess.

Acute dermatolymphangioadenitis (ADLA) resembles cellulitis or erysipelas, and is often associated with secondary bacterial infection and impaired lymphatic flow, ascending lymphangitis and limb oedema. ADLA is more common than AFL, and is an important cause of lymphoedema and elephantiasis.

Chronic lymphatic filariasis may develop over months or years even without a history of acute symptoms. Lymphatic obstruction eventually leads to **elephantiasis**, most commonly affecting the legs, scrotum, arms and breast. Recurrent secondary bacterial skin infections (often streptococcal) cause acute pain and fever, and may be complicated by acute glomerulonephritis.

Other presentations of lymphatic filariasis include:

- hydrocoele, usually unilateral
- swelling of the scrotum
- acute epididymitis
- funiculitis (inflammation of the spermatic cord)
- monoarthritis
- glomerulonephritis
- chyluria, chylous diarrhoea, chylous ascites (due to rupture of dilated lymphatics). (Malabsorption of fat-soluble vitamins may complicate chylous diarrhoea.)

Brugian filariasis is usually less severe than Bancroftian filariasis.

The most severe symptoms generally appear in adults, and in males more often than in females. In endemic communities, around 10–50% of men suffer genital damage

TABLE 6.3.C.F.1 Recommended treatment strategies for mass drug distribution, individual drug administration, and morbidity control and treatment of lymphatic filariasis

Mass drug administration		Individual drug administration	Morbidity control and treatment
Africa	Rest of world		
IVM + ALB for at least 5 years	DEC + ALB for at least 5 years	(a) DEC (with or without ALB) 6 mg/kg single dose[1] (b) DEC 12-day course of 6 mg/kg per day in two or three divided doses **or** (c) doxycycline 200 mg/day for 4 weeks followed by one dose IV or IM	Lymphoedema: hygiene, physiotherapy, doxycycline 200 mg/day for 6 weeks Hydrocoele: surgical hydrocoelectomy, doxycycline 200 mg/day for 6 weeks Tropical pulmonary eosinophilia: doxycycline 200 mg/day for 4 weeks followed by one dose IV or IM

Based on Taylor M *et al.* (2010) *Lancet*, **376**, 1175–85.

[1] If the patient continues to live in an endemic area, or is less than 8 years of age (contraindication of doxycycline).

ALB, Albendazole; DEC, diethylcarbamazine (omit if there is onchocerciasis co-infection or a risk of serious adverse events with *Loa loa*); IVM, ivermectin (omit if there is a risk of serious adverse events with *Loa loa*).

Doxycycline: the doses above are suitable for children aged ≥ 8 years and weighing > 45 kg. Children aged ≥ 8 years but weighing < 45 kg should receive 4.4 mg/kg/day. Doxycycline should not be used for children < 8 years.

(hydrocoele and elephantiasis of the penis and scrotum). Elephantiasis of the entire leg or arm, the vulva and the breast may affect up to 10% of men and women.

In endemic areas, chronic and acute manifestations of filariasis tend to develop more often and sooner in refugees or newcomers than in local populations. Lymphoedema may develop within 6 months, and elephantiasis as soon as 1 year after arrival.

Tropical pulmonary eosinophilia (TPE)

A hypersensitivity response to microfilariae in the lungs can develop in some patients, causing cough and wheeze, especially at night. There may also be an enlarged liver, spleen and lymph nodes. Chest X-ray may show diffuse miliary shadows. Untreated TPE may progress to irreversible lung fibrosis. The condition is usually associated with high eosinophilia and high microfilaria titres. Microfilariae are usually absent from peripheral blood, but the rapid antigen test is usually positive.

Treatment and control of filariasis

A number of antihelmintic agents are effective, although care must be taken in the choice of antihelmintic depending on the risk of co-infection with onchocerciasis and/or *Loa loa*. Mass drug administration is an important strategy in community control. The treatment and control options are summarised in Table 6.3.C.F.1.

Treating endemic communities (*see* Table 6.3.C.F.1) The goal is to eliminate microfilariae from the blood of infected individuals in order to interrupt the cycle of transmission by mosquitoes. A single dose of diethylcarbamazine citrate (DEC) has the same long-term (1-year) effect in decreasing levels of microfilaraemia as the formerly recommended 12-day regimen of DEC. More importantly, the use of single doses of two drugs administered together (optimally albendazole with DEC or ivermectin) is 99% effective in removing microfilariae from the blood for a full year after treatment. The following recommended drug regimens need to be administered once a year for at least 5 years, with coverage of at least 65% of the total at-risk population:

- 6 mg/kg of body weight diethylcarbamazine citrate (DEC) + 400 mg albendazole,

or

- 150 micrograms/kg of body weight ivermectin + 400 mg albendazole (in areas that are also endemic for onchocerciasis).

Treating individuals

Most problems result from bacterial and fungal 'super-infection' of tissues, linked to compromised lymphatic function caused by earlier filarial infection. Antibiotics against streptococcal and other bacterial infections are important. Surgical procedures are available to correct hydrocoele.

Because secondary bacterial infections play an important role in precipitating acute adeno-lymphangitis episodes and progression of lymphoedema, simple hygiene (either alone or in combination with antibiotic treatment) plays an important role in preventing episodes of acute disease and in the management of lymphoedema. Daily washing of affected limbs with soap and safe water to prevent secondary infection, combined with simple exercises, elevation of the limb, and treatment of cracks and entry points, provides significant relief from acute episodes and slows progression of the disease.

Vector control

Avoidance of mosquito bites through personal protection measures or community-level vector control is the best option for preventing lymphatic filariasis. If possible, malaria and lymphatic filariasis vector control should be integrated. Periodic examination of blood for infection and initiation of the above treatment is essential.

6.3.C.g Onchocerciasis

BOX 6.3.C.G.1 Minimum standards
- Rapid diagnostic tests.
- Ivermectin and doxycycline.

Introduction

Onchocerciasis is caused by the filarial worm *Onchocerca volvulus*, and is an important cause of blindness and skin disease in tropical Africa, Yemen and Central and South America. It is transmitted by the bite of blackflies (*Simulium* species).

Epidemiology

This infection mainly affects people living or working near fast-flowing rivers (*Simulium* breeding sites), but may be more widely distributed by flies carried on winds.

Pathology

Adult worms evade the host immune response and cause few symptoms. The main problems are the result of immunological reactions to dying and dead microfilariae and their endosymbiotic bacteria (*Wolbachia*), which release bacterial mediators that trigger the innate immune system. In addition, activated eosinophils release cellular proteins that cause connective tissue damage.

Onchocerciasis may increase the risk of HIV-1 sero-conversion. Treatment of onchocerciasis is associated with reduced HIV-1 viral replication. Onchodermatitis is more severe in HIV-positive patients.

Clinical features

The incubation period is usually 15–18 months. Infected patients may be asymptomatic. Palpable firm painless subcutaneous nodules (intertwined adult worms), several centimetres in diameter, may be most obvious over bony prominences.

Skin disease

A variety of different skin manifestations are seen, usually with a significant degree of overlap:

- Acute papular onchodermatitis (APOD): an intensely itchy papular rash, sometimes with local oedema.
- Chronic papular onchodermatitis (CPOD): larger pruritic (itchy) hyperpigmented papules.
- Lichenified onchodermatitis (LOD): discrete or confluent pruritic hyperpigmented papulonodular plaques, often with lymphadenopathy.

Severe itching may give rise to excoriation and secondary bacterial infection. Healing is associated with progressive hyperpigmentation, blackening and thickening of the skin.

Unrelenting itching may result in chronic sleep disturbance, poor concentration and depression.

Heavy infections in childhood can impair growth. After some years, skin atrophy and depigmentation give a wrinkled prematurely aged appearance (presbydermia). Patchy depigmentation, especially of the legs, results in a 'leopard-skin' appearance.

Inguinal or femoral lymphadenopathy may give rise to the so-called 'hanging groin' appearance.

Eye disease

Early symptoms include itching, redness and excess lacrimation. Late disease leads to varying degrees of loss of vision, and eventually to blindness.

Anterior eye disease

- Punctate keratitis due to death of microfilariae in the cornea may appear as a reversible 'snow-flake' opacity.
- Pannus forms as blood vessels invade the cornea from the sides and below. The pannus may cover the pupil (sclerosing keratitis) and cause blindness.
- Iritis leads to a loss of the pigment frill and to synechiae that cause a deformed, often pear-shaped pupil. Secondary cataracts occasionally result.

Posterior eye disease

- Chorioretinitis with pigmentary changes.
- Optic atrophy.
- 'Tunnel vision' and various other forms of visual loss may become evident in young adults.

Diagnosis

- Skin snips in saline examined under the microscope for microfilariae.
- Slit-lamp examination for microfilariae in the anterior chamber of the eye.
- Rapid diagnostic tests. A new luciferase immunoprecipitation systems (LIPS) assay has 100% sensitivity and specificity for *O. volvulus* using a rapid 15-minute format (QLIPS).
- Biochemical methods: Recent advances include a serum antibody test card using recombinant antigen to detect *O. volvulus*-specific IgG4 in finger-prick whole-blood specimens, a triple-antigen indirect ELISA rapid-format card test, and a highly sensitive and specific urine antigen dipstick test.
- Surgery: Subcutaneous nodules can be removed to demonstrate adult worms, or aspirated with a needle to look for microfilariae.

- DEC patch test: Diethylcarbamazine (DEC), although no longer recommended for the treatment of onchocerciasis because of the risk of provoking a Mazzotti reaction (see below), may be used in the following manner in patients with repeatedly negative skin snips, where other diagnostic techniques are unavailable. A 1-cm square of filter paper soaked in a solution of DEC is applied to the skin of the patient. If positive, this will provoke intense localised itching and inflammation at the site of application. DEC patch testing of children aged 3–5 years is advocated as an effective low-cost method for monitoring the endemicity and transmission of onchocerciasis in Africa.
- **Warning: A DEC patch test may precipitate a full-blown Mazzotti reaction**. This consists of microfilaria death resulting in an intensely itchy papular rash, may be accompanied by fever, limb oedema, hypotension and worsening of eye damage, and may be fatal. It is commonly associated with the use of oral DEC, and is rarely caused by ivermectin.

Treatment

Ivermectin kills microfilariae by immobilising them so that they are carried away via the lymphatics.

Warning: Ivermectin may precipitate meningoencephalitis or renal failure in patients who have Loa loa with a high microfilariaemia (> 2500 microfilariae/mL).

It is therefore important to exclude *Loa loa* if there is any possibility of co-infection, before giving ivermectin.

Doxycycline kills the endosymbiotic *Wolbachia*, resulting in the slow, less pathogenic death of the microfilariae. The drug also blocks worm embryogenesis and has a significant macrofilaricidal effect. Contraindications to doxycycline include age less than 9 years, pregnancy and breastfeeding.

Treatment of individual patients

Provided that the patient does not have a high *Loa loa* microfilaraemia, and ivermectin (or doxycycline) is not otherwise contraindicated, the following options are available:

- If the patient will continue to live in an endemic area, or is less than 9 years old and weighs more than 15 kg, give **ivermectin** 150 micrograms/kg every 3–6 months.
- If interruption of worm embryogenesis and cessation of microfilariae production is desired, give **doxycycline** 200 mg/day for 4 weeks, or 100 mg/day for 6 weeks, followed by one dose of **ivermectin** after 4–6 months (children aged > 9 years).
- If a strong macrofilaricidal effect is desired, give **doxycycline** 200 mg/day for 6 weeks, followed by one dose of ivermectin after 4–6 months.

Patients with onchocerciasis who do have a high *Loa loa* microfilaraemia may be treated with **doxycycline** 200 mg daily for 6 weeks, unless contraindicated. If they are under 9 years of age, in which case doxycycline is contraindicated, *Loa loa* microfilaraemia must be reduced by treatment with **albendazole** prior to treatment with **ivermectin**.

Surgical removal of head nodules (nodulectomy) was advised in the past in an attempt to reduce the likelihood of eye disease. There is no guarantee that this will eliminate the risk of eye disease, because not all nodules are evident, and the remaining nodules continue to produce

microfilariae. Improved drug treatment has reduced the justification for nodulectomy.

Control
There has been rapid progress in the past 30 years, largely due to successful international public–private partnerships, sustained funding for regional programmes, and technical advances.

Initial efforts in vector control using the organophosphate larvicide **temephos** proved inadequate.

A major breakthrough came with Merck's donation of ivermectin. Thereafter larviciding was abandoned in favour of regular mass drug treatment.

The African Programme for Onchocerciasis Control (APOC) is a Community-Directed Treatment with Ivermectin (CDTI) programme that aims to treat over 90 million people annually in 19 countries, protecting an at-risk population of 115 million, and should prevent over 40 000 cases of blindness every year. High-risk foci of *Loa loa* are currently excluded from community ivermectin programmes.

The Onchocerciasis Elimination Programme for the Americas (OEPA) adopts a similar approach to APOC, except that ivermectin is administered twice a year until transmission has been interrupted. By the end of 2012, transmission of the infection, judged by surveys following WHO guidelines, had been interrupted or eliminated in four of the six endemic countries in the WHO Americas Region.

6.3.C.h Strongyloidiasis

BOX 6.3.C.H.1 Minimum standards
- Hygiene, sanitation and shoes are useful in prevention.
- Ivermectin is the treatment of choice.
- Albendazole.

Introduction
This parasite affects 50–100 million people worldwide, and occurs in warm, wet, tropical and subtropical regions where sanitation is poor. *Strongyloides stercoralis* is the main species infecting humans. However, *Strongyloides fülleborni*, which is principally a parasite of primates, also occurs in humans in Africa and Papua New Guinea.

Human infection is due to percutaneous penetration of filariform larvae in contaminated soil. Filariform larvae travel via the lungs to the small intestine, where they develop into adults and penetrate the duodenal and jejunal mucosa. Fertilised females produce eggs which hatch in the intestinal mucosa and release the first-stage rhabditiform larvae, which are excreted in faeces. In favourable conditions, the rhabditiform larvae transform into infectious filariform larvae within 48 hours, and remain viable in the soil for weeks.

An important feature of *Strongyloides* is auto-infection. This occurs when rhabditiform larvae transform into infectious dwarf filariform larvae in the gut lumen and penetrate the mucosa or the peri-anal skin. Infection may persist for decades without further exposure. Person-to-person transmission may also occur.

Clinical features
Initial skin penetration may cause itching, urticaria and sometimes a snake-like (serpiginous) rash. Migration through the lungs may cause cough, wheeze and evidence of pneumonitis. Invasion of the small bowel may cause abdominal pain, vomiting, malabsorption and paralytic ileus.

Chronic infection is often asymptomatic, but may cause intermittent abdominal pain, diarrhoea and urticaria. Malabsorption and a protein-losing enteropathy may occur. A transient, intensely itchy serpiginous rash, known as 'larva currens' or 'creeping eruption', may appear on the trunk, buttocks or elsewhere.

Episodic pneumonitis and, more rarely, a reactive arthritis may occur.

Strongyloides hyperinfection syndrome
One of the major dangers associated with *Strongyloides* infection occurs as a result of massive auto-infection. Risk factors include immunosuppression induced by various drugs, including corticosteroids, or associated with diseases such as malignancies (particularly leukaemia and lymphoma), severe malnutrition and severe infections, including advanced AIDS and human T-cell leukaemia virus type 1 (HTLV-1).

Hyperinfection syndrome may present with severe diarrhoea, often with blood in the stool. Bowel inflammation with micro-perforations may give rise to paralytic ileus, peritonitis and Gram-negative septicaemia. Proliferation and dissemination of larvae and enteropathogens may cause widespread pathology, including endocarditis, pneumonitis and meningitis.

All patients with a history of possible exposure to *Strongyloides* should be screened before being treated with any drugs that cause immunosuppression. Those at significant risk should be treated empirically even if investigations are negative.

Investigations
Eggs are rarely found in the stool, and larvae may be difficult to identify. Stool culture (e.g. on charcoal or agar) is recommended.

Larvae may be seen in duodenal aspirates or using the string capsule technique (Enterotest).

Larvae may also be found in sputum, CSF and urine in hyper-infection syndrome.

Serology is useful for immune-competent patients who are not normally resident in an endemic area. However, interpretation of a positive test may be a problem due to cross-reactions with filarial antigens.

Eosinophilia is common in immune-competent patients, but may be absent in hyperinfection syndrome.

Treatment
Ivermectin is the drug of choice for children over 5 years old

or weighing more than 15 kg. An oral dose of 200 micrograms/kg/day for 2 days gives excellent results.

Albendazole 400 mg every 12 hours for 7 days may also be effective, and can be used in children over 2 years of age.

Hyperinfection syndrome can be very difficult to manage. There may be problems with administration or absorption of oral medication, and no IV or IM preparations of ivermectin or albendazole are licensed for use in humans. However, parenteral ivermectin, available as a veterinary preparation, has been administered subcutaneously in the successful treatment of *Strongyloides* hyperinfection. Patients with hyper-infection syndrome also require treatment for Gram-negative septicaemia.

Prevention and control
- Improve hygiene and sanitation.
- Wear shoes.
- Avoid contact with contaminated soil.