CHAPTER 5

Tropical Fevers: C. Important human parasitic fevers of the tropics

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1. INTRODUCTION

Fever, an elevation of body temperature above the normal daily variation resulting from an alteration of the hypothalamic set-point by exogenous or endogenous cytokines and pyrogens, characterizes a number of disease states.[1] It is a common and very important presenting symptom of many tropical diseases, including many important parasitic infections. Making the correct diagnosis and selecting effective therapy is challenging but potentially life-saving. It is essential to remember that fever is more likely to be a manifestation of a "common" rather than a "rare" disease. Life threatening conditions, like malaria, must always be considered first when treating a patient in or from the tropics, presenting with acute febrile illness and ill-defined localizing signs.

A patient or their family members' perceptions of fever often complicate diagnosis, as these may vary enormously and include a feeling of warmth or chilliness, sweating or an actual elevation of body temperature. When properly measured, body temperature is a simple, objective and accurate indicator of a disease state.[2] However, due to the fluctuating nature of many parasitic febrile diseases, a history of fever should not be ignored, particularly if the patient lives in, or has returned from, a malaria-endemic area. Traditionally, undue emphasis has been placed on the pattern of fever occurrence. The most useful distinction is between acute and sub-acute onset, but even this feature may be unreliable. The incubation period is potentially useful, when time of exposure can be accurately determined.

Health professionals trained in teaching hospitals, particularly in developed countries, are inclined to rely excessively on expensive special investigations for ascertaining the cause of fever. An awareness of the local epidemiology of important diseases, a thorough history, including recent migration or travel, a complete physical examination, performance of rapid immunochromatographic card tests, or simple laboratory investigations, including a blood smear, full blood count with a white blood cell differential (where available) and urine microscopy, will usually identify the causative organism if a parasitic aetiology if responsible for the febrile disease.

It is important when managing tropical fevers, that although infectious diseases must be excluded first, other conditions including immune disorders, vascular inflammation or thrombosis, tissue trauma, granulomatous conditions, inflammatory bowel disease, neoplasms and metabolic disorders, can all cause fever.

There is ongoing debate over whether fever associated with an infectious disease should be treated. Reasons given for not treating fever include its possible beneficial host-defence response through Interleukin 1 production, with increased neutrophil release from the bone marrow, and modulation of a variety of sub-cellular acute phase responses. Fever suppression may also create an illusion of disease improvement. Antipyretics are not without adverse events, including gastrointestinal bleeding, diaphoresis and hypotension. However, fever causes discomfort; can increase oxygen demand in patients with pre-existing cardiac or pulmonary insufficiency; and can cause mental state changes in patients with organic brain syndrome, heat stroke or malignant hyperthermia. These latter factors provide support for reducing fever. Recently it was found that the "stickiness" of red blood cells parasitized with *Plasmodium falciparum* increased *in vitro* upon heating, providing evidence for reducing fever associated with malaria infection.[3]

If the decision is made to suppress a patient's fever, it is preferable to do so by continuous administration of antipyretics for a period of at least 48 hours, followed by withholding the antipyretic to determine whether the fever still persists. Tepid sponging of the body surface with cool saline or water is helpful but its effect may be negated if continuous use induces cutaneous vasoconstriction and shivering. It should be emphasized that the focus should always be on effectively treating the underlying infection, rather than on symptom relief alone.

2. MALARIA

2.1 Introduction

Plasmodium falciparum infection results in the deaths of 1-2 million people each year, predominantly young African children. This is more deaths than any other infectious agent.[4] The four human plasmodia species, *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*, infect 300-500 million people annually, and malaria accounts for 9% of all disease in Africa. The past decade has seen a dramatic increase in prevalence of African malaria. This trend has been attributed to resistance of *P. falciparum* to chloroquine and more recently sulphadoxine-pyrimethamine (SP), anopheline resistance to insecticides and large-scale human migration, and has been accompanied by increasing malaria-specific mortality.[5,6] Antimalarial drug resistance alone appears to have increased malaria mortality four to eight-fold.[7] It is discouraging that despite rapid global economic development, more people die from malaria now than half a century ago.[8] Malaria's ability to fuel poverty and restrain economic growth is now well-documented.[9] Thus the World Health Organization (WHO) has embarked on a Roll Back Malaria campaign that aims to expand prevention and treatment to substantially reduce morbidity and mortality before 2010.[10]

2.1 Epidemiology

Malaria occurs in about 100 predominantly developing countries in Africa, Central and South America, the Arabian peninsula, south and south-east Asia, and certain Western Pacific island countries.[11] These countries are almost exclusively located between 60^0N and 40^0S. Humans are the only important parasite reservoir and female anopheline mosquitoes ingest parasites during

blood-meals that are necessary for their egg development. Sixty anopheline species are vectors of malaria, but only half of these are major contributors to transmission.

After ingestion the parasites develop in and around the mosquito's gut over a period of approximately one to four weeks, and finally migrate to the salivary glands of the vector for injection during a blood-meal. The injected sporozoites migrate in the human bloodstream to the liver where they develop over a period of 7-10 days into pre-erythrocytic schizonts before merozoites are released, red blood cells (erythrocytes) are invaded and clinical disease begins. After two or three erythrocytic cycles, gametocytes are formed and the infected individual becomes infectious to feeding anopheline mosquitoes.

P. vivax predominates in South America and parts of Asia. Resistance of this parasite to chloroquine is still geographically limited, but this is likely to increase. Although *P. vivax* causes relapsing and debilitating infections due to long-lived dormant parasites in the liver (hypnozoites), it is rarely fatal. These features are shared by *P. ovale*, while *P. malariae* results in a more sub-acute clinical presentation and, like *P. falciparum*, is a non-relapsing malaria, as hypnozoites are not formed.

2.2 Prevention and control

Effective malaria prevention demands an integrated approach to disrupting the transmission cycle. This includes targeting the vector's development, reducing contact between vectors and potential human hosts, and protecting individuals from malaria infection and disease.

To optimally target a vector requires an understanding of it breeding, feeding, and resting behaviour.[12] This may allow source reduction if water-bodies preferred for breeding can be drained. Alternatively, vector larvae may be targeted either by biological (predation, competition, larviciding with biological agents) or chemical means. Where humans are not the preferred host, there may be potential for locating preferred animal host species between breeding sites and human dwellings (zooprophylaxis). A recent study from Pakistan documented a marked decrease in malaria incidence following insecticide sponging of cattle and goats by Afghan refugees.[13] Depending on the flight patterns and range of vectors, homes may be located an adequate distance from breeding sites, or raised from the ground on poles, or other structural modifications made to considerably reduce the likelihood of infection.[14]

Travellers or expatriate workers in malaria endemic areas should be encouraged to use effective personal protection measures and chemoprophylaxis, where malaria risk exceeds the slight risk associated with medication. Personal protection measures include: visiting malaria areas during the lowest risk period; avoiding outdoor activities during the preferred vector mosquito feeding period, or covering skin surface with clothing, preferably of light-coloured material; impregnating clothes with synthetic pyrethroids; repeated application of insect repellents containing DEET (di-ethyl toluamide) to exposed skin surfaces during the preferred mosquito feeding period (should be avoided in babies because of concerns about encephalopathy); selecting dwellings with good quality window- and door-screens; sleeping under mosquito nets, preferably impregnated with insecticides; using knock-down insecticides in dwellings; and either burning mosquito coils or using vaporising mats where electricity is available.[15]

Unfortunately cost is a major barrier against broad application of many personal protection measures by those communities most at risk of malaria.[16] In endemic areas control is often affected by indoor spraying with residual insecticides, usually DDT or synthetic pyrethroids, and/or wide-scale deployment of insecticide-treated mosquito nets, which reduce the number of infective bites and have a mass insecticidal effect. Careful evaluation has demonstrated that both methods contribute enormously to reducing malaria morbidity and mortality, although the resultant decrease in naturally occurring immunity may be a negative mid-term consequence.[17,18] Factors that threaten the future utility of these control methods, include increasing vector resistance to insecticides, dwindling community use and re-treatment of mosquito nets where these are deployed in national programmes, and vector feeding in areas of unstable transmission during the dusk and dawn periods, when people may not be inside their homes or in their beds. DDT use has evoked enormous outcry from environmental lobby groups, but its restricted use in malaria control has been sanctioned while alternative effective insecticides are sought. Thus there is an urgent need for novel effective vector control strategies that are acceptable to affected communities.[19]

Although elucidation of the *Plasmodium* genome has prompted a greater investment in malaria candidate vaccine development than at any previous time, an effective vaccine for public health application still appears to be a distant prospect as the immune mechanisms underlying protection remain inadequately understood.[20,21] Vaccines target different stages of the parasite cycle, with sporozoite and liver-stage vaccines attracting the greatest financial investment due to their potential market amongst travellers and the armed forces.

The mainstay medications for chemoprophylaxis are doxycycline, mefloquine, and chloroquine plus proguanil. More recently, Malarone has been registered for use in a number of countries as an alternative where other chemoprophylaxis is contraindicated. Doxycycline is contraindicated for use in pregnancy, breast-feeding, and in children under eight years of age because it affects bone and teeth formation. Additional adverse effects, whether gastrointestinal or Candida infection of the gut and vagina, may be so severe that prophylaxis is discontinued. Severe skin sensitivity to sunburn may also develop and there is limited experience with prolonged use beyond six months. Mefloquine use may be associated with insomnia, strange dreams, mood changes, nausea, diarrhoea and headache. Severe neuropsychiatric reactions (psychosis, convulsions) are infrequent occurring in 1/10,000 to 1/13,000 persons. As there is inadequate experience with mefloquine use during the first three months of pregnancy, it should not be used during this period but in the event of a pregnancy, available safety data does not support termination. Mefloquine is not recommended while breastfeeding or in babies of less than 5kg because of insufficient safety data. It may cause spatial disorientation and affect fine coordination, and should thus not be used where fine coordination is required, for example pilots and underwater divers. Chloroquine plus proguanil provides some protection against chloroquine-resistant *P. falciparum* but there is inadequate information on its efficacy. It may have application when there are contraindications to mefloquine and doxycycline use, for example during early pregnancy, breastfeeding and with intolerance. Serious side-effects are rare, but may occur with long-term use. Periodic eye examinations are recommended after five years of use. Mild reversible side effects include headache, gastrointestinal effects, skin rashes and mouth ulcers.

2.3 Clinical presentation

The key to diagnosing malaria is for health professionals working in tropical environments to maintain a high index of suspicion in all cases of febrile "influenza-like" disease. Malaria often mimics other diseases, with common symptoms and signs including fever, headaches, chills or shivering attacks, diaphoresis, muscular and joint pain, nausea and vomiting, diarrhoea and dysentery, weakness, fatigue and pallor. As mentioned earlier, symptoms begin some seven to ten days after initial infection, and are due to parasite development in red blood cells and subsequent erythrocytic rupture. Although malaria species were traditionally categorised according to the duration of fever cycles, the variability of this synchronicity has become apparent.

Pathophysiological effects of infection include: surface changes of infected red blood cells with "stickiness", endothelial adherence (particularly common with *P. falciparum* infection) and decreased microcirculation, diffuse intravascular coagulation, disturbed haemoglobin formation with haemozoin production and iron deficiency anaemia. These effects all contribute to tissue anoxia, which affects the adrenal glands (shock), pancreas (hypoglycaemia), gastro-intestinal tract (diarrhoea, dysentery), brain (hyperpyrexia, disturbed mentation), placenta (abortion), liver (jaundice), lungs (pulmonary oedema) and kidneys (renal failure). The destruction of red blood cells also results in hypersplenism and splenomegaly, haemoglobinuria ("black water fever", which is more often common with concurrent quinine therapy), and immune-mediated nephritis (*P. malariae*).

If *P. falciparum* malaria is not promptly and effectively treated, the rapid multiplication and invasion by parasites may lead to early decompensation and complicated disease. Common features of complicated malaria, include depressed consciousness and convulsions (cerebral malaria), severe haemolytic anaemia (Hb <6gm/l), hypoglycaemia (blood glucose <2.4 mmol/litre), acidosis, non-cardiogenic pulmonary oedema, acute renal failure (mainly in adults), haemoglobinuria, systolic hypotension, and complications such as aspiration pneumonia or gram-negative septicaemia. Jaundice and hyperparasitaemia (>5%) are also common features of severe disease. The mortality of severe malaria, a condition that can largely be prevented through adequate malaria prevention measures, prompt diagnosis and early initiation of effective therapy, still exceeds 20%.

Evidence is now emerging that HIV has a more deleterious impact on malaria than previously believed. A cohort study in rural Uganda found that parasitaemia and clinical malaria were significantly more common in HIV-infected individuals, and associated with falling CD4 counts and advancing HIV disease.[22] A cross-sectional study of pregnant Malawian women found an increased incidence of malaria in those that were HIV-infected irrespective of their number of previous pregnancies.[23] Individuals infected with malaria have a higher HIV-1 RNA burden than those without malaria, but this viral load can be reduced by antimalarial therapy.[24]

2.4 Diagnosis

A correctly prepared and stained blood smear or rapid immunodiagnostic card test is usually

sufficient to confirm a diagnosis of malaria. A negative test does not, however, exclude the diagnosis and repeated tests at 6-12 hour intervals may be necessary to confirm diagnosis. Unfortunately, access to diagnostic facilities in many malaria-endemic areas is limited, and malaria treatment is commonly initiated on the basis of clinical or self diagnosis, which are both unreliable diagnostic methods.[25] This is not a situation that should be encouraged because unnecessary therapy is wasteful and potentially toxic, and may also accelerate the selection of drug-resistant parasites.

Microscopic examination of Giemsa-stained thin and/or thick blood smears remains the standard diagnostic approach in most tropical environments where malaria is endemic. Under optimal conditions, microscopy can detect 20-50 parasites/µL blood, but this is rarely achieved during routine diagnosis, as regular quality assurance, retraining of microscopists and adequate maintenance of equipment are unusual in many tropical countries. Thus, there is considerable interest in more widespread deployment of rapid card tests for definitive malaria diagnosis.[26] These tests detect parasite-specific histidine-rich protein 2 (HRP2) or lactate dehydrogenase (pLDH) and generally display sensitivities and specificities exceeding 90% for *P. falciparum* diagnosis.[27,28] They require little training and can be completed in less than 15 minutes. Unfortunately, HRP2 persists for a number of weeks after effective treatment and thus cannot be relied upon for monitoring response to therapy. Rapid card tests are also less sensitive for diagnosing other malaria species. Cost-effectiveness has been the major factor constraining wider use but the introduction of more expensive first-line therapy means that definitive diagnosis with card tests may prove cost-effective. It is worth emphasising that the presence of parasites in a blood smear in a high-transmission area, where a large proportion of the population is semi-immune and infected at any one time, does not mean that malaria is the cause of a febrile illness, although it should remain the principal suspect.

Although alternative laboratory methods, including the quantitative buffy-coat centrifugal (QBC) haematology system, ELISA tests for detecting *P. falciparum* antigen, immunofluorescence and PCR, are accurate, none of these tests is routinely used as they are too expensive or complex for most tropical environments.

2.5 Treatment

Prompt treatment with effective therapy is probably the most cost-effective component of malaria management through preventing severe disease.[29] The number of effective drugs available for treating malaria is limited (Table 1). Newer drugs are more expensive than chloroquine and SP, and counterfeit medication is widely available, particularly in Africa. Although resistance of *P. falciparum* to chloroquine, and more recently SP is widespread, they are still used in many parts of the tropical world. Chloroquine has been the mainstay of treatment for other human plasmodia species but chloroquine-resistant *P. vivax* is now being increasingly recognised.

Mefloquine is used for first-line treatment of *P. falciparum* malaria in some South American countries and for uncomplicated malaria caused by multi-drug resistant *P. falciparum* in Thailand, mefloquine combined with artesunate (an artemisinin derivative) has proven efficacious.

Table 1. Characteristics of treatment for uncomplicated malaria

Drug	Composition	Adult dosage	Toxicity
Chloroquine	4-aminoquinoline	Oral: 600mg stat; 300mg 6hrs later; 300mg next two days (base) IV: 5mg/kg (max. 300mg) e 8hrs (total – 25mg/kg)	Gastro-intestinal (GI); Urticaria; Hypotension; Visual loss, particularly with chronic use (retinopathy)
Sulphadoxine-Pyrimethamine	Sulpha antibiotic & dihydrofolate reductase inhibitor	Oral: single dose with minimum of 1.25mg/kg pyrimethamine	Severe skin reactions (Stevens-Johnson syndrome); Hepatitis; Blood dyscrasias
Mefloquine	4-quinoline methanol	Oral: 750mg-1gm stat	Headache; Dizziness; Sleep disturbance; Seizures; Psychoses
Halofantrine	Phenanthrene methanol	Oral: 500mg e6hrs for three doses. Repetition of dose should be considered	Prolongation of cardiac conduction; Sudden cardiac
Amodiaquine	4-aminoquinoline	Oral: 600mg stat; 300mg 6hrs later; 300mg next two days (base)	Gastro-intestinal (GI); Urticaria; Hypotension; Agranulocytosis
Primaquine	8-aminoquinoline	Oral: 15mg per day for 10-14 days (base)	Gastro-intestinal; Acute haemolysis (G6PD deficiency); Methaemoglobinaemia (in toxic doses)
Quinine	Alkaloid	Oral: 600mg e8hr for 7-14 days; IV: Loading dose 20mg/kg over 4hrs (max 1.4g); Maintenance dosage 10mg/kg over 2hrs e 12hr	Cinchonism (tinnitus, deafness, nausea); Hypoglycaemia (esp. pregnancy); Hypotension; Abortion with overdose
Qinghaosu (artemesinins)	Sesquiterpene lactone	Oral: In combination with another effective antimalarial as artesunate, 4mg/kg/day for 3 days Alone, 4mg/kg stat, followed by 2mg/kg/day for 7 days IV or IM: in severe disease	Rare Type 1 hypersensitivity reactions

Wide-scale implementation of artemisinin-based combination therapy (ACT) is probably the most promising measure that could enable malaria-endemic countries to achieve the ambitious goals set in Abuja to "Roll Back Malaria", particularly the halving of malaria morbidity and mortality by 2010. The value of ACT in improving cure rates, decreasing malaria transmission through its impact on gametocyte production, and delaying development of drug resistance was initially documented on the western border of Thailand and recently confirmed in African field trials.[30-34] By combining an artemisinin derivative with another antimalarial that has an alternate mechanism of action and is effective against the local strain of *P. falciparum,* resistance will be avoided or at least delayed. Antimalarials that are proposed include chloroquine (very limited application), SP, amodiaquine, mefloquine or lumefantrine.

When treating *P. vivax* or *P. ovale* malaria it is not sufficient to target only blood-stage parasites, usually with chloroquine where it remains effective, but it is also necessary to clear liver hypnozoites to avoid relapses. Therefore, it is necessary to give a two-week treatment course with primaquine. Primaquine and similar chemical compounds should not be used in people with severe variants of glucose-6-phosphate dehydrogenase (G6PD) deficiency.

The two most important groups of drugs for treating complicated malaria are quinine and the artemisinins. In severe disease, parenteral administration of artemether and artesunate is as effective as intravenous quinine, and they remain active against quinine-resistant parasites while generally being easier to use. Home or village-based rectal artesunate administration is a promising approach for treating patients who cannot take oral antimalarials to prevent disease progression while awaiting urgent referral to a hospital. Where resistance exists in *P. falciparum,* quinine is usually combined with sulphadoxine-pyrimethamine or doxycycline.

The management of severe disease has been expertly reviewed elsewhere and will not be detailed in this chapter.[35,36] A few key points are, however, worth emphasizing. Severe malaria may occur with a low parasitaemia in peripheral venous blood, as the peripheral blood picture does not take account of parasitised red blood cells sequestrated within target organs. Although a patient may appear clinically stable, this may be deceptive, as malaria can progress rapidly. Delays in presentation, diagnosis and initiation of effective therapy, and inadequate monitoring can result in a fatal outcome. Regular monitoring should include fluid input/output, blood pressure, pulse, respiratory rate, neurological status and blood glucose, particularly when intravenous quinine is being administered as this can cause hypoglycaemia. Ideally a base-line haemoglobin and blood electrolyte determination should be conducted and repeated when clinically indicated. Careful monitoring is immensely important in pregnant women and small children who are prone to develop severe disease.

It is instructive to briefly review the findings of an African confidential inquiry into malaria deaths, conducted to determine avoidable factors or deviations from minimum acceptable standards of case management that may have contributed to fatal outcomes.[37] The principal factors elucidated were delays in seeking medical attention, particularly among patients that sought advice from traditional or spiritual healers; unavailability of effective anti-malarial treatment at the primary point of contact with the formal ("western") health care system; unacceptable delays in initiating malaria therapy at hospitals due to delays in diagnosis; incomplete administration of prescribed therapy in hospitalised patients; and inadequate

assessment of target-organ function.

3. AFRICAN TRYPANOSOMIASIS

3.1 Introduction

Human African trypanosomiasis (HAT), also known as sleeping sickness, is a febrile disease found exclusively in Africa. HAT is notable for its disastrous outcomes if not promptly and correctly treated. In recent decades, HAT has achieved re-emerging disease status with an expansion of its distribution.[38]

3.2 Epidemiology

HAT is caused by a protozoan, *Trypanosoma brucei*, which is transmitted to humans by the bite of various tsetse fly species (*Glossina sp*). *Trypanosoma brucei gambiense* is found in west and central Africa, and *T. b. rhodesiense* in east and southern Africa. The patchy distribution of vector species is mirrored by HAT being confined to about 200 geographical foci in sub-Saharan Africa, between 15^0N and 20^0S. Although only a couple of hundred cases of *T. b. rhodesiense* trypanosomiasis are currently reported each year, *T. b. gambiense* infection has surged in central Africa during the past three decades. Over 27,000 cases were reported in the Congo in 1998, and recent epidemics in Angola, southern Sudan and Uganda have resulted in approximately 100,000 new infections each year.[39]

According to the World Health Organization, about 500,000 people currently carry trypanosomes and will die if not treated.[40] West African sleeping sickness, caused by *T. b. gambiense* is transmitted by tsetse flies (*Glossina palpalis, G. tachinoides* and *G. morsitans*) that breed in forests alongside river courses and take blood-meals from humans and other mammals, particularly domestic pigs, that enter these riverine habitats. East African sleeping sickness, caused by *T. b. rhodesiense*, is transmitted during blood-meals by tsetse flies (*G. morsitans, G. pallipedes* and *G. fuscipes*) that also breed along watercourses but travel extensively under savannah bushveld cover, often feeding on bushbuck and other wild game animals. These tsetse flies prefer feeding on large dark objects. People, whose occupations bring them into contact with these areas, are at risk of infection.

HAT was previously considered an unusual occurrence only affecting individuals living in tropical rural Africa and traversing tsetse-infested habitats. More recently its potential for causing outbreaks in displaced communities or international tour groups has been recognised.[41]

3.3 Prevention and control

HAT can be controlled by combining reservoir reduction, through active case finding and treatment, with vigorous vector control measures. No vaccine is currently under development.

Vector control has been successfully accomplished in West Africa by selectively clearing the undergrowth along watercourses, which provide tsetse flies with shade. This is usually

performed within 500 meters of known river crossings, water collection points or human settlements, and large trees do not have to be removed. In East Africa it is necessary to clear or ring-bark bush for at least a kilometre, and preferably even more, around places of human habitation or work. Targeted insecticide spraying of watercourses has also been successfully employed. Large black fly-traps that are impregnated with residual insecticides and are well-maintained have also proved successful in reducing vector numbers. The large-scale slaughter of wild-animal reservoirs, which was previously practiced, has fallen into disrepute.

During epidemics human populations can be screened for infection, usually by mass blood-slide surveys or occasionally by lymph-node puncture. It is useful to particularly target individuals with persistent fever and headache, or those whose occupations place them at risk of exposure.

3.4 Clinical presentation

The first symptoms occur at the site of the tsetse fly bite, five or more days after inoculation, and take the form of a painful trypanosomal chancre, which is typically accompanied by enlargement of the draining regional lymph nodes. A chancre is more common in East African trypanosomiasis than West African trypanosomiasis.

Progression of disease is heralded by the onset of fever, which has an irregular pattern over many weeks or months while parasites multiply in the bloodstream. In East African trypanosomiasis, disease can progress swiftly, with ten percent of untreated or inadequately treated patients succumbing rapidly, most commonly due to myocardial involvement. With Gambian infection, a long asymptomatic stage progresses to sub-acute febrile illness. Lymphadenopathy, especially in the posterior triangle of the neck (Winterbottom's sign), is a characteristic feature. Other common signs include hepatosplenomegaly and a mild rash. This is termed, stage 1 or haemolymphatic disease.

After weeks, in East African trypanosomiasis, or months, in West African disease, trypanosomes invade the central nervous system, with a resultant progressive encephalopathy, disturbed mentation and headache. This is known as stage 2 or encephalitic disease. Eventually these patients enter a terminal somnolent state, “sleeping sickness” with a chronic meningoencephalitis. If untreated, human African trypanosomiasis progresses inexorably to death.

3.5 Diagnosis

Unfortunately many of the recent sophisticated diagnostic advances, such as the quantitative buffy coat technique, are unlikely to have field application.[42] Thus, detection of the morphologically indistinguishable trypanosomes responsible for East and West Africa sleeping sickness will continue to rely on conventional diagnostic approaches, including lymph node puncture, bone marrow aspirate and blood film examination, with various techniques used to concentrate parasites. These techniques require considerable training and a critical mass of exposure to maintain expertise. As trypanosome densities in the blood fluctuate, being occasionally undetectable in West African trypanosomiasis, repeated regular examinations may be required. A rapid agglutination card test is available which is proving a useful complementary

screening tool for West African trypanosomiasis.[43]

After detecting trypanosomes in blood or lymph, disease is staged (1 or 2) by means of lumbar puncture examination. Evidence of cerebrospinal fluid activity, reflected by increased lymphocyte counts (>20 cells/μl), increased protein levels (>35 mg/dl), or the presence of trypanosomes in cerebrospinal fluid confirms central nervous system involvement (stage 2 disease). Staging is crucial for determining the correct choice of treatment.

3.6 Treatment

Only a limited range of drugs are active against HAT (Table 2). New treatments are urgently needed as available treatment is costly, there is increasing parasite resistance against pentamidine and melarsoprol (an arsenic-containing compound), and treatment-related mortality is unacceptably high (approximately 10% with melarsoprol).[44,45]

Treatment should be administered for a minimum of ten days and this should preferably occur in hospital. Hospitalisation is essential for stage 2 disease, as intensive monitoring and nursing care are required. The ideal length of treatment is not clear, but recent trials show some advantage of longer therapy (14 days) for stage 2 disease, while shorter treatment courses (7 days) may be more appropriate for stage 1 disease.[46-48] Prednisolone should also be administered with melarsoprol in stage 2 disease, as this appears to reduce the likelihood of treatment-associated encephalopathy.[49]

Table 2. Recommended treatment regimes for African Trypanosomiasis

	East African trypanosomiasis	West African trypanosomiasis
Stage I	First line: suramin Second line: melarsoprol	First line: pentamidine Second line: eflornithine or melarsoprol
Stage 2	First line: melarsoprol Second line: nifurtimox and melarsoprol	First line: melarsoprol Second line: eflornithine

4. CHAGAS' DISEASE

4.1 Introduction

Chagas' disease (South American trypanosomiasis) is a parasitic infection of considerable pubic health importance in Latin America. Chronic Chagas' disease results in significant morbidity and mortality, and considerable expenditure on hospitalisation, chronic medication or pacemakers for arrhythmias, and surgery. Recently, programmes developed to control Chagas' disease have demonstrated remarkable success.[50] It is possible that molecular typing may offer an opportunity for even more targeted control, allowing public health officials to distinguish between residual domestic vector populations that have survived insecticide spraying and

reinvasion of bugs from sylvatic habitats.[51,52]

4.2 Epidemiology

Chagas' disease is the most important parasitic infection in Latin America, with more than 10 million people harbouring the protozoan agent *Trypanosoma cruzi*. It is a zoonotic disease, primarily transmitted by reduviid (triatomine) bugs, which infest poor quality housing. There are more than 130 species of triatomine bug and most American triatomine species are able to transmit .*T cruzi*.[53]

T. cruzi is transmitted when abraded skin, mucous membranes or conjunctiva are exposed to faeces of infected triatomine bugs. More rarely bugs may faecally contaminate food items, resulting in oral transmission of infection. Chagas' disease can also be transmitted by blood transfusion or organ transplantation. Rarely, infants born to infected mothers are congenitally infected.

Although transmission may occur in sylvatic and domestic settings, it is the latter that accounts for the gross burden of human disease. Triatomine bugs do not fly to their hosts to take blood-meals but wait for potential hosts to enter the area they are colonizing. In the wild, opossums, armadillos and other mammalian hosts serve as the reservoir of infection. In these environments triatomine bugs, like *Rhodnius brethesi*, survive in tree-holes, or crevices in rocks or the ground, and individual sporadic human cases of Chagas' disease result from inopportune contact of human with bugs.[54]

Sylvatic and domestic transmission cycles may be separate or overlap. In the domestic environment triatomine bugs feed on domestic mammals, chickens or humans. A few triatomine species have adapted to colonise and thrive in houses, particularly *Triatoma infestans*, the domestic vector of Chagas' disease in the southern cone region of South America (Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay). This vector is very rarely found in sylvatic locations. Other species, such as *T. brasiliensis* in north-eastern Brazil, may reinvade houses from adjacent sylvatic locations.

4.3 Prevention and control

Insecticide spraying of houses infested with triatomine bugs has proven very effective in controlling Chagas' disease.[55] This strategy was employed in the multi-country southern cone initiative launched in 1991, which targeted all houses and domestic animal shelters infested with *T. infestans* for spraying with residual pyrethroid insecticides to eliminate this species.[56] The spraying programme was combined with an intensive health education campaign to ensure that communities participated in surveillance for persistent bug infestations and provided access to their homes for spraying. Serological surveys of children born after initiation of the control programme have been used to identify remaining pockets of transmission. Uruguay was certified free of transmission in 1997, Chile in 1999, and large regions of Brazil, Argentina and Paraguay have also achieved cessation of transmission.[57] The initiative has resulted in enormous economic savings.[58] Subsequent initiatives that have been launched include a Central American control programme and an Andean Pact control programme, covering Venezuela, Colombia, Peru and

Ecuador.

Vector control is more difficult where triatomine species that have adapted to both domestic and sylvatic environments, like *T. brasiliensis*, exist. Available molecular tools are now being used to identify areas where transmission cycles overlap and assess the risk of reinvasion.

Unfortunately no effective chemoprophylaxis or promising vaccine candidates against Chagas' disease currently exist, nor does treatment of infection necessarily result in complete elimination of *T. cruzi*.

Thus, ongoing improvements in rural housing that ensure a reduction in cracks and crevices in walls, providing fewer resting places for bugs, are important for ensuring the long term sustainability of these public health programme successes. Bed-nets also provide a measure of personal protection.

Screening of blood and organ donors serologically for *T. cruzi* infection allows interruption of this transmission route but has also resulted in additional medical benefits through greatly improved blood and blood product safety throughout Latin America.

4.4 Clinical presentation

Although the initial phase of infection is usually asymptomatic, an inflammatory lesion may develop at the site of exposure to infected faeces (cutaneous chagoma), as a result of local multiplication of *T cruzi*. If the eye is exposed, then unilateral conjunctivitis and oedema may result (Romaña's sign). When symptomatic, acute disease is characterised by variable fever, malaise, lymphadenopathy and hepatosplenomegaly.

T. cruzi multiplies forming nests of amastigotes inside cells, particularly those of the heart and various smooth muscles, including those of the colon and oesophagus. In the chronic phase of infection many individuals remain asymptomatic but up to a third develop severe electrocardiographic abnormalities (especially right bundle branch block) and cardiomyopathy, sometime associated with a left ventricular apical aneurysm. Megaoesophagus and megacolon are other classic presentations associated with the chronic phase of infection. Chronic disease presentation varies markedly between affected geographical areas, with megaoesophagus and megacolon, for example, being common in southern South America but rare in the northern parts of the continent. The determinants of this heterogeneity are not fully understood.

In immunocompromised individuals, a recurrent acute phase occasionally occurs. Severe meningoencephalitis and acute myocarditis occur more frequently in immunocompromised patients or congenital cases. Meningoencephalitis has a very poor prognosis.

4.5 Diagnosis

After infection, microscopy may reveal trypanosomes in blood, particularly if concentration methods are used. Following initial infection serological evidence of infection is usually life-long unless effective treatment is provided. During the chronic phase of infection, parasitaemia

is detectable only by intensive blood culture or xenodiagnosis. For xenodiagnosis, laboratory-bred triatomine bugs are allowed to feed on the suspected case and later dissected or their stools examined to ascertain infection by *T. cruzi*. It is possible to distinguish between different *T. cruzi* strains by DNA polymorphism analysis.

4.6 Treatment

Benznidazole is the treatment of choice for the acute phase of infection and is potentially life saving. This is administered for 60 days and hospitalization is preferred to monitor for adverse events, which are common, and ensure adherence. Nifurtimox is no longer readily available, is associated with many adverse drug events, but must be given for 90 days if used.

The prolonged use of benznidazole for the chronic stage of disease is debatable, due to the high frequency of side effects and development of resistance.[59] In chronic disease, supportive drug therapy is essential. Heart disease can usually be treated by judicious use of vasodilators and diuretics. Arrhythmias should also be treated, currently usually with amiodarone. Occasionally surgical intervention is required for ventricular aneurysms. Acute meningoencephalitis should be managed with sedatives and anticonvulsants. Although mild megaoesophagus and megacolon may be successfully managed by diet modification or laxative use, respectively, more severe disease requires surgical resection.

5. VISCERAL LEISHMANIASIS

5.1 Introduction

Visceral leishmaniasis (kala-azar) is transmitted by the bite of phlebotomine sandflies. Following infection parasitisation of tissue macrophages results and this appears to be life-long. The devastating effect of dual infection with leishmaniasis and HIV in the tropics has led to renewed interest in improving diagnosis and treatment of this disease.[60] Although there are three main forms of leishmaniasis, the cutaneous and mucocutaneous forms will not be discussed in this chapter, as they rarely present with fever (see chapter 10).

5.2 Epidemiology

Although leishmaniasis occurs in at least 88 countries and visceral leishmaniasis is endemic in 47 countries, more than 90% of the visceral cases occur in India and Sudan. Of the Indian cases, which account for approximately half of the global burden of kala-azar, ninety percent occur in Bihar state.[61] An outbreak in southern Sudan in 1984 caused 100,000 deaths in a population of less than a million people.[62] Other regions affected include rural foci in Asia, the Mediterranean, Central and South America, and sub-Saharan Africa.

There are 21 haemoflagellate *Leishmania* species that cause human infection, most importantly *L. donovani*, *L. infantum*, *L. tropica* and *L. chagasi*. Female sandflies from 30 species have been implicated in transmission to humans.

Leishmania-HIV co-infection has been reported in more than 30 countries and visceral leishmaniasis is an opportunistic disease in HIV-infected people. Dual infection accelerates the course of AIDS and dually infected patients suffer frequent relapses and may have unusual presentations.[63]

5.3 Prevention and control

Phlebotomine sandflies, the vector of leishmaniasis, breed in damp organic material, animal burrows, anthills or caves. Piles of refuse or building sites may be important breeding sites. As sandflies do not travel far from their breeding sites, these should be actively reduced or sprayed with residual insecticides. In some areas breeding occurs in pit latrines, and these should then be targeted. Insecticide spraying of houses has also proven effective for control. Reduction of domestic canine reservoirs may also be necessary. Personal protection with insect repellents and protective clothing should be encouraged.

5.4 Clinical presentation

Most visceral infections are sub-clinical. The disease affects people of all ages and typically presents with fever and evidence of reticuloendothelial disease, particularly hepatosplenomegaly and pancytopaenia. Emaciation and weakness characterise progressive disease. Kala-azar is well recognized as a mimic of other systemic conditions, particularly malaria, schistosomiasis, African Trypanosomiasis, brucellosis and typhoid fever.

Despite correct treatment kala-azar patients may experience relapses many years later. In patients that are immunosuppressed by chemotherapy, such as transplant recipients, or those with advanced HIV disease, kala-azar behaves like an opportunistic infection. Most cases of kala-azar associated with HIV have been reported in southern Mediterranean countries.[64]

5.5 Diagnosis

As leishmaniasis can mimic so many other conditions, it is essential to maintain a high index of suspicion in endemic areas, and to obtain a definitive diagnosis before initiating therapy. Diagnosis of leishmaniasis is made by microscopic detection of amastigotes in smears of tissue aspirates from spleen or bone marrow, or biopsy samples. Where microscopy is negative but infection is clinically or epidemiologically suspected, the parasite can sometimes be cultured using special media, for example NNN, from a biopsy sample or a tissue aspirate from the spleen or bone marrow. Although diagnostic sensitivity is highest from splenic aspiration, there is unfortunately also a risk of haemorrhage.[65] Non-specific serological tests are rarely used because they are cumbersome and have a relatively low sensitivity and specificity.

The accuracy of immunochromatographic rapid card tests for detecting leishmania-specific antibody in finger-prick blood has been demonstrated.[66] This test makes use of the rK39 (recombinant kinesin protein) antigen, which is a sensitive marker of the onset of disease manifestation in kala-azar patients. It also has the potential for monitoring success of chemotherapy and detecting clinical relapse, particularly in patients dually infected with HIV.[67,68]

PCR has proven valuable for detecting parasite DNA in tissue aspirates or peripheral blood, overcoming some of the sensitivity limitations of microscopy and culture techniques. It also is useful for distinguishing between past and present infections, for monitoring treatment success. Unfortunately, PCR requires well-equipped laboratories with well-trained staff, and thus it cannot currently be used routinely in the field. A latex agglutination test for detecting leishmanial antigens in patient urine has been developed but its utility is still to be confirmed.[69]

5.6 Treatment

Pentavalent antimony (sodium stibogluconate or meglumine antimonate) has been first-line treatment for all forms of leishmaniasis for the past half century. These treatments are administered intravenously or intramuscularly at a daily dose of 20mg/kg for 30 days. Side effects are common, particularly myalgia, headache, ECG abnormalities, and occasionally more severe adverse events, including severe arrhythmias and even, rarely, sudden death. Strains resistant to pentavalent antimonials have emerged, particularly in Bihar State, India. The response to treatment in patients co-infected with HIV is also sub-optimal.

Other treatment regimens for treating kala-azar include conventional amphotericin B (infusion-related side effects and renal toxicity are common), injectable paramomycin (aminosidine), short courses (5-10 days) of a lipid formulation of amphotericin B (less toxic than conventional amphotericin), and oral miltefosine.[70] The cost of these latter three treatments will restrict their application worldwide. Vaccine development is under way, and a killed promastigote plus BCG vaccine is being tested during Sudanese epidemics.

Miltefosine (hexadecylphosphocholine) is the first effective oral agent against kala-azar. This drug, initially used as anti-cancer agent, stimulates T cells and macrophages to secrete activating cytokines and is effective in antimony-resistant cases.[71,72] The recommended adult dose is 100mg/day for 28 days. It should not be used in pregnant women because of teratogenic effects found in animal studies. Gastrointestinal side-effects are common initially, and there may be elevated liver enzymes in the first few weeks of treatment, but there are fewer adverse events when compared to antimonials and amphotericin.

Useful means for monitoring kala-azar response to therapy include increasing haemoglobin, total serum protein and albumin, white blood cell count, and decreasing erythrocyte sedimentation rate and serum liver enzyme levels.

6. AMOEBIASIS

6.1 Introduction

Amoebiasis remains a leading parasitic cause of death worldwide, and is a disease that is endemic in many tropical countries where faecally contaminated water consumption is common. *Entamoeba histolytica* is the causative agent and although infection with this organism is often asymptomatic, it may cause amoebic colitis with dysentery, and many forms of extra-intestinal

amoebiasis, most commonly amoebic liver abscesses (see also Chapters 6 & 7). Humans, and possibly non-human primates, are the only natural hosts. Prior to the antibiotic era, hepatic amoebic abscesses were virtually synonymous with death. *E. histolytica* trophozoites secrete enzymes that cause local destruction of host cells and tissue, whether in the intestinal mucosa or systemically after invasion. Although fever is not a prominent feature of amoebic colitis, it is an important feature of amoebic liver abscess.

6.2 Epidemiology

It is estimated that between 40,000 and 100,000 people die annually from amoebiasis.[73] *E. histolytica* is distributed globally but is particularly common in tropical countries where most infection results from ingestion of food or water contaminated with faeces containing *E. histolytica* cysts. Less common forms of transmission include oral and anal sex, particularly among homosexual men. Although amoebic colitis affects all age-groups, amoebic liver abscess predominantly affects young and middle-aged men.[74] Rates are also higher among elderly women and individuals that consume excessive alcohol.

6.3 Prevention and control

Unfortunately there is little likelihood of an effective vaccine in the foreseeable future. Natural infection with *E. histolytica,* even in patients with amoebic liver abscess, does not provide long-term immunity against re-infection. Thus the focus must remain on improving the provision of clean water and safe food supply. Education on personal hygiene and sanitary disposal of faeces are integral to interrupting transmission.

6.4 Clinical presentation

Many *E. histolytica* infections are asymptomatic, but approximately 10% of infections result in disease (see Chapter 6). This usually takes the form of amoebic colitis, which presents with abdominal pain, tenderness and dysentery, although watery diarrhoea is not uncommon early in disease. In children, rectal bleeding without diarrhoea may occasionally occur. Although white blood cells are often present in the stool, these are usually at much lower levels than seen with campylobacter and shigella infection. Fever is present in about half the patients. After amoebas invade the mucosa into the sub-mucosal tissues, they may extend through the sub-mucosal tissues to form a flask-shaped ulcer, which is characteristic of amoebiasis.

If intestinal perforation occurs then an acute severe picture results, with profuse bloody diarrhoea, fever, abdominal pain and peritoneal signs. If neglected, this condition is associated with a poor outcome. Patients who are immunocompromised, receiving corticosteroids or pregnant are more likely to develop this severe form of disease.[75] Occasionally, progressive invasion is associated with localized inflammatory masses, usually in the caecum or ascending colon, called amoebomas. These may cause obstructive symptoms and are often initially investigated as bowel cancer.

The most common extra-intestinal manifestation of disease is amoebic liver-abscess (see also Chapter 7). This occurs when invading trophozoites traverse the portal circulation and reach the

liver. Resulting abscesses consist of *E. histolytica* trophozoites surrounded by dead hepatocytes and liquefied cell debris. Pus cells are absent unless secondary bacterial infection has occurred. This destruction is due to production of enzymes, particularly cysteine proteinases, by *E. histolytica*. The liver tissue adjacent to the abscess often appears completely normal. Liver abscesses continue to expand unless correctly managed and thus were historically almost always fatal. Currently mortality rates are below 3%.[76] Most patients with a liver abscess do not have bowel symptoms, and stool microscopy is usually negative for *E. histolytica*.

Amoebic liver abscesses usually present with acute onset of fever, right upper quadrant abdominal pain, severe hepatic tenderness and often with a raised right diaphragm on X-ray. Although jaundice is rare, cough is common. When the presentation is more sub-acute, anorexia and weight loss are frequent features. Right hepatic lobe abscess often result in a transudate in the pleural cavity and coughing. However, if a patient develops pleuritic chest pain or respiratory distress, then liver-abscess rupture through the diaphragm with empyema should be suspected. About 15% of patients with liver-abscess develop this complication.

Should the disease process extend into a bronchus, the resulting fistula leads to expectoration of copious brown sputum containing necrotic material and even amoebic trophozoites. If the liver abscess ruptures either into the peritoneum or pericardium, dramatic decompensation and shock occurs. In the latter case, signs of pericarditis or cardiac tamponade (chest pain, pericardial rub, dyspnoea) are prominent.

Uncommon complications included amoebic brain and lung abscesses, rectovaginal fistulas and cutaneous lesions, particularly in the peri-anal region (see Chapter 10).

6.5 Diagnosis

It is not possible to accurately distinguish between *E. histolytica* and *E. dispar* (a bowel commensal amoeba) by stool microscopy, but this method is still commonly deployed in areas where amoebiasis is epidemiologically suspected (see Chapter 6). Unfortunately, in many of these areas, dysentery due to shigellosis and Campylobacter is also common, and appropriate antibiotic therapy might be delayed by misdiagnosis. Thus, the availability of sensitive commercially available ELISA assays for identifying *E. histolytica*-specific antigens in stool are a welcome addition to the diagnostic arsenal.[77] Stool culture and PCR are currently almost exclusively restricted to research use.

In cases of acute colitis, where amoebiasis is suspected but *E. histolytica* cannot be detected in stools, colonoscopy or flexible sigmoidoscopy may be used to obtain colon scrapings or biopsies for detecting amoebic trophozoites.

Ultrasound and computer tomography (CT) are both sensitive means for detecting amoebic liver abscesses, but lack some specificity. Thus, in addition to imaging the abscesses, amoebic serology should be performed.[78] Amoebic liver abscesses, are often associated with a peripheral leucocytosis, mild anaemia, a raised erythrocyte sedimentation rate and elevated liver enzymes, particularly alkaline phosphatase.

6.6 Treatment

Treatment for amoebiasis is with nitroimidazole derivatives, either metronidazole, tinidazole or ornidazole. Metronidazole is the most commonly used agent against amoebic colitis but should be followed by either paromomycin, iodoquinol or diloxanide furoate to eradicate amoebic colonization from the intestine.[79] Even severe amoebic colitis, with or without perforation, is usually managed conservatively, although antibiotics are added to cover against peritonitis secondary to bowel flora. Where CT is available, monitoring of peritoneal septic fluid volume is possible and careful percutaneous drainage has been successful.

Surgical drainage of uncomplicated amoebic liver abscesses is generally not necessary and should not be attempted.[80] Most abscesses respond well to treatment with metronidazole, and clinical symptoms, including fever and abdominal pain significantly improve within 3-4 days. A luminal agent, such as diloxanide furoate, should also be administered to eliminate amoebic colonization of the intestine. The role of ultrasound or CT guided percutaneous aspiration for treating uncomplicated amoebic liver abscess is unclear, as a randomized controlled study failed to demonstrate a significant difference in length of hospitalization or time to fever clearance, between patients treated with metronidazole alone and those treated by percutaneous aspiration.[81] Aspiration should be considered where: large amoebic liver abscesses (>300 cm^3) are present; it is unclear whether the liver abscess is of pyogenic origin or secondarily infected; there has been an inadequate response to metronidazole after four days of therapy; a large left-lobe abscess exists with a risk of pericardial rupture; or patients are severely ill. Where a liver abscess is aspirated, examination of the terminal portion of the aspirate may reveal haematophagous trophozoites on microscopy.

7. LYMPHATIC FILARIASIS

It is estimated that approximately 120 million people worldwide in 80 countries, predominantly within the tropics, are infected with one of the three lymph dwelling filariae, *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori* (see Chapters 6 and 13). Infective larvae are inoculated by mosquitoes and adult worms are found in lymph nodes or adjacent lymphatics, and their offspring, microfilariae, circulate in the blood, often only at night. A programme has been established to eliminate lymphatic filariasis as a public health problem worldwide by 2020.[73] The focus of this programme is sustained microfilarial suppression by the mass annual administration of single dose combinations of albendazole plus diethylcarbamazine or ivermectin.

The variable clinical manifestations of lymphatic filariasis include sub-clinical microfilaraemia or asymptomatic carriage of adult worms, acute adenolymphangitis (ALA), and lymphatic obstruction with hydrocoele or elephantiasis. The pathogenesis of adenolymphangitis and obstruction is complex but includes immune-mediated inflammatory processes, with secondary bacterial infection being an important contributory factor.[74] Details on lymphatic filariasis prevention and control can be found in Chapter 13. In this chapter our focus will be on the acute febrile presentations of lymphatic filariasis.

Episodic ALA is an important characteristic clinical manifestation of lymphatic filariasis.[75] Recurrent ALAs contribute to disease progression and have important socioeconomic implications as the temporary incapacitation they cause leads to considerable loss of productive working days.[76] Bacterial and fungal super-infections appear to play an important role in triggering many episodes and this may explain some of the observed geographical variability in ALA incidence.[77]

Attacks consist of acute episodes of local swelling and pain following initial numbness of the affected area, particularly the upper and lower extremities and occasionally the neck. Transient redness, usually in the form of broad streaks that spread in a retrograde direction, is common. Affected lymphatic vessels are often palpable and tender, but adenitis, fever, chills and malaise are more unusual. When the latter do occur they are mild and of short duration. Attacks generally resolve within 3-5 days, but occasionally persist for a number of weeks. Two important causes for attacks have been distinguished; death of adult worms and secondary bacterial infections.[78]

In ALA, local hygiene, skin care, antipyretics and analgesics are recommended, together with oral diethylcarbamazine. Topical antibiotic cream is also useful if secondary infection is present.[79]

Diagnosis and treatment of lymphatic filariasis are considered in Chapter 13.

8. SCHISTOSOMIASIS

Human infection with any of the five common species of this trematode infecting humans, *Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum* and *S. mekongi*. can cause serious disease in multiple organs. Attempts to implement and sustain control of this disease in many endemic areas have not been successful, at least partly due to pressure to develop land for agricultural use with irrigation schemes that provide breeding sites for the intermediate snail hosts.

Although schistosomiasis is discussed in more detail in Chapter 6 & 8, it is important to briefly mention Katayama syndrome in this chapter on tropical febrile presentations. This acute systemic manifestation usually occurs during the migratory stage of the schistosomules around the body after the first exposure to cercariae but occasionally also after repeated exposure. The syndrome of fever, malaise, rigors, sweating, myalgia and headache, usually occurs 2-6 weeks after exposure. Additional clinical features may include urticarial skin rash, lymphadenopathy, mild hepatosplenomegaly and cough, and these are accompanied by intense eosinophilia.

Diagnosis and treatment of schistosomiasis is dealt with in Chapters 6 & 8.

9. OTHER PROTOZOAL AND HELMINTHIC CAUSES OF TROPICAL FEVER

A number of additional protozoal and helminthic infections of humans may cause febrile disease

in the tropics.[89] Generally, however, fever is not the prominent feature or is an infrequent finding. These infectious diseases will therefore be discussed in the Chapters documenting their more common presentations.

Important protozoal infections, include toxoplasmosis due to *Toxoplasma gondii*, where fever may be a key feature both in the initial acute glandular-fever type infection and during reactivation, particularly in AIDS patients (see Chapter 14), and a number of intestinal protozoal infections, including *Giardia intestinalis*, *Balantidium coli* and *Cryptosporidium parvum* (see Chapter 6).

Food-borne trematodes causing systemic disease may also be associated with fever, whether liver flukes (*Fasciola spp.*), intestinal flukes (*Fasciolopsis buski*) or lung flukes (*Paragonimus spp*.). These are discussed in Chapter 6, 7, 9 & 14. Soil-transmitted Helminths (Chapter 6), like hookworm may cause fever soon after infection, or like strongyloidiasis, during severe disease.

Zoonotic helminthic infections are covered in Chapter 14. Those that commonly cause fever, include visceral larva migrans (*Toxocara spp.*) and *Trichinella spp.* (see also Chapters 6 & 7).

10. REFERENCES

1. Blumberg L, Ogunbanjo GA, Durrheim DN. Fever in adults - approach to diagnosis and management. *SA Fam Pract* 2000; **22:** 23-26.
2. Lambert HP. Clinical approach to the patient with suspected infection. *In: Oxford Textbook of Medicine. 3rd ed.* Oxford: Oxford Medical Publications; 1996: 265-268.
3. Udomsangpetch R, Pipitaporn B, Silamut K, *et al*. Febrile temperatures induce cytoadherence of ring-stage *Plasmodium falciparum*-infected erythrocytes. *Proc Natl Acad Sci* 2002; **99:** 11825-11829.
4. Murray HW, Pepin J, Nutman TB, *et al*. Tropical medicine. *Br Med J* 2000; **320:** 490-494.
5. Nchinda TC. Malaria: A reemerging disease in Africa. *Emerg Infect Dis* 1998; **4:** 398-403.
6. Marsh K. Malaria disaster in Africa. *Lancet* 1998; **352:** 924.
7. Trape JF. The public health impact of chloroquine resistance in Africa. *Am J Trop Med Hyg* 2001; **64:** 12-17.
8. White NJ, Nosten F, Looareesuwan S, *et al*. Averting a malaria disaster. *Lancet* 1999; **353:** 1965-1967.
9. Gallup JL, Sachs JD. The economic burden of malaria. *Am J Trop Med Hyg* 2001; **64:** 85-96.
10. Nabarro DN, Tayler EM. The “roll back malaria” campaign. *Science* 1998; **280:** 2067-2068.
11. Wilson ME. *A world guide to infections*. Oxford: Oxford University Press, 1991.
12. Durrheim DN, Govere JM, Braack LEO, *et al*. Malahlapanga – exploiting nature’s bounty for malaria control. Canyon DV, Speare R (editors). *Rural and Remote Environmental Health I.* Australasian College of Tropical Medicine: Townsville, 2001.
13. Rowland M, Durrani N, Kenward M, *et al*. Control of malaria in Pakistan by applying deltamethrin insecticide to cattle: a community-randomised trial. *Lancet* 2001; **357:** 1837-1841.
14. Lindsay SW, Jawara M, Paine K, *et al*. Changes in house design reduce exposure to malaria mosquitoes. *Trop Med Int Health* 2003; **8:** 512-517.

15. Durrheim DN, Leggat PA. Prophylaxis against malaria. Preventing mosquito bites is also effective. *Br Med J* 1999; **318:** 1139.
16. Guyatt HL, Ochola SA, Snow RW. Too poor to pay: charging for insecticide-treated bednets in highland Kenya. *Trop Med Int Health* 2002; **7:** 846-850.
17. Sharp BL, le Sueur D. Malaria in South Africa – the past, the present and selected implications for the future. *S Afr Med J* 1996; **86:** 83-89.
18. Lengeler C. *Insecticide-treated bednets and curtains for preventing malaria*. *Cochrane Database of Systematic Reviews*. Oxford: Update Software, 2000.
19. Durrheim DN, Govere JM. Malaria outbreak control in an African village by community application of 'deet' mosquito repellent to ankles and feet. *Med Vet Entomol* 2002; 16; 112-115.
20. Miller LH, Hoffman SL. Research toward vaccines against malaria. *Nature Med* 1998; **4:** 520-524.
21. Richie TL, Saul A. Progress and challenges for malaria vaccines. *Nature* 2002; **415:** 694-701.
22. Whitworth J, Morgan D, Quigley M, *et al*. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet* 2000; **23:** 1051-1056.
23. Verhoeff FH, Veenmans J, West CE. HIV-1 infection and malaria parasitaemia. *Lancet* 2001; **357:** 232-233.
24. Hoffman IE, Jere CS, Taylor TE, *et al*. The effect of *Plasmodium falciparum* malaria on HIV-1 RNA blood plasma concentration. *AIDS* 1999; **13:** 487-494.
25. Guerin PJ, Olliaro P, Nosten F, *et al*. Malaria: current status of control, diagnosis, treatment, and a proposed agenda for research and development. *Lancet Infect Dis* 2002; **2:** 564-573.
26. Durrheim DN, Govere JM, la Grange JJP, Mabuza A. Rapid immunochromatographic diagnosis and Rolling Back Malaria - experiences from an African control program. *Afr J Med Med Sci* 2001; **30:** Suppl 21-24.
27. Beadle C, Long W, Weiss W, *et al*. Diagnosis of malaria by detection of *Plasmodium falciparum* HRP-2 antigen with a rapid dipstick antigen-capture assay. *Lancet* 1994; **343:** 564-568.
28. Durrheim DN, la Grange JJ, Govere J, *et al*. Accuracy of a rapid immunochromatographic card test for *Plasmodium falciparum* in a malaria control programme in South Africa. *Trans R Soc Trop Med Hyg* 1998; **92:** 32-33.
29. Goodman CA, Coleman PG, Mills AJ. Cost-effectiveness of malaria control in sub-Saharan Africa. *Lancet* 1999; **354:** 378-385.
30. Price RN, Nosten F, Luxemburger C, *et al*. Effects of artemisinin derivatives on malaria transmissibility. *Lancet* 1996; **347:** 1654-1658.
31. Barnes KI, Durrheim DN, Jackson A, *et al*. Morbidity and mortality of malaria following implementation of artemether - lumefantrine as first-line treatment of uncomplicated disease in KwaZulu-Natal, South Africa. *Antibiotics Chemotherapy* 2003; **7:** 6.
32. Adjuik M, Agnamey P, Babiker A, *et al*. Amodiaquine-artesunate versus amodiaquine for uncomplicated *Plasmodium falciparum* malaria in African children: a randomised, multicentre trial. *Lancet* 2002; **359**: 1365-1372.
33. Nosten F, van Vugt M, Price R, *et al*. Effects of artesunate mefloquine combination on incidence of *Plasmodium falciparum* malaria and mefloquine resistance in Western Thailand: a prospective study. *Lancet* 2000; **356:** 297-302.

34. von Seidlein L , Milligan P, Pinder M *et al*. Efficacy of artesunate plus pyrimethamine–sulfadoxine for uncomplicated malaria in Gambian children: a double blind, randomized, controlled trial. *Lancet* 2000; **355:** 352-357.
35. World Health Organization. Severe *falciparum* malaria. Trans R Soc Trop Med Hyg 2000; **94:** supplement 1.
36. White NJ. Malaria. In: *Manson's Tropical Diseases, 20th edition*, Cook GC (editor). London: WB Saunders, 1996: 1138-1143.
37. Durrheim DN, Fieremans S, Kruger P, *et al*. Confidential inquiry into malaria deaths. *Bull World Health Organ* 1999; **77:** 263-266.
38. Smith DH, Pepin J, Stich A. Human African trypanosomiasis: an emerging public health crisis. *Brit Med Bull* 1998; **54:** 341-355.
39. Ekwanzala M, Pepin J, Khonde N, *et al*. In the heart of darkness: sleeping sickness in Zaire. *Lancet* 1996; **348:** 1427-1430.
40. World Health Organization. *Control and surveillance of African trypanosomiasis*. *Technical report Series 881*. Geneva: WHO, 1998.
41. Ripamonti D, Massari M, Arici C, *et al*. African sleeping sickness in tourists returning from Tanzania: the first 2 Italian cases from a small outbreak among European travelers. *Clin Infect Dis* 2002; **34:** 18-22.
42. Bailey JW, Smith DH. The quantitative buffy coat for the diagnosis of trypanosomes. *Trop Doctor* 1994; **24:** 54-56.
43. Truc P, Bailey JW, Doua F, *et al*. A comparison of parasitological methods for the diagnosis of gambian trypanosomiasis in an area of low endemicity in Cote d'Ivoire. *Trans R Soc Trop Med Hyg* 1994; **88:** 419-421.
44. Brun R, Schumacher R, Schmid C, *et al*. The phenomenon of treatment failures in human African typanosomiasis. *Trop Med Int Health* 2001; **6:** 906-914.
45. Dumas M, Bouteille B. Treatment of human African trypanosomiasis. *Bull World Health Organ* 2000; **78:** 1474.
46. Bronner U, Doua F, Ericsson O, *et al*. Pentamidine concentrations in plasma, whole blood and cerebrospinal fluid during treatment of Trypanosoma gambiense infection in Cote d'Ivoire. *Trans R Soc Trop Med Hyg* 1991; **85:** 608-611.
47. Burri C, Nkunku S, Merolle A, *et al*. Efficacy of new, concise schedule for melarsoprol in treatment of sleeping sickness caused by *Trypanosoma brucei gambiense*: a randomised trial. *Lancet* 2000; 355: 1419-1425.
48. Pepin J, Khonde N, Maiso F, *et al*. Short-course eflornitine in Gambian sleeping sickness: a multicentre randomised controlled trial. *Bull World Health Org* 2000; **78:** 1284-1295.
49. Pepin J, Milord F, Guern C, *et al*. Trial of prednisolone for prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. *Lancet* 1989; **1:** 1246-1250.
50. Schofield CJ, Dias JC. The southern cone initiative against Chagas' disease. *Adv Parasitol* 1999; **42:** 1-27.
51. Miles MA, Feliciangeli MD, de Arias AR. American trypanosomiasis (Chagas' disease) and the role of molecular epidemiology in guiding control strategies. *Br Med J* 2003; **326:** 1444–1448.
52. Gaunt GW, Yeo M, Frame IA, *et al*. Mechanism of genetic exchange in American trypanosomes. *Nature* 2003; **421:** 936-939.
53. Carcavallo RU, Galindez Giron I, Jurberg J, Lent H. *Atlas of Chagas disease vectors in the Americas*. Rio de Janeiro: Editora Fiocruz, 1998.

54. Coura JR, Junqueira AC, Fernandes O, *et al*. Emerging Chagas disease in Amazonian Brazil. *Trend Parasitol* 2002; **18:** 171-176.
55. WHO: *Control of Chagas disease. 2nd ed. Technical Report Series 905*. WHO: Geneva, 2002.
56. Schofield CJ, Maudlin I. Trypanosomiasis control. *Int J Parasitol* 2001; **31:** 614-619.
57. Dias JC, Silveira AC, Schofield CJ. The impact of Chagas disease control in Latin America: a review. *Mem Inst Oswaldo Cruz* 2002; **97:** 603-612.
58. Basombrio MA, Schofield CJ, Rojas CL, Del Rey EC. A cost-benefit analysis of Chagas disease control in Northwest Argentina. *Trans R Soc Trop Med Hyg* 1998; **92:** 137-143.
59. Coura JR, de Castro SL. A Critical Review on Chagas Disease Chemotherapy. *Mem Inst Oswaldo Cruz* 2002; **97:** 3-24.
60. Lyons S, Veeken H, Long J. Visceral leishmaniasis and HIV in Tigray, Ethiopia. *Trop Med Int Health* 2003; **8:** 733-739.
61. Herwaldt BL. Leishmaniasis. *Lancet* 1999; **354:** 1191-1199.
62. Seaman J, Mercer AJ, Sandorp E. The epidemic of visceral leishmaniasis of Upper Nile, Southern Sudan: course and impact from 1984 to 1994. *Int J Epidemiol* 1996; **25:** 862-871.
63. Harms G, Feldmeier H. HIV infection and tropical parasitic diseases - deleterious interactions in both directions? *Trop Med Int Health* 2002; **7:** 479-488.
64. Alvar J, Canavate C, Gutierrez-Solar B, *et al*. Leishmania and human immunodeficiency virus coinfection: the first 10 years. *Clin Microbiol Rev* 1997; **10:** 298-319.
65. Singh S, Sivakumar R. Recent advances in the diagnosis of Leishmaniasis. *J Postgrad Med* 2003; **49:** 55-60.
66. Sundar S, Reed SG, Singh VP, *et al*. Rapid accurate field diagnosis of Indian visceral leishmaniasis. *Lancet* 1998; **351:** 563-565.
67. Singh S, Gilman-Sachs A, Chang KP, Reed SG. Diagnostic and prognostic value of K39 recombinant antigen in Indian leishmaniasis. *J Parasitol* 1995; **81:** 1000-1003.
68. Zijlstra EE, Nur Y, Desjeux P, *et al*. Diagnosing visceral leishmaniasis with the recombinant K39 strip test: experience from the Sudan. *Trop Med Int Health* 2001; **6:** 108-113.
69. Santos-Gomez G, Gomes-Pereira S, Campino L, *et al*. Performance of immunoblotting in diagnosis of visceral Leishmaniasis in human immunodeficiency virus-Leishmania sp-co-infected patients. *J Clin Microbiol* 2000; **38:** 175-178.
70. Sundar S, Gupta LB, Makaria MK, *et al*. Oral treatment of visceral leishmaniasis with miltefosine. *Ann Trop Med Parasitol* 1999; **93:** 589-597.
71. More B, Bhatt H, Kukreja V, Ainapure SS. Miltefosine: great expectations against Visceral Leishmaniasis. *J Postgrad Med* 2003; **49:** 101-104.
72. Jha TK, Sundar S, Thakur CP, *et al*. Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniasis. *N Eng J Med* 1999; **341:** 1795-1800.
73. Walsh J. Prevalence of Entamoeba histolytica infection. In: Ravdin JI, ed. *Amebiasis: human infection by Entamoeba histolytica*. New York: John Wiley and Sons, 1988: 93-105.
74. Elsdon-Dew R. The epidemiology of amoebiasis. *Adv Parasitol* 1968; **6:** 162.
75. Takahashi T, Gamboa-Dominguez A, Gomez-Mendez TJ, *et al*. Fulminant amebic colitis: analysis of 55 cases. *Dis Colon Rectum* 1997; **40:** 1362-1367.
76. Adams EB, MacLeod IN. Invasive amebiasis: amebic liver abscess and its complications. *Med* 1977; **56:** 325-334.
77. Haque R, Mollan NU, Ali IK, *et al*. Diagnosis of amebic liver abscess and intestinal infection with the TechLab Entamoeba histolytica II antigen detection and antibody tests. *Clin Microbiol* 2000; **38:** 3235-3239.

78. Krupp IM. Antibody response in intestinal and extraintestinal amebiasis. *Am J Trop Med Hyg* 1970; **19:** 57-62.
79. Pehrson PO, Bengtsson E. A long-term follow up study of amoebiasis treated with metronidazole. *Scan J Infect Dis* 1984; **16:** 195-198.
80. Stanley SL. Amoebiasis. Lancet 2003; **361:** 1025-1034.
81. Allan RJ Van, Katz MD, Johnson MB, *et al*. Uncomplicated amebic liver abscess: prospective evaluation of percutaneous therapeutic aspiration. *Radiology* 1992; **183:** 827-830.
82. Ottesen EA, Duke BOL, Karam M, *et al*. Strategies and tools for the control/elimination of lymphatic filariasis. *Bull World Health Organ* 1997; **75:** 491-503.
83. Dreyer G, Medeiros Z, Netto MJ, *et al*. Acute attacks in the extremities of persons living in an area endemic for bancroftian filariasis: differentiation of two syndromes. *Trans R Soc Trop Med Hyg* 1999; **93:** 413-417.
84. Shenoy RK, Sandhya K, Suma TK, Kumaraswami V. A preliminary study of filariasis related acute adenolymphangitis with special reference to precipitating factors and treatment modalities. *Southeast Asian J Trop Med Pub Health* 1995; **26:** 301-305.
85. Das PK, Srividya A, Pani SP, *et al*. Cumulative exposure and its relationship with chronic filarial disease in bancroftian filariasis. *Southeast Asian J Trop Med Pub Health* 1994; **25:** 516-521.
86. Addiss DG, Eberhard MI, Lammie PJ. "Filarial" adenolymphangitis without filarial infection. *Lancet* 1994; **343:** 597.
87. Melrose WD. Lymphatic filariasis: new insights into an old disease. *Int J Parasitol* 2002; **32:** 947-960.
88. Addiss, DA, Dreyer G. Treatment of lymphatic filariasis. In: Nutman TB, ed. *Lymphatic filariasis*. London: Imperial College Press, 1999: 151-199.
89. Mandell G, Bennett JE, Dolin R. *Mandell, Douglas, and Bennet's principles and practice of infectious diseases. 5th ed*. New York: Churchill Livingstone, 2000.

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