Different species of the protozoan *Trypanosoma* are of similar appearance (Figure 1), and all are termed ‘kinetoplastids’ because they move using a flagellum that obtains energy from a mitochondrion called a plastid. However, trypanosomes also differ in many ways, including aspects of their molecular and cellular biology, their transmission, and the diseases that they cause.¹

- Infection with *T. brucei* causes two forms of sleeping sickness in humans (Figure 2) – acute infection of the East African type, caused by *T. b. rhodesiense*, and a more chronic infection caused by *T. b. gambiense* (West African type). Both are fatal if untreated.
- *T. cruzi* infection acquired in Central or South America progresses over many years to Chagas disease in up to 30% of patients.

Sleeping sickness and Chagas disease are neglected, particularly because they are only rarely imported into Europe. Two brothers returning from an East African safari were recently diagnosed with African trypanosomiasis,² but fewer than a dozen cases were diagnosed in Europe in the last 5 years. Chagas disease is even less common in Europe. Both can be transmitted through blood.

**African trypanosomiasis**

**Life cycle and epidemiology**

African trypanosomiasis is transmitted by the tsetse fly (*Glossina* spp.), which is found across Africa in regions south of the

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**What’s new?**

- Short-course (10 days) melarsoprol treatment for stage II African trypanosomiasis is now preferred to longer courses
- New methods for studying drug resistance in trypanosomes are being developed
- Proteomic methods for diagnosis of sleeping sickness are being studied

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Trypanosoma cruzi trypomastigotes. Characteristic ‘C’ shape and posterior kinetoplast. 

Trypanosoma brucei trypomastigotes. (Giemsa-stained human blood films.)

Sahara and north of the Kalahari Desert (14°N and 29°S of the equator). Flies feed on infected mammalian hosts, and parasites taken up with the blood meal develop in the insect (the procyclic form) before multiplying. About 2 weeks later, parasites (termed ‘epimastigotes’ at this stage) migrate to the salivary glands and then transform into the forms infective in humans (the metacyclic form, Figure 3). When the fly next feeds, the parasites are injected and the cycle restarts. The number of individuals with African trypanosomiasis is estimated at 300,000–500,000.

Pathogenesis and clinical features

East African trypanosomiasis progresses more rapidly (over weeks or months) than the West African type, which has a more insidious onset and a protracted course that can last for years. Rhodesiense infection generally produces many more circulating organisms than gambiense, making parasitological diagnosis easier in the former. The number of organisms in the blood also fluctuates widely depending on the immunological response to infection; antibodies that develop to one antigenic type of trypanosome can lyse this type, but do not stop multiplication of organisms of a different type. It therefore takes time for the immune system to respond to new variants. Host inflammatory (cytokine) responses are prominent and may also contribute to the pathophysiology.

There are two stages of infection, determining choice of treatment and attendant risks. It is important to distinguish these.

Haemolymphatic stage (stage I): a few days after the infective tsetse fly bite, and more often in East African than in West African sleeping sickness, a small papule may develop. As the organisms multiply locally, they excite inflammatory responses, and an erythematous tissue reaction with oedema and lymphadenopathy (the ‘chancre’) can follow. However, many patients do not notice this stage of infection. The organisms then invade the haemolymphatic system, where they multiply and are associated with symptoms of fever, rigors, headache and arthralgia. These may be less prominent in gambiense infection.

Lymphadenopathy is common in African trypanosomiasis. When found in, for example, the posterior triangle of the neck (Winterbottom’s sign, Figure 4), it is diagnostically useful, because the parasites can be seen in the fluid, confirming the diagnosis. Involvement of the lymphatic system may be associated with swelling, causing ‘puffy-face syndrome’ or peripheral oedema.

Meningoencephalitic stage (stage II): trypanosomes cross the blood–brain barrier within weeks after stage I in rhodesiense infection and months in gambiense. This begins the sleeping sickness phase, which is associated with personality changes, headaches, withdrawal from the environment and other signs of neurological involvement. Patients find it difficult to perform all but the simplest tasks, and exhibit ‘mental tunnel-vision’. Changes in circadian rhythm include nocturnal insomnia and daytime somnolence. Unless treated, these symptoms progress and are associated with apathy, inanition and, eventually, secondary infections such as pneumonia, heralding death.

<table>
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<th>Principal features of West and East African sleeping sickness</th>
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A third subspecies (Trypanosoma brucei brucei) causes disease in cattle and is considered non-pathogenic in humans.
Life cycles of trypanosomes infecting humans

Trypanosoma cruzi

Ingestion of parasite with blood meal

Defecation of parasite near wound

Trypanosoma brucei

Ingestion of parasite with blood meal

Inoculation of parasite in saliva

Upper cycles show the different stages that occur in the insect vectors. Lower cycles show the different stages in humans and other mammalian hosts. Cellular invasion and presence of clusters of amastigotes in striated muscle is shown for T. cruzi.


Diagnosis

African trypanosomiasis should be suspected (in addition to more common imported infections such as malaria) in patients presenting with an appropriate travel history, perhaps a history of being bitten by tsetse flies, and systemic symptoms of fever. Parasites seen in blood, lymph node fluid or CSF confirm infection, but are difficult to detect in gambiense infection. Samples for direct microscopy must be examined immediately after they are obtained, and in all cases within 20 minutes. Examination for trypanosomes is best undertaken in a specialized centre, but should not delay blood film examination for malarial parasites.

The insidious onset of gambiense sleeping sickness can lead to delayed presentation, perhaps with symptoms of organic psychosis rather than infection. Serological tests such as the card agglutination test for trypanosomiasis can help in diagnosis, but are usually not definitive. More accurate techniques are under development.

All cases of African trypanosomiasis should be staged by CSF examination. Stage II infection is associated with lymphocytic pleiocytosis (usually defined as > 5 cells/µl in CSF and associated with protein > 0.35 g/litre); occasionally, trypanosomes are visible after double centrifugation of CSF samples, and rarely the morular cells of Mott (activated plasma cells) are also visible.

Prevention and management

There is no recommended chemoprophylaxis for African trypanosomiasis. Fly repellents are of limited use against tsetse flies, but wearing bright clothing (avoidance of black or dark blue) can decrease the individual’s attractiveness to flies.

The diagnosis is best confirmed and treatment given in a specialized centre, particularly because the repertoire of available drugs is limited, and they carry a high risk of toxicity and can be difficult to obtain.

American trypanosomiasis (Chagas disease)

Life cycle and epidemiology

T. cruzi is carried by blood-sucking triatome bugs that live in cracks in house walls, in thatched roofs or in palm trees (Figure 3). They feed at night, taking up trypanosomes in the blood meal. The trypanosomes develop into epimastigotes in the hind-gut of the insect and are transmitted at the next meal, when they are
Treatment of African and American trypanosomiasis

African trypanosomiasis

Stage I
- Pentamidine (an aromatic diamidine), 4 mg/kg i.m. daily or on alternate days for seven to ten injections, is suitable for gambiense infection. These painful injections are associated with risks of hypotension and shock, pancreatic, renal or hepatic dysfunction, bone marrow suppression and polyneuropathy.
- Suramin (an acidic hexasulphated naphthylamide), day 1 test dose of 4–5 mg/kg (given as an infusion in 5% dextrose) followed by 20 mg/kg (maximum 1 g) on days 3, 10, 17, 24 and 31, is preferred in rhodesiense infection. Side-effects include renal impairment, peripheral neuropathy and bone marrow suppression.

Stage II
- Melarsoprol (a trivalent arsenical), 2.2 mg/kg on days 1–10 given by slow intravenous injection. Encephalopathy is common (5–14%), often occurring after three or more doses. Pre-treatment with prednisolone, up to 40 mg/day, may reduce the incidence of this complication.
- Eflornithine (a fluorinated analogue of ornithine that inhibits parasite ornithine decarboxylase), 100 mg/kg infused over 30 minutes every 6 hours for 14 days. This is an expensive drug that is usually reserved for melarsoprol-refractory gambiense infection, because it is less effective in rhodesiense infection.

Acute Chagas disease
- Benznidazole (a nitroimidazole), 5–10 mg/kg/day in two divided doses for 30–60 days
- Nifurtimox (a nitrofuran derivative), 8–10 mg/kg in three divided doses after meals for 30–120 days


Pathogenesis and clinical features

Early phase: local oedema and lymphadenopathy occur at the site of inoculation (chagoma). Periorbital oedema (Romaña’s sign) develops when infection begins in the eye. After about 2 weeks, a toxæmic phase may ensue and accompany the first waves of parasitaemia, though this phase can be asymptomatic. Severe cardiac involvement at this stage can cause death.

Chronic phase: once established, T. cruzi infection becomes predominantly intracellular, with few if any symptoms. Diagnosis in this ‘indeterminate’ stage is particularly difficult. In about 15–30% of individuals, the infection progresses silently to the symptomatic chronic phase; 10–20 years after inoculation, symptoms begin to develop, reflecting the organs involved. Severely disabling complications occur that can be managed only symptomatically.
- In the heart, pseudocysts gradually destroy conducting fibres, ganglion cells and muscle, leaving a dilated heart (cardiomyopathy) with conduction defects such as right bundle and bifascicular block.
- In the intestinal tract, destruction of the intramural parasympathetic plexus causes dilatation of the intestinal organs leading to, for example, mega-oesophagus and megacolon.
- In the urinary tract, mega-ureter may develop.

Diagnosis
Diagnosis is difficult, because the parasites are often scanty in blood in the acute phase of infection. Tissue biopsy may show intracellular parasites (amastigotes), or xenodiagnosis using laboratory-raised bugs fed on patient blood can show epimastigotes in the gut after some weeks. Serological tests can be useful for screening.

Prevention and management
Prevention is by eliminating the insect vector and avoidance of bites. There are two available drugs (Figure 5) used in the early and indeterminate stages of infection. There are no effective drugs for the late stage.

REFERENCES