African sleeping sickness

Human African trypanosomiasis is a parasitic disease, found only in sub-Saharan Africa, transmitted by tsetse flies. Disease is caused by an extracellular protozoan belonging to the species *Trypanosoma brucei*. Two subspecies of *T. brucei* are pathogenic in humans: *T. b. gambiense* and *T. b. rhodesiense*. Although both pathogens cause human African trypanosomiasis, they should be considered as two distinct diseases with very separate epidemiological and clinical patterns plus different treatments.

T. b. gambiense accounts for 98% of human African trypanosomiasis infections. It is found in west and central Africa, and typically causes a chronic disease syndrome. *T. b. rhodesiense* is found in east and southern Africa and causes a small minority of reported human African trypanosomiasis infections which present as acute and rapidly progressive disease. Sleeping sickness is a colloquialism often used to encompass both forms of human African trypanosomiasis but alludes to the late meningo-encephalitic phase common to both. Other pathogenic trypanosomal species are recognized including *T. cruzi*, which causes Chagas disease, exclusive to the Americas, but will not be discussed in this article.

Pathogenesis

Parasite and life cycle

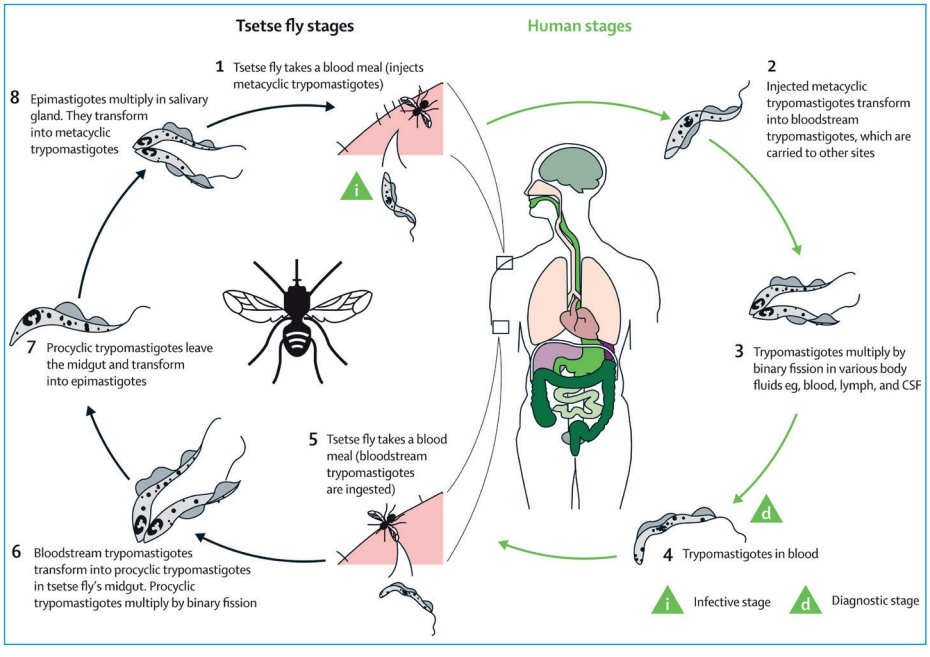
Trypanosomes are unicellular extracellular parasites. Humans are the main reservoir of anthroponotic (i.e. mostly transmitted human to human) *T. b. gambiense* subspecies. Wild animals and cattle are the main reservoir of zoonotic (i.e. mostly transmitted animal to human) *T. b. rhodesiense*. Tsetse flies are the only vector for transmission of human African trypanosomiasis. During a blood meal an infected tsetse fly injects trypomastigotes into host skin (*Figure 1*). These enter regional lymph nodes to reach the bloodstream and potentially the CSF. They multiply in all compartments by binary fission. When ingested by a tsetse fly, metacyclic trypomastigotes reach the midgut, replicating and transforming into procyclic trypomastigotes. These migrate to the salivary gland of the fly some 3 weeks later where they become epimastigotes and finally new infective metacyclic trypomastigotes (*Figure 1*).

The metacyclic form is characterized by a variant surface glycoprotein coat that protects the parasite membrane. Each trypanosome genome has over 1000 variant surface glycoprotein genes and trypanosomes are capable of rapid antigenic variation (Barry et al, 2012). A sub-population of bloodstream parasites may be killed but residual trypanosomes can express different variant surface glycoproteins to evade host immune responses, precipitating waves of rebound parasitaemia.

Vector and transmission

Trypanosomes are transmitted by tsetse flies of the genus *Glossina*. There are 30 species and subspecies that all transmit *T. brucei* with varying degrees of efficiency (Marquardt, 2004). Both male and female flies are vectors. Any activity that increases the likelihood of host–vector contact makes parasite transmission more likely. *T. b. gambiense* is principally an infection of native

Figure 1. Life cycle of human African trypanosomiasis. From Centers for Disease Control (2015).



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> Human African trypanosomiasis is a focal disease; transmission can only occur within a circumscribed geographical area, where the environment is adequate for parasite, reservoir, vector and host

work-aged adults acquired during hunting, fishing, forest clearing, mining or simply washing clothes. *T. b. rhodesiense* affects local populations but is also recognized in tourists typically visiting east African animal reserves especially in Tanzania (Jelinek et al, 2002; Moore et al, 2002). Transmission rates are highest during the rainy season when *Glossina* populations peak.

Epidemiology

In the last century there have been three catastrophic epidemics. The second outbreak in the 1920s prompted systematic surveillance and treatment of cases to the point of near-eradication of human African trypanosomiasis by the 1960s. Subsequent civil unrest in human African trypanosomiasis-endemic countries, with collapse of health systems and large-scale displacement of populations, has seen a resurgence of the disease since the 1970s. By 1997 approximately 300 000 cases had been reported (Anon, 1998). Intervention by the World Health Organization reduced reported cases to 6228 in 2013 (Franco et al, 2014). The real annual incidence of human African trypanosomiasis in endemic regions is likely to be closer to 20 000 cases as remote rural areas make rigorous diagnosis and study challenging (World Health Organization, 2013).

Human African trypanosomiasis is a focal disease; transmission can only occur within a circumscribed geographical area, where the environment is adequate for parasite (trypanosome), reservoir (humans and animals), vector (tsetse fly) and host (humans) (Franco et al, 2014). There are 360 discrete human African trypanosomiasis foci across 36 sub-Saharan countries (Simarro et al, 2012). These foci have remained relatively stable over time but incidence and distribution are sensitive to sociopolitical upheaval that alters local environments.

T. b. gambiense is found in west and central Africa. Since 2009 it has accounted for 98% of all new cases of human African trypanosomiasis; 82% reported in the Democratic Republic of Congo (Simarro et al, 2012; World Health Organization, 2013). Prevalence rates are typically between 1 and 5% in endemic areas (Pépin and Méda, 2001). *T. b. rhodesiense* is found in east and southern Africa, accounting for approximately 2% of new human African trypanosomiasis cases, with 67% detected in Uganda. Across the continent it is estimated that nearly 70 million individuals are at risk of human African trypanosomiasis infection(Simarro et al, 2012). The classical geographical separation of the two forms of human African trypanosomiasis conforms approximately to the location of the Rift valley.

Clinical features

Clinical disease differs between the two subspecies: *T. b. gambiense* evolves slowly; *T. b. rhodesiense* is more acute. However, both subspecies manifest two distinct stages: early infection or first stage, and late CNS infection or second stage.

Early infection: stage one

Both subspecies may present with chancre, a painful itchy nodule, at the site of tsetse fly bite approximately 1 week after inoculation. These are rare in *T. b. gambiense* and resolve typically by 2 weeks. From 6–8 weeks after infection a different transient erythematous, urticarial or macular rash on the trunk may be seen (McGovern et al, 1995). Stage one is characterized by non-specific systemic features: fever, malaise, myalgia, arthralgia and pruritus. Lymphadenopathy is a cardinal sign with cervical groups most commonly affected. Winterbottom's sign describes soft mobile posterior cervical nodes (Kennedy, 2013).

Other features associated with systemic early infection include hepatosplenomegaly, myopericarditis and adrenal insufficiency (Maudlin et al, 2004). Stage one is more florid in *T. b. rhodesiense* infection, behaving more like undifferentiated sepsis, and may progress over months to death. Early *T. b. gambiense* infection lasts approximately 3 years and is more clearly demarcated from stage two or late infection (Checchi et al, 2008).

Late infection: stage two

Late infection, or stage two human African trypanosomiasis, principally describes meningo-encephalitis. Marked disruption of circadian sleep patterns is a hallmark of human African trypanosomiasis with chaotic fragmented sleeping behaviour. It may present initially as apparent psychiatric illness. Later, a wide range of neurological symptoms and signs is recognized: restlessness, dysphasia and ataxia, sensory disturbances (Kennedy, 2006). Death is inevitable without therapy and is characterized by progressive dementia and fluctuating consciousness. Social isolation and inability to self-care leads to cachexia and often to opportunistic infection (Blum et al, 2006).

Diagnosis

T. b. gambiense

Three stages of diagnosis are used: screening using clinical assessment and/or serology testing, microscopy confirmation and disease staging.

In the field, screening for trypanosomal antibody is undertaken using the card agglutination test for trypanosomisais. Confirmation of the diagnosis is made by microscopy of peripheral blood, lymph nodes or CSF. In areas where resources permit, antibody detection is possible using immunofluorescence antibody test or enzyme-linked immunosorbent assay.

Microscopic diagnosis is made by examining fresh, wet preparations of peripheral blood or CSF. Giemsa-stained smears of chancre aspirate, lymph node aspirate, peripheral blood smears, buffy coat preparations or CSF are also performed. Fluorescence microscopy of peripheral blood using the quantitative buffy coat is more sensitive then conventional microscopy and is comparable to the mini anion-exchange centrifugation technique in sensitivity. Microscopy must be performed on fresh samples to avoid lysis of trypanosomes ex vivo.

Polymerase chain reaction for trypanosome DNA is available in only a few centres at present.

T. b. rhodesiense

Serological testing is of limited value in the diagnosis of *T. b. rhodesiense* infection. In stage one infection, trypanosomes are quite numerous, so diagnosis is usually

straightforward using conventional parasitology techniques provided the microscopist is familiar with their appearance. This may not be the case in non-endemic areas where the disease is seen very infrequently.

Staging of human African trypanosomiasis requires CSF examination and is indicated in all patients to confirm or exclude stage two disease. CSF sampling should only be undertaken after therapy for stage one has rendered blood samples aparasitaemic. This should avoid seeding of parasites into the CSF during potentially traumatic lumbar puncture. According to World Health Organization recommendations, the presence in CSF of more than five white blood cells per µl, trypanosomes, or increased protein content (>370 mg/litre) defines second-stage disease (Brun et al, 2010). High immunoglobulin M level in CSF also strongly supports CSF infection. The clinical significance of polymerase chain reaction-positive CSF remains controversial.

Treatment

All patients diagnosed with human African trypanosomiasis should receive treatment. Choice depends upon the infecting subspecies and the stage of the disease (*Table 1*). All drugs, apart from pentamidine and prednisolone, are unlicensed but available via the World Health Organization in the UK.

Infection prevention

There is no vaccine or chemoprophylaxis available for human African trypanosomiasis; awareness of risk and insect bite avoidance is the only method of prevention. Humans are the significant disease reservoir for *T. b. gambiense*, so active case finding followed by treatment remains fundamental to disease control. *T. b. rhodesiense* infects a variety of animal hosts, therefore vector control is the primary strategy used via traps, screens, fly attractants and insecticides.

Advice to travellers

Human African trypanosomiasis is very low risk for travellers: between 2000 and 2012 16 cases were reported in the UK (Public Health England, 2012). However, travellers working in or visiting woodland and savannah areas, particularly game parks in central and east Africa, are at risk. The following prevention advice is recommended:

Table 1. Human African trypanosomiasis treatment according to subspecies and stage of infection

	T. b. gambiense	T. b. rhodesiense
Stage 1	Pentamidine deep intramuscular injection preferred* or slow intravenous infusion 4 mg/kg daily for 7 days Treat until aparasitaemic before lumbar puncture Adverse effects: hypoglycaemia (up to 40% patients)†, hypotension, prolonged QT syndrome, gastrointestinal upset	Suramin slow intravenous infusion Day 1: 5 mg/kg, day 3: 10 mg/kg, days 5, 11, 17, 23, 30: 20 mg/kg Maximum 1 g per dose (doses up to 1.5 g have been used but expert opinion suggests little advantage >1 g) In view of the anaphylaxis risk with suramin, the first dose is given as a 2-hour infusion under close monitoring to allow the infusion to be stopped if necessary Treat until aparasitaemic before lumbar puncture Adverse effects: rare acute hypersensitivity (first dose given as a test dose as above), nephrotoxicity (monitor for proteinuria before each dose), peripheral neuropathy, bone marrow toxicity (all reversible)
Stage 2	Nifurtimox‡ oral and eflornithine intravenous infusion (given over a minimum of 45 minutes) Eflornithine 200 mg/kg twice daily for 7 days plus nifurtimox 5 mg/kg three times daily for 10 days Stagger doses to reduce side effects Adverse effects: bone marrow toxicity (anaemia, leucopenia, thrombocytopenia up to 50% patients), seizures (up to 7%), gastrointestinal upset	Melarsoprol§ slow intravenous infusion and oral prednisolone ¶ Prednisolone 40 mg daily oral, starting 24–48 hours before first dose of melarsoprol and continuing for duration of melarsoprol treatment, then wean over 6 days Melarsoprol 2.2 mg/kg daily for 10 days The patient should be in the supine, fasting state during injection and for several hours after administration Adverse effects: encephalopathy (up to 10% patients with 50% mortality), skin reactions, thrombophlebitis at injection sites, hepatotoxicity, peripheral neuropathy
	Eflornithine intravenous infusion 100 mg/kg four times daily for 14 days	

*adapted from Hospital of Tropical Diseases guidelines October 2012 (unpublished). *After intravenous infusion, plasma levels of pentamidine fall rapidly during the first 2 hours to one twentieth of peak levels, followed by a much slower decline thereafter. After intramuscular administration, the apparent volume of distribution of pentamidine is significantly greater (>3 times) than that observed following intravenous administration (Sanofi, 2014). † Pentamidine safety data are limited and are derived largely from studies in HIV-positive individuals where treatment was not for human African trypanosomiasis. High blood pentamidine levels predict dysglycaemia, but this is most common in the setting of concurrent renal and/or liver dysfunction. Increasing cumulative dose significantly predicts hypoglycaemia but higher daily dosage may not (O'Brien et al, 1997). The summary of product characteristics for pentamidine quotes common risk (≥ 1/100 to < 1/10) for both hypo- and hyperglycaemia. Fasting blood glucose measurements daily during therapy and at regular intervals after completion of therapy are indicated. Hyperglycaemia and diabetes mellitus, with or without preceding hypoglycaemia, have occurred up to several months after cessation of therapy but the relative risk is unknown. ‡ Nifurtimox is registered for the treatment of American trypanosomiasis but not for human African trypanosomiasis. Nevertheless, after safety and efficacy data provided by clinical trials, its use in combination with eflornithine has been accepted and included in the WHO List of Essential Medicine, and it is provided free of charge for this purpose by WHO to endemic countries. § Melarsoprol can also be used to treat* T. b. gambiense *with a different dosing regimen. ¶Prednisolone is used as an adjunct to prevent melarsoprol encephalopathy. The drugs used for stage one are less toxic and easier to administer, plus, the earlier disease is identified and treated, the better the prospect of cure. Treatment success in stage 2 depends upon the drug's ability to cross the blood–brain barrier, and entails more complex administration with more toxic side effects. In addition, melarsoprol resistance may be as high as 30% in some areas (Brun et al, 2001). Cure rate of stage 2 disease for both subspecies after one cycle of treatment is in excess of 90% (Priotto et al, 2009; Kuepfer et al, 2012). After treatment, patients require follow-up examination of their CSF for 2 years to detect relapse (Centers for Disease Control, 2016).*

KEY POINTS

- Human African trypanosomiasis is very low risk in travellers but remains a significant cause of morbidity and mortality in remote focal areas of sub-Saharan Africa in working-aged adults.
- *Trypanosoma brucei rhodesiense* subspecies is less common, often causing prominent early infection which progresses to late CNS infection over months.
- *T. b. gambiense* subspecies accounts for more than 90% of cases of human African trypanosomiasis in Africa, causing milder acute disease and has a more discrete late CNS phase of illness that progresses over years.
- Initial diagnosis includes serology and microscopy; CSF studies (disease staging) are indicated in all confirmed cases to exclude CNS disease.
- Treatment of human African trypanosomiasis depends upon subspecies and stage of disease and is fatal without treatment.

- Inspect vehicles before entering. Tsetse flies are attracted to the motion and dust from moving vehicles. Windows should remain closed when driving through endemic areas
- Avoid bushes. The tsetse fly is less active during the hottest part of the day and rests in bushes.
- Take insect bite avoidance measures. Tsetse flies are capable of biting through loose weave fabrics. Insecticide-treated close weave, wrist or ankle-length khaki- or olive-coloured clothing is advised. Tsetse flies are attracted to very dark or bright colours, particularly blue, and metallic fabric.

USEFUL RESOURCES

Burri C, Brun R (2014) Human African Trypanosomiasis. In: Cook GC, Zumla A, eds. *Manson's Tropical Diseases*. Saunders, London

World Health Organization – Human African trypanosomiasis www.who.int/trypanosomiasis_african/en/

Centers for Disease Control and Prevention www.cdc.gov/parasites/sleepingsickness/index.html

- Many insect repellents are ineffective; repellents containing at least 30% DEET should be applied. If sunscreen is used, repellent must be applied after sunscreen
- Sleep in screened or air-conditioned rooms
- Travellers to endemic areas, who experience bites and become unwell, should seek prompt medical care.

Conclusions

There remains a risk of resurgent human African trypanosomiasis caused by *T. b. gambiense* if control measures become disrupted. Sporadic cases of *T. b. rhodesiense* human African trypanosomiasis will continue to occur in travellers visiting from non-endemic areas. There is a risk of missed diagnoses because of the non-specific nature of most of the clinical features of human African trypanosomiasis.

Malaria is an important differential diagnosis and laboratory staff examining blood films for trypanosomes should actively look for the presence of malaria parasites and vice versa. **BJHM**

Figure 1 *is reproduced with permission of CDC, Life cycle image and information courtesy of DPDx.*
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