CHAPTER 27

# Human African Trypanosomiasis (Sleeping Sickness)

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Human African trypanosomiasis (HAT), or African sleeping sickness, is a parasitic infection caused by the flagellated protozoa of the *Trypanosoma brucei* complex, which is spread by the tsetse fly. Sleeping sickness occurs in more than 30 countries in Africa, putting 60 million people at risk of infection. HAT ranks third among the world's most important parasitic diseases, behind malaria and schistosomiasis, in calculated disability-adjusted life years (DALYs) lost (Kennedy 2008), and as a result it remains on the World Health Organization (WHO) list of neglected tropical diseases. The most affected countries include the Democratic Republic of the Congo (DRC), which accounts for more than 70% of cases; South Sudan; Angola; the Central African Republic (CAR); Uganda; Tanzania; Malawi; and Zambia (Barrett et al, 2003; Krishna and Stitch, 2012). The past several years have shown progress toward the elimination of HAT, though this disease remains a public health threat in many areas of Africa, especially those that are plagued by poverty, conflict, and lack of effective governmental control.

## EPIDEMIOLOGY

In 1995, the WHO's Expert Committee on Trypanosomiasis estimated that there were approximately 300,000 new cases of HAT in Africa each year and that less than 10% of these cases were appropriately diagnosed and treated (WHO, Human African Trypanosomiasis). The number of new cases reported annually has decreased significantly in recent years, with 2009 marking the first time in more than 50 years that less than 10,000 new cases were reported. A further decrease was seen in 2010, with the WHO reporting only 7,139 cases that year. Although there has been a general decrease in disease prevalence, disease transmission is characterized by focal epidemics during periods of political unrest, war, and famine—largely due to decreased surveillance and treatment (Kennedy 2008).

Transmission of HAT requires the presence of a competent vector, the tsetse fly (*Glossina* species). These insects are found in warm, shaded areas in a geographic region between 14° North and 19° South of the equator in Africa (Kennedy 2004). They inhabit an area that covers approximately one-third of Africa's landmass and is roughly the size of the United States (Kennedy 2008). The average lifespan of a tsetse fly is between 1 and 6 months, and once a fly is infected, it remains so for life (Kennedy 2004). Although an infected tsetse fly remains a vector for disease transmission for the duration of its lifecycle, the trypanosome undergoes complete transformation in only about 10% of infected flies (Berriman et al. 2005).

While exclusively endemic to the African continent, there are approximately 50 cases of HAT per year diagnosed outside Africa, mostly in travelers returning from visits to East African game reserves (Kennedy 2008).

## PATHOGEN/LIFECYCLE

There are two forms of HAT, both of which are transmitted by the bite of the tsetse fly. The disease caused by the species *Trypanosoma brucei rhodesiense* occurs mostly in Southern and Eastern Africa (and therefore is often referred to as "East African sleeping sickness") and causes a more rapidly progressive disease, while infection with *Trypanosoma brucei gambiense* occurs mostly in West and Central Africa ("West African sleeping sickness") and leads to a more chronic form of disease. In either case, the infected tsetse fly bites its host, thereby injecting metacyclic trypomastigotes into the skin (Kennedy 2004). The trypomastigotes then transform into bloodstream trypomastigotes, allowing them to travel throughout the body, where they multiply by binary fission (CDC, Parasites—African Trypanosomiasis). To complete the lifecycle, the host must then be bitten by another tsetse fly. During the second ingestion, the trypomastigotes move to the midgut of the fly where they transform and, after approximately 3 weeks, migrate to the salivary gland of the tsetse fly. In the salivary gland, they undergo a final transformation to the infective form, which allows them to be transmitted to another host with the next meal (**Fig. 27.1**).

The genome of *T. brucei* was fully sequenced in 2005. It contains approximately 9000 genes, with 10% of these coding for variable surface glycoproteins. The lifecycle of *T. brucei* involves near continuous modulation of these proteins, which allows the parasite to rapidly switch expression of surface proteins to constantly evade host immune responses, a process known as antigenic shift (Kennedy 2008). As a result, there are typical waves of parasitemia that occur with each antigenic shift, and then subside as the immune system begins to develop a response.

## CLINICAL MANIFESTATIONS

Trypanosome infection involves both an early, or hemolymphatic, stage and a late stage in which there is central nervous system (CNS) involvement. In *T.b. gambiense* infection, this is a slowly progressive process marked by indolent symptoms that persist for months to years. In *T.b. rhodesiense*, there is a more rapid progression, often associated with early onset of CNS involvement (Barrett et al. 2003) (**Table 27.1**).

In either form of disease, a trypanosomal chancre may be the herald of infection and typically appears about 5-15 days after a tsetse fly bite. These are well-circumscribed, painful, indurated lesions at the site of the bite and are more common with *T.b. rhodesiense* than *T.b. gambiense* infections (**Fig. 27.2**).

For 1-3 weeks after the initial bite, the trypanosome parasites spread through the bloodstream and lymph nodes in the hemolymphatic stage of infection. It is during this stage that trypomastigotes can be seen on blood smear.

Early symptoms of disease are nonspecific and include fevers, malaise, headaches, and arthralgias. Symptoms may coincide with waves of parasitemia as the trypanosomes undergo antigenic variation, thus evading host immune response. Conversely, symptoms may temporarily subside as the immune system begins to develop a response. This leads to nonspecific polyclonal B cell activation with large production of IgM and resultant enlargement of the spleen and lymph nodes (Kennedy 2004). Diffuse lymphadenopathy, hepatomegaly, and, more commonly, splenomegaly, are often present. Lymphadenitis can occur anywhere, but in the *T.b. gambiense* form it is classically seen in posterior cervical nodes, with painless enlargement of these mobile nodes referred to as Winterbottom sign (Barrett et al. 2003). This phase can last up to 3 years in the *T.b. gambiense* form, whereas *T.b. rhodesiense* is more rapidly progressive and can lead to death within weeks or months (Malvy and Chappuis 2011). Other nonspecific symptoms that are recognized include pruritus, rash, weight loss, and facial swelling (Barrett et al. 2003).

Because the trypomastigotes can pass through blood vessel walls, they easily spread into connective tissue and can enter the cerebrospinal fluid (CSF) (Kennedy, 2004). Progression to the second stage of infection (the "late" or encephalitic stage) occurs when parasites cross the blood–brain barrier. This may happen within weeks in *T.b. rhodesiense* infection or

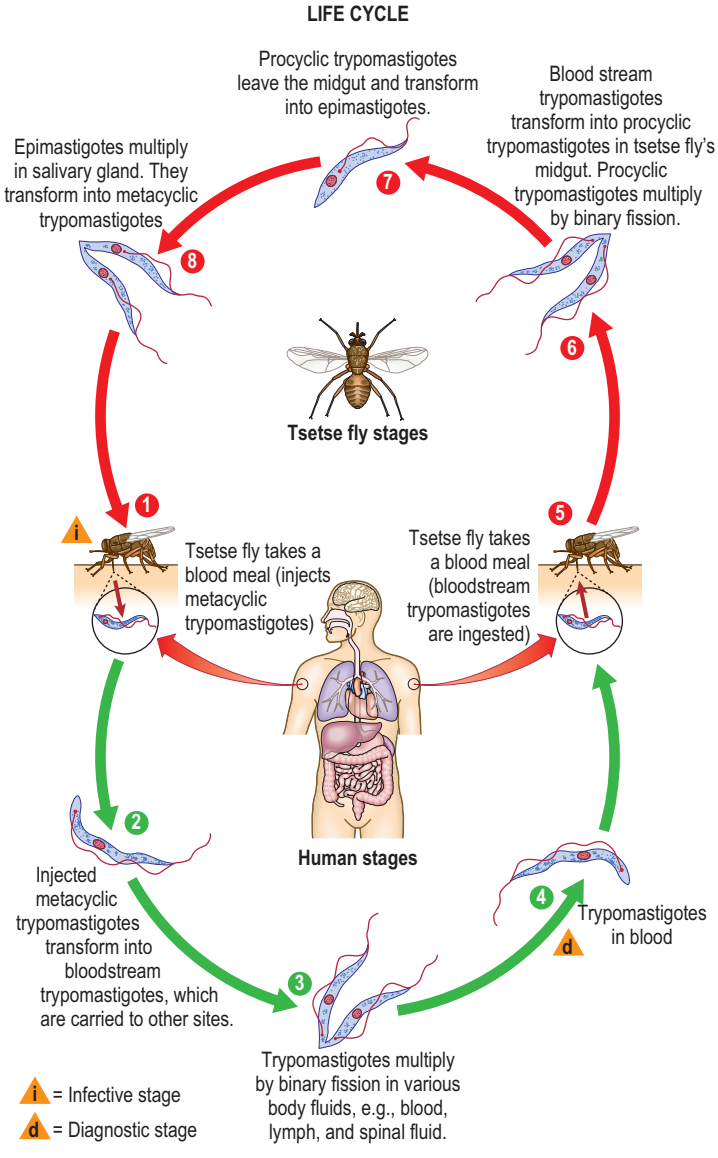


**Fig. 27.1 Lifecycle and transmission of trypanosomiasis.** (From: http://www.cdc.gov/parasites/sleepingsickness/biology.html.)

**TABLE 27.1 Routes of Trypanosome Infection**

| | *T.b. rhodesiense* | *T.b. gambiense* |
|---|---|---|
| Location | East Africa | West and Central Africa |
| Reservoir | Animals: wild game, cattle | Humans (domestic pigs) |
| Progression | Weeks to months | Months to years |

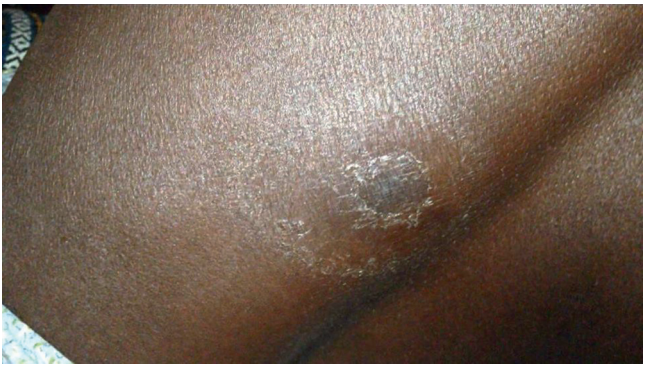

**Fig. 27.2 Trypanosomal chancre on the back of a patient with human African trypanosomiasis, Uganda 2013.** (Courtesy of N. Stone.)

months in *T.b. gambiense* infection. This stage is defined by increased white blood cells (WBCs) in the CSF.

Clinically, stage II disease manifests as a progressive, diffuse meningoencephalitis, which can have a broad range of features, including headaches, poor concentration, difficulty completing tasks, psychosis, personality change, tremor, and/or ataxia. One of the hallmarks of late disease is alteration in the normal circadian rhythm, with reversal of the sleep–wake cycle, hence the name "sleeping sickness." Convulsions may occur as the disease progresses, especially in children, though meningismus and focal neurologic signs are often absent (Barrett et al. 2003). As the disease progresses, there is clinical deterioration until coma or stupor results. Wasting and cachexia are common. Stage 2 disease is universally fatal without treatment.

## TESTING AND DIAGNOSIS

Because clinical features are nonspecific, diagnosis depends on appropriate laboratory testing. Numerous nonspecific laboratory findings are associated with HAT infection. Common findings include anemia, leukocytosis, and thrombocytopenia, likely due to splenic sequestration (Barrett et al. 2003). Hypergammaglobulinemia with polyclonal IgM is characteristic. Other common findings include elevated erythrocyte sedimentation rate and C-reactive protein, and hypoalbuminemia.

There is neither antigen nor antibody testing for *T.b. rhodesiense*. Antibody testing is available for *T.b. gambiense* but is not sufficient for definitive diagnosis. The most frequently used detection method is the card agglutination test for *T.b. gambiense* (CATT), which relies on the agglutination of trypanosomes and antibodies and has a sensitivity of 94-98% (Truc et al. 2002). This test is not available in the United States but is often used in large-scale

screening programs in endemic areas. All patients with a positive CATT require further evaluation.

Definitive diagnosis requires detection of parasites in blood, CSF, or lymph node aspirates. Microscopic detection of parasites is relatively straightforward and more widely available than serologic testing. Diagnosis is often made incidentally, with trypanosomes being visualized on a smear done to look for malaria parasites, as HAT is often clinically suspected to be malaria in early stages. Because *T.b. rhodesiense* disease is often associated with a high parasite load, parasites are usually seen on microscopy. When available, examination of the buffy coat from centrifuged specimens can increase sensitivity if parasite counts are low and organisms are not easily seen (CDC, Parasites—African Trypanosomiasis). *T.b. gambiense* is more difficult to detect and has been traditionally tested via biopsy of suspicious enlarged posterior lymph nodes when present. Serologic testing for *T.b. gambiense* may be useful in screening programs but requires confirmation for definitive diagnosis (see below). If initial testing is negative and clinical suspicion remains high, repeat smears should be collected on subsequent days, as parasitemia fluctuates during the course of disease due to antigenic shift and immune response (**Fig. 27.3**).

CSF testing is essential in anyone with suspected diagnosis of HAT both to confirm and to stage the disease. Typical CSF findings include pleocytosis, elevated protein, and increased opening pressure (Barrett et al. 2003). A rare but pathognomonic finding is the presence of eosinophilic plasma cells with high levels of IgM, or so-called morula cells of Mott (Lejon and Buscher 2005). It may also be possible to visualize trypanosomes in the CSF. Antitrypanosomal antibody testing has been developed for CSF analysis, but these tests lack sensitivity and it is generally felt that a WBC count >5-6 or high levels of IgM in the CSF are the most sensitive markers for CNS involvement (Lejon and Buscher 2005).

Both antigen detection via enzyme-linked immunosorbent assay testing and polymerase chain reaction-based testing methods have been developed but are not yet commercially available. Other clinical tests, such as magnetic resonance imaging and electroencephalography, may show nonspecific abnormalities but are not yet widely available in endemic areas at this time.

## TREATMENT

Treatment for HAT is based on the type and stage of infection. CSF analysis should always be performed, even in the absence of CNS symptoms, in order to stage the infection. All

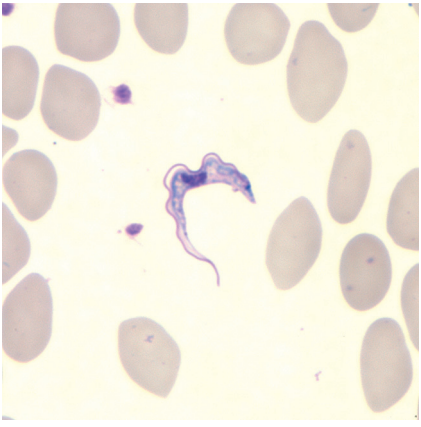

**Fig. 27.3 Trypanosome in blood smear.** (From: CDC Public Health Image Library/Blaine Matheson ID 11820.)

**TABLE 27.2 Treatment of Trypanosomiasis**

| | Stage 1 (Hemolymphatic stage) | Stage 2 (CNS involvement) |
|---|---|---|
| *T.b. gambiense* | Pentamidine | Nifurtimox plus Eflornithine combination therapy |
| *T.b. rhodesiense* | Suramin | Melarsoprol |

*CNS*, Central nervous system.

of the drugs used to treat HAT are toxic, and appropriate therapeutic monitoring is indicated. As such, any patient diagnosed with HAT should consult with an expert and ideally transferred to a specialist center with experience in treating this rare and potentially life-threatening infection. Patients will often require admission to an intensive care setting, particularly those presenting with stage 2 disease (i.e., CNS involvement).

Antitrypanosomal drugs are generally not routinely available. In the United States, melarsoprol, eflornithine, and suramin are available from the CDC, which can also provide specialist treatment advice (telephone 404-718-4745; email parasites@cdc.gov). Pentamidine is more widely available.

It is crucial to determine both the stage of infection and the species of trypanosomes causing infection (*T.b. gambiense* or *T.b. rhodesiense*), as this has significant consequences for the selection of treatment, as summarized in **Table 27.2**. A careful travel history and knowledge of the geographical distribution of each subspecies is therefore essential, as this is usually sufficient information to make an initial treatment decision while awaiting laboratory confirmation. Awaiting laboratory sub-speciation should not delay the initiation of treatment, especially when the travel history is suggestive of East African (*T.b. rhodesiense*) trypanosomiasis, which tends to run a more aggressive clinical course.

As a neglected tropical disease, there is a paucity of clinical trial data to guide treatment strategies, although there have been recent advances in this respect. Randomized trial data is now available for second stage *T.b. gambiense* infection; however, particularly in the case of stage 2 *T.b. rhodesiense* trypanosomiasis, the optimal therapy often remains at the level of expert opinion on a case-by-case basis. **Treatment regimens vary considerably depending on local and national guidelines. The doses given in this chapter are given as a guide only—each case should be discussed with an expert in managing the disease**.

## Treatment of *T.b. gambiense* Trypanosomiasis

### *Stage 1*

Pentamidine

Dose 4 mg/kg/day IV or IM for 7-10 days

Pentamidine has poor CNS penetration and limited activity against *T.b. rhodesiense*, therefore its indication is confined to early-stage *T.b. gambiense* infection; it has been used in this capacity since the 1940s. It is generally well tolerated, but side effects are common. The intravenous route is associated with hypotension and is irritating to veins; therefore, central venous access may be required. A slow infusion, over 2 hours, can reduce the risk of hypotension. Other significant adverse reactions include hypo- and hyperglycemia, electrolyte disturbance (particularly hyperkalemia), and cardiac dysrhythmias including QT interval prolongation. Nephrotoxicity can occur with prolonged use, as can leukopenia and thrombocytopenia. Liver enzymes may also be elevated. Careful blood glucose, blood count, and blood chemistry monitoring is therefore required.

Intramuscular administration is painful and can lead to sterile abscess, although is less likely to cause hypotension and is widely administered this way in resource-limited settings.

### *Stage 2*

Nifurtimox/Eflornithine Combination Therapy (NECT)

In a landmark clinical trial by Priotto et al. (2009), which evaluated a cohort of 103 adults with stage 2 *T.b. gambiense* trypanosomiasis in the DRC, researchers demonstrated non-inferiority of a combination of eflornithine of 200 mg/kg intravenously every 12 hours for 7 days plus nifurtimox (15 mg/kg/day orally every 8 hours for 10 days) as compared with a 14-day course of eflornithine at a dose of 400 mg/kg/day intravenously in four divided doses for 14 days. It was a remarkable achievement to perform a randomized trial in such a challenging setting, and its results have changed practice. NECT is less toxic and less costly than 14 days of IV eflornithine, and as such it has since been placed on the WHO list of essential medicines. NECT is therefore now the recommended treatment regimen for stage 2 West African HAT.

Nifurtimox

15 mg/kg/d orally in three divided doses for 10 days (given in combination with eflornithine)

Significant side effects are primarily gastrointestinal, with anorexia, weight loss, nausea, and vomiting commonly experienced. Neurological side effects include dizziness, headaches, insomnia, myalgia, and paresthesias. Occasionally, leukopenia can occur, warranting CBC monitoring.

Eflornithine

200 mg/kg IV every 12 hours for 7 days (given in combination with nifurtimox)

Numerous side effects have been observed with parenteral eflornithine, including dizziness, headache, arthralgias, cardiac arrhythmias, pruritus, nausea, vomiting, abdominal pain, and neutropenia.

Staggering the doses of nifurtimox and eflornithine is recommended, as concurrent administration of the two potentially toxic medications is associated with more severe side effects.

## Treatment of *T.b. rhodesiense* Trypanosomiasis

### *Stage 1*

Suramin

1 g IV on days 1, 3, 7, 14, and 21 (*Note*: local and national guidelines may vary on precise dosing intervals)

Suramin has been in clinical use for nearly a century, having been discovered in 1916. It is given intravenously at a dose of 1 g on days 1, 3, 7, 14, and 21. There is a small risk of an anaphylactic reaction, therefore a test dose of 100 mg is recommended prior to initiating full dose therapy. Nephrotoxicity, myelosuppression, and peripheral neuropathy have been reported but are uncommon side effects. It is generally well tolerated; however, it does not cross the blood–brain barrier and therefore is not effective in stage 2 trypanosomiasis—highlighting the critical importance of CSF testing for appropriate staging prior to initiation of treatment.

Pretreatment with suramin prior to lumbar puncture is performed in some centers, because there is a theoretical risk that performing a lumbar puncture can mechanically introduce trypanosomes from the bloodstream into the central nervous system. This must be weighed against a delay in staging the infection. Pre-treatment with suramin is also believed to reduce the risk of a severe reaction to melarsoprol if it is required, by reducing the parasitic load prior to its administration. However, there is no firm evidence supporting this approach.

### *Stage 2*

Melarsoprol

2.2 mg/kg IV daily for 10 days

Melarsoprol, an arsenic derivative, is the only currently available treatment for stage 2 *T.b. rhodesiense* trypanosomiasis. It is highly trypanocidal but is also toxic to the patient. Until

recently, a complex treatment schedule of three dose cycles followed by a rest period of 5-7 days was used, requiring lengthy hospitalization. Thankfully, recent evidence suggests that a shortened and condensed protocol is as effective and no more toxic; therefore, it is now given at a dose of 2.2 mg/kg daily for 10 days (Priotto et al. 2009). Common side effects include irritation at the injection site, abdominal pain, vomiting, diarrhea, myocarditis, and peripheral neuropathy. The most feared complication is an encephalopathic reaction. This has been reported in up to 10% of cases and carries a mortality of 50% for those who experience it. There is some evidence that corticosteroids reduce the risk of this devastating complication; therefore, daily prednisone during melarsoprol therapy is often given. The significant toxicity of this drug raises two important issues in the treatment of sleeping sickness: first, the importance of staging and speciating HAT in order to be sure of the need to commit the patient to such a toxic therapy and, second, the desperate need for development of new drugs. At present, melarsoprol remains the only treatment option for stage 2 *T.b. rhodesiense* trypanosomiasis, which is universally fatal if left untreated.

## NEW DRUGS

There is renewed impetus in drug discovery for trypanosomiasis. At the time of writing this chapter, an oral nitroimidazole agent, fexinidazole, is being investigated in clinical trials in the DRC and CAR for stage 2 *T.b. gambiense* trypanosomiasis. This is an oral agent and has activity against both species of trypanosomes in vitro, and the results of this study are eagerly awaited.

## PREVENTION

Travelers to areas where sleeping sickness is endemic should be counseled regarding the nature of the disease and its transmission. In a Western setting, those at risk are most often travelers planning to visit game reserves in eastern and southern Africa or aid workers planning to spend prolonged periods of time in remote settings in West or Central Africa. It should be emphasized that the disease is very rare in travelers; however, the severity of HAT warrants awareness, and providers should take time to counsel travelers on appropriate exposure prevention measures. At present, the only effective prevention is avoidance of tsetse fly bites. No vaccine against HAT exists, in part because of the challenges associated with antigenic variation. Given the toxicity of trypanocidal drugs and the relative rarity of the disease in travelers, prophylactic chemotherapy cannot be recommended.

Wearing ankle- and wrist-length clothes with neutral colors that blend into the environment (khaki or beige) is recommended because tsetse flies are attracted to vivid dark colors, particularly dark blue. The CDC recommends that travelers wear medium-weight fabric, as tsetse flies can bite through lightweight clothing (Moore 2015). DEET is relatively ineffective in repelling tsetse flies but may be of some benefit. Because tsetse flies are day biters, sleeping under a bed net has little impact on reducing tsetse fly bites. Travelers should be reassured, however, that even in the event of tsetse fly bites, the vast majority will not result in infection with trypanosomes. They should be aware of the symptoms and be encouraged to seek healthcare advice in the event of developing symptoms or signs, such as a chancre at the bite site.

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