8.8.11 Human African trypanosomiasis 1451

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8.8.11 Human African trypanosomiasis 1451 Clinical features and treatment A noninvasive diarrhoeal illness lasting from 3 to 10 days is attrib- uted to this organism, sometimes symptoms continue for weeks or months. Associated features are abdominal bloating, flatu- lence, and anorexia. Symptoms are more prolonged in immuno- compromised subjects. Some studies of patients with AIDS report higher prevalences or more numerous parasites in the stool. There is no definite association with irritable bowel syndrome or urticaria. Illnesses are self-limiting in most people, but infection and symp- toms can usually be eliminated with metronidazole or tinidazole. The organism is also sensitive to cotrimoxazole, furazolidine, and hydroxyquinoline. Blastocystis has been reported once in a liver abscess aspirate but the patient was later shown to have amoebiasis. Another pa- tient with faecal Blastocystis and rectocolitis responded rapidly to metronidazole but it appears that amoebiasis was not properly excluded. Evidence for pathogenicity Definite histopathology in humans is still lacking, although serum antibody has been reported in symptomatic subjects. A good labora- tory animal model remains elusive; pigs are a natural host in whom the parasite is located in the caecal and colonic lumen with no mu- cosal attachment or pathology, rats are not a normal host and when experimentally infected some showed lamina propria inflammatory cells. A convincing in vitro cytopathic model awaits discovery al- though cultured colonic epithelial cells release cytokines in the presence of Blastocystis. The parasite may damage actin filaments in epithelial cells. Cysteine proteinase has been postulated as a viru- lence factor. The genetic heterogeneity of Blastocystis isolates correlates weakly with host species. In some human studies, subtype determined by polymerase chain reaction correlated with symptoms. Clinical re- sponse to metronidazole is hardly compelling evidence for patho- genicity since concurrent infection with other enteropathogens is common and this drug has a wide spectrum of activity includ ing an effect upon small bowel bacterial overgrowth. More well-documented outbreaks and cytopathic evidence are needed. FURTHER READING Andersen LO, Stensvold CR (2016). Blastocystis in health and disease: are we moving from a clinical to a public health perspective? J Clin Microbiol, 54, 524–8. Janarthanan S, Khoury N, Antaki F (2011). An unusual case of invasive Blastocystis hominis infection. Endoscopy, 43 Suppl 2 UCTN, E185–6. Li J, et al. (2013). A rat model to study Blastocystis subtype 1 infections. Parasitol Res, 112, 3537–41.

Roberts T, et al. (2014). Update on the pathogenic potential and treat- ment options for Blastocystis sp. Gut Pathogens, 6, 1–9. Tan KS, et al. (2010). Current views on the clinical relevance of Blastocystis spp. Curr Infect Dis Rep, 12, 28–35. Wawrzyniak I, et al. (2013). Blastocystis, an unrecognized parasite: an overview of pathogenesis and diagnosis. Ther Adv Infect Dis, 1, 167–78. 8.8.11 Human African trypanosomiasis Reto Brun and Johannes Blum ESSENTIALS Human African trypanosomiasis (sleeping sickness) is caused by subspecies of the protozoan parasite Trypanosoma brucei. The dis- ease is restricted to tropical Africa where it is transmitted by the bite of infected tsetse flies (Glossina spp.). Control programmes in the 1960s were very effective, but subsequent relaxation of control measures led to recurrence of epidemic proportions in the 1980s and 1990s. Control is now being regained and elimination is being envisaged. Clinical features Trypanosomal chancre—a papule at the site of the bite is sometimes seen, and may be associated with regional lymphadenopathy. Haemolymphatic stage (human African trypanosomiasis stage 1)—manifests with fever, chills, rigors, headache, and joint pains; hepatosplenomegaly and generalized lymphadenopathy are common. Meningoencephalitic stage (human African trypanosomiasis stage 2)—insidious onset of headache, sometimes with change in behav- iour and personality; convulsions are common; sleep pattern be- comes fragmented, eventually leading to somnolence and coma. Progress tends to be fast in rhodesiense human African tryp- anosomiasis and slow—sometimes lasting years—in gambiense human African trypanosomiasis. Diagnosis, staging, prognosis, and treatment Diagnosis—by detection of trypanosomes (usually by direct mi- croscopy) in chancre aspirate, blood, lymph, or cerebrospinal fluid. Serology and polymerase chain reaction-based tests can be useful for mass screening. Staging—the cerebrospinal fluid must be examined in every pa- tient found positive for trypanosomes in blood or lymph aspirate. Treatment—untreated human African trypanosomiasis is almost invariably fatal. Specific treatment depends on the trypanosome subspecies and the stage of the disease. Drugs used for stage 1 in- clude pentamidine and suramin, and for stage 2 include melarsoprol, eflornithine, and nifurtimox, but regimens are not standardized and treatment is difficult and dangerous; all of the drugs used have many side effects, some potentially lethal. However, a new oral drug should soon be available. Prevention Control can be achieved by a combination of mass screening pro- grammes, treatment of patients, and vector control, which together can lead to a complete break of the transmission cycle. There is no vaccine. Acknowledgement: The authors and editors gratefully acknowledge the inclu- sion in this chapter of material contributed to previous editions of the Oxford Textbook of Medicine by Professor August Stich.

 Introduction Human African trypanosomiasis (HAT) or sleeping sickness is caused by subspecies of the protozoan flagellate Trypanosoma bru cei and transmitted to humans and animals by tsetse flies (Glossina spp.). The distribution of the vector restricts sleeping sickness to the African continent between 14° north and 29° south. Human dis- ease occurs in two clinically and epidemiologically distinct forms, gambiense or Central/West African and rhodesiense or East African sleeping sickness (Table 8.8.11.1). A third subspecies of the parasite, T. b. brucei, causes disease in animals but is nonpathogenic for hu- mans. Uganda is the only country where gambiense and rhodesiense sleeping sickness both occur (Fig. 8.8.11.1). The first case reports of the disease go back to the 14th century. In the past, its impact on health in Africa was enormous. Many areas were long rendered uninhabitable for people and livestock. During the early decades of the 20th century, millions may have died in Central Africa around Lake Victoria and in the Congo basin (Fig. 8.8.11.2). The success of control programmes in the 1960s promised

the disappearance of sleeping sickness as a public health problem. After all African countries had gained independence, the rigorous control measures introduced by the colonial powers were not maintained. As a consequence, the numbers of cases increased again mainly in the Democratic Republic of Congo, northern Angola, southern Sudan, the Central African Republic, and Uganda. According to estimates by the World Health Organization (WHO) at the end of the 20th century, the achievements in sleeping sickness control during colonial times had been nearly completely reversed. However, strong efforts of control programmes run by national institutions and various nongovernmental organizations reduced transmission and prevalence to fewer than 4000 cases in 2014. The goal is now to eliminate sleeping sickness; that is, to bring down the number of cases below 2000 by the year 2020 (see Box 8.8.11.1). Today, HAT is a focal disease with probably fewer than 15 000 infected people in about 10 countries. However, millions of Africans in about 20 countries are exposed to the potential risk of HAT. Almost all patients are infected with T. b. gambiense, while only about 100 cases of T. b. rhodesiense were reported from Uganda, Tanzania, Zambia, and Malawi in 2013. For tourists and expatriates, sleeping sickness has always been a rare disease; occasional cases have been reported in tourists visiting National Parks in Tanzania, Zambia, and Malawi. Aetiology In 1895, Sir David Bruce (1855–1931) suggested an association between trypanosomes and 'cattle fly fever', a major problem for livestock in southern Africa. In 1902, Robert M Forde and Everett Dutton from the Liverpool School of Tropical Medicine identified trypanosomes in the blood of a patient during a research exped- ition in the Gambia (see Fig. 8.8.11.3a and b), and in 1903, Aldo Castellani isolated trypanosomes from the cerebrospinal fluid of a patient. In the same year, tsetse flies were identified as vectors. Trypanosoma brucei (phylum Sarcomastigophora, order Kinetoplastida) is an extracellular protozoan parasite. Like leish- mania, it possesses a centrally placed nucleus and a kinetoplast, a distinct organelle containing mitochondrial DNA. The kinetoplast is the starting point of the flagellum which extends on the surface of the cell body forming an undulating membrane and ending as a free flagellum.

Table 8.8.11.1 The principal features of Gambiense and Rhodesiense sleeping sickness

Disease	Gambiense sleeping sickness	Rhodesiense sleeping sickness
Parasite	Trypanosoma brucei gambiense	Trypanosoma brucei rhodesiense
Vector	Transmitted by riverine tsetse flies (Palpalis group)	Transmitted by savannah tsetse flies (Morsitans group)
Clinical course	Insidious onset, slow progression, death in stage II after many months or years	Acute onset, chancre frequent, rapid course, death frequently in stage I (cardiac failure)
Diagnosis	Parasitaemia scanty, Winterbottom's sign, serology	Parasitaemia usually higher and easily detectable, serological tests unreliable
Treatment	See Table 8.8.11.3	
Epidemiology	Tendency for endemicity, humans as main reservoir, animal reservoir unlikely, latent public health problem in many Central and West African countries	Wild (antelopes e.g. bushbuck) and occasionally domestic animals as reservoir and source of case clusters and epidemic outbreaks

Fig. 8.8.11.1 Geographical distribution of human African trypanosomiasis cases in endemic populations and in travellers. Courtesy of Dr. Bernhard Beck, Swiss Tropical and Public Health Institute.

 The three subspecies of T. brucei are indistinguishable morpho- logically. However, they differ in their interaction with their mam- malian host and the epidemiological pattern of the diseases they cause. Formerly, T. b. gambiense and T. b. rhodesiense isolates were characterized either by isoenzyme analysis or by animal inocula- tion. The advent of molecular techniques created expectations of more reliable tools for their differentiation. However, genomic characterization has revealed several more subdivisions than the three that were expected. Whereas West African isolates proved relatively homogeneous, East

African isolates from humans and animals did not simply conform to what is still called T. b. rhod esiense and T. b. brucei but showed a complex relationship with evidence of genetic exchange in the vector. T. b. rhodesiense and T. b. brucei are almost identical, the only difference being the pres- ence of the SRA (human serum resistance associated) gene present in T. b. rhodesiense. Transmission The main mode of transmission is through the bite of an infected tsetse fly (Glossina spp., order Diptera; Fig. 8.8.11.4). Congenital transmission may play an occasional role; other modes of transmis- sion are highly unlikely. Tsetse flies are biologically unique insects, which occur only in Africa, with 31 distinct species and subspecies, of which less than half are potential vectors of HAT. Their distinctive behaviour, ecology, and chosen habitat explain many epidemio- logical features of sleeping sickness. Tsetse flies can live for many months in the wild, are viviparous, and give birth to maximal eight larvae per lifetime. Both sexes feed on blood. They are fastidious in requiring warm temperatures, shade, and humidity for resting and larviposition and so their distribution is highly focal. Mapping and monitoring of possible HAT transmission foci has become possible with the use of satellite imaging techniques. During the blood meal on an infected mammalian host, the tsetse fly takes up trypanosomes (‘short-stumpy form’) into its mid- gut, where they differentiate to procyclic forms and multiply. After 2–3 weeks, they migrate to the salivary glands as epimastigote forms where they attach to the gland epithelium and finally develop into infective metacyclic forms. At the next blood meal, some of them are injected with the saliva into a new vertebrate host where they develop to ‘long-slender’ trypomastigotes and multiply by binary Fig. 8.8.11.2 Sleeping sickness patients on an island in Lake Victoria; historical photograph taken during Robert Koch’s research expedition to East Africa. Box 8.8.11.1 Control of human African trypanosomiasis • Diagnosis and treatment of patients • Active case finding • Vector control • Implementation and continuation of a surveillance system • Training, health education, and community participation (a) (b) Fig. 8.8.11.3 (a) Trypanosomes in thin human blood film (Giemsa stain, x1000). (b) Everett Dutton’s painting of trypanosomes. Fig. 8.8.11.4 Adult tsetse fly Glossina morsitans.

section 8 Infectious diseases 1454 fission. The mature (salivary glands) infection rate in the field is extremely low with less than one fly in a thousand. In contrast to Leishmania species and T. cruzi, T. brucei is an exclusively extracel- lular parasite. Antigenic variation The bloodstream forms of T. brucei are covered with a dense coat of identical glycoproteins. Being highly immunogenic, they stimulate the production of specific antibodies, mainly of the IgM subclass. Once the surface glycoproteins have been recognized by host anti- bodies, the parasite will be attacked and destroyed through com- plement activation and cytokine release, giving rise to local and systemic inflammatory reactions. However, about 2% of T. brucei in each new generation change the expression of their specific surface glycoprotein. The ‘coat’ will then be different in the new clone (thus called variant surface glycopro- tein, VSG). This phenotypic switch is done mainly by programmed DNA rearrangements, moving a silent VSG gene into an active, telomeric expression site. Each T. brucei parasite has hundreds of different VSG genes, and within all trypanosome populations, the potential repertoire for such different VSG types seems to be al- most infinite. Antigenic variation is the major hindrance for vaccine development. Every new VSG copy is antigenically different, thus stimulating the production of a new IgM population. This antigenic variation is the major immune evasion strategy of the parasite, enabling the trypanosome to persist in its vertebrate host. It also reduces parasite load and prolongs the infection. But the inevitable outcome is im- mune exhaustion of the host (supported by additional immunosup- pressive metabolites of the parasites), penetration of trypanosomes into immune-privileged sites

such as the central nervous system, and finally death of the host. Clinical features The clinical presentation of HAT depends on the parasite species, the stage of the disease and on the host. T.b. rhodesiense HAT is usually an acute disease progressing to stage II within a few weeks and death within 6 months (Fig. 8.8.11.5). T.b. gambiense HAT is characterized by a chronic progressive course that is mostly fatal if untreated. The disease occurs in two stages, the first, or haemolymphatic stage, and the second, or meningoencephalitic stage, with invasion of the central nervous system by the trypanosomes. Neurological signs and symptoms, including sleep disturbances, are characteristic of stage II. However, most of the symptoms of both stages overlap, making the distinction between the stages based on clinical features not clear. Therefore, this distinction relies on the analysis of the cere- brospinal fluid (see diagnosis). Clinical signs and symptoms are nonspecific, and their frequency varies between individuals and between disease foci. T.b.gambiense HAT T.b.gambiense HAT is characterized by a chronic progressive course leading mostly to death if untreated. Fever, headache, pruritus (Fig. 8.8.11.6), lymphadenopathy and, to a lesser extent, hepatosplenomegaly are the leading signs and symptoms of stage I, but are also present to a lesser extent in stage II. Fever is intermit- tent, with attacks lasting from a day to a week, separated by inter- vals of a few days to a month or longer, and is rarely seen in stage II. Lymphadenopathy with enlarged firm, mobile, nonsuppurate, and painless lymph nodes and enlargement of the posterior cervical lymph nodes is the so-called Winterbottom’s sign. Oedema mainly affects the face (puffy face). HAT causes a meningoencephalitis involving different parts of the brain. Nonspecific neurological or psychiatric symptoms, such as headaches and mood or behavioural changes, are commonly found in both stage I and II, but their intensity and persistence increase as the illness evolves. The neurological symptoms include tremor, fasciculation, general motor weakness, paralysis of an extremity,
Fig. 8.8.11.5 Patient with stage II sleeping sickness. Fig. 8.8.11.6 Scratch marks on the back of a stage I sleeping sickness patient. Photo by Dr. Johannes Blum, Swiss Tropical and Public Health Institute.

 epilepsy, akinesia, and abnormal movements such as dyskinesia or choreoathetosis, Parkinson-like movements, unspecific movement disorders, speech disorders, and abnormal archaic reflexes. Sensory involvement is often described as hyperaesthesia, paraesthesia, an- aesthesia, or pruritus. In addition, psychiatric symptoms, such as irritability, psychotic reactions, aggressive behaviour, or inactivity with apathy, might dominate the clinical picture. Sleep disorder is a leading symptom, hence the name ‘sleeping sickness’. Somnographic studies have revealed a fragmentation with frequent sleep episodes of short durations at day and night caused by a dysregulation of the circadian rhythm of the sleep/wake cycle: The patient has somnolence during the day, with uncontrollable urges to sleep, and nocturnal insomnia. Cardiac involvement includes QTc prolongation with risk of fatal arrhythmias, repolarization changes, and low voltage (observed in 50–70% of patients) but rarely leads to relevant clinical heart failure. Endocrine disorders of the thyroid, adrenocortical, and sexual func- tion comprise hypo- and hyperfunction, but rarely demand specific treatment. T.b. rhodesiense HAT T.b. rhodesiense HAT is an acute febrile disease rapidly progressing to stage II and leading to death within 6 months. Recent descriptions of the clinical presentation show a high variability in different foci, possibly due to different parasite strains. The clinical presentation is similar to T.b. gambiense HAT, but more acute and trypanosomal chancres as a primary lesion at the site of the infection bite are more frequently seen. It appears a few days following the bite of an in- fected tsetse fly as an erythematous and tender swelling, which later becomes indurated and eventually may ulcerate. It

is often accom- panied by a satellite lymphadenopathy. The localization of enlarged lymph nodes is usually submandibular, axillary, and inguinal rather than nuchal, and oedema is more frequently observed. Compared to T.b. gambiense HAT, thyroid dysfunction, adrenal insufficiency, and hypogonadism are more frequent and myopericarditis can be more severe. Liver involvement with hepatomegaly is usually moderate. HAT in travellers The symptomatology in Caucasians differs markedly from the textbook descriptions of African HAT patients. The disease onset is almost invariably acute and of the febrile type, regardless of the involved trypanosome species. The incubation time of T.b. gambi ense HAT in travellers is often shorter than 1 month, but might be as long as 7 years in immigrants. T.b. rhodesiense HAT has an incu- bation time of less than 3 weeks. It is an acute, life-threatening dis- ease with the cardinal symptoms being high fever, headache, and a trypanosomal chancre (Fig. 8.8.11.7). The classical sleep disorders and neurological findings of HAT are not a hallmark in travellers, irrespective of the trypanosome species. Since most of the travellers are in the first stage and have a short duration of the disease, sleep disorders and neuropsychi- atric findings might not be present at the time of the first clinical assessment. Headache, lymphadenopathy, hepatosplenomegaly, and even icterus are nonspecific findings seen in about a quarter to half of the patients. Gastrointestinal symptoms such as nausea, vomiting, and diarrhoea may dominate the clinical presentation. Electrocardiographic abnormalities due to myopericarditis and conduction abnormalities such as transient second and third degree atrioventricular block, supraventricular tachycardia, and ventricular premature captures have been reported. In a few travellers HAT has been complicated by renal failure requiring haemodialysis, multiorgan failure, disseminated intravascular coagulopathy, and coma with a fatal outcome. Differential diagnosis The differential diagnosis depends on the stage of the disease. In stage I the differential diagnosis is broad and includes any febrile dis- ease such as malaria, typhoid fever, viral diseases (dengue, chikun- gunya), rickettsiosis (also causes chancre), meningitis, leptospirosis, brucellosis, and gastrointestinal infection. In travellers the history of visit to a game park or hunting, the bite of a tsetse fly and the pres- ence of a chancre should alert the clinician. In stage II HAT other causes of chronic meningoencephalitis in- clude HIV-related diseases such as cryptococcal meningitis, toxo- plasmosis, and tuberculosis. Clinical investigations Diagnosis The diagnosis is based on the visualization of the parasite in lymph node aspirate, peripheral blood, or cerebrospinal fluid, polymerase chain reaction (PCR) technology, and serologic testing. Parasite numbers in the peripheral blood of patients with T.b. gambiense HAT vary between more than 10 000 trypanosomes/ ml to fewer than 100 trypanosomes/ml, which is below the de- tection limit of microscopic examination of wet blood films, Giemsa-stained thin blood films or thick blood films (5000–10 000 trypanosomes/ml). The sensitivity can be improved by using con- centration methods such as the microhaematocrit centrifugation technique or quantitative buffy coat (detection limit: 450–500 Fig. 8.8.11.7 Trypanosomal chancre on the calf of a missionary returning from the Congo.

 trypanosomes/ml) or the mini-anion-exchange centrifugation technique (50–100 trypanosomes/ml), or a combination of both techniques (10 trypanosomes/ml). In contrast, the parasitaemia is more constant and higher in T.b. rhodesiense patients and the visu- alization of the parasite in the blood smear poses fewer problems. A simple LED-based microscope for both bright-field and fluor- escence microscopy has recently been developed by FIND, the Foundation for Innovative New Diagnostics, and Carl Zeiss. The use of fluorescence microscopy increases the sensitivity and ease of demonstration of trypanosomes. Lymph node aspiration is widely used, especially for the diagnosis of T.b. gambiense HAT. Fluid in enlarged lymph nodes, preferably of the posterior triangle of the neck (Winterbottom’s sign), is as- pirated and examined

immediately at ×400 magnification without additional staining. Mobile trypanosomes can be detected for a few minutes between the numerous lymphocytes. The sensitivity of parasitological examination of lymph node aspirate varies between 40% and 80%. The Card Agglutination Test for Trypanosomiasis (CATT) is a cost-efficient antibody detection test for mass screening of T.b. gam biense HAT. In most endemic regions its sensitivity varies from 87% to 98%. However, the CATT test is not suitable for T.b. rhodesiense. A first rapid diagnostic test has recently been developed by FIND and Standard Diagnostics. It is a lateral flow test that requires a drop of finger prick blood with the result available in 15 minutes. Molecular diagnosis with PCR has a good sensitivity, but is la- borious and mostly not available in the field. A real alternative is loop-mediated isothermal amplification, which amplifies target DNA at a constant temperature. FIND and partners developed this technology which is feasible for field laboratories. Some practical issues are crucial for the correct diagnosis. A delay between sampling and examination can lead to a false negative re- sult since trypanosomes do not survive a long time after the blood sample is taken. Additionally, the sample should be sent to the la- boratory at a temperature of 2–8°C (not frozen), be protected from sunlight, and tested within 12 hours. As treatment differs markedly between stage I and stage II HAT, staging of the disease by examination of the cerebrospinal fluid is essential. Stage II HAT is defined by an elevated white blood cell count (WBC >5 /mm3) or the presence of trypanosomes in the cere- brospinal fluid. However, this has limited sensitivity and may lead to incorrect staging. Laboratory findings Among T.b. gambiense HAT patients in endemic regions anaemia and impaired renal function are frequent, but liver enzymes, lac- tate dehydrogenase, creatinine kinase, and blood sugar are usually normal. In tourists with T.b. rhodesiense HAT, elevated creatinine (81%), liver enzymes (82%), low platelets (92%), and elevated levels of C reactive protein are frequent. Severe haematological disorders and abnormal kidney function tests have been reported. Magnetic resonance imaging Since the knowledge on imaging changes in HAT is scarce, this method cannot be used for the diagnosis of HAT. The findings are multifarious and include symmetrical focal lesions, diffuse hyperintensity, brain oedema with demyelination, brain atrophy, and multiple abnormal signals. Treatment General considerations HAT is curable, especially if the diagnosis is made at an early stage of the disease. In the stark reality of the African setting, however, there are many obstacles to successful patient management: Sleeping sickness is a disease of rural places. The active foci of sleeping sickness are usually in remote and insecure places, which are difficult to reach. Many treatment centres work under emer- gency conditions with extremely restricted resources. Numerous affected patients, without proper access to healthcare, are left unattended. • Diagnosis is difficult. Initial diagnosis and exact staging of sleeping sickness require sophisticated methods that are often dangerous to the patient and justified only in the hands of experienced per- sonnel. Repetitive training programmes, constant supervision, and continuous quality control are necessary but in reality, rarely available. • Treatment of trypanosomiasis is extremely costly, although the drugs themselves are now covered by a donation programme. Invariably, demand exceeds the locally available resources. External funding and sustainable donor commitments for rural Africa are generally decreasing. • Treatment is complicated. Treatment of HAT is dangerous, pro- longed, and usually requires hospitalization. Most patients with stage II trypanosomiasis are severely ill and malnourished. Adverse drug reactions during treatment are difficult to assess because of concomitant pathologies. Their management requires considerable medical skill and good nursing care. Hospitals in rural Africa are often inadequately equipped and staffed to accom- plish good patient care. • HAT treatment is not standardized. Trypanosomiasis treatment regimens vary considerably between countries and treatment centres. Results from different centres are comparable to only a very limited extent. Few properly conducted and sufficiently powered clinical

trials are available to evaluate duration, dosage, and possible combinations of drugs. Sufficient infrastructure for carrying out clinical research exists in only a handful of places. Stage I drugs The treatment of HAT depends on the trypanosome subspecies (T. b. gambiense or T. b. rhodesiense) and the stage of the disease (stage I or stage II) (Table 8.8.11.2). Pentamidine Since its introduction in 1940, pentamidine has become the drug of choice for gambiense HAT stage I, achieving cure rates as high as 98%. However, there are frequent failures in rhodesiense HAT. Table 8.8.11.2 The choice of drugs in the treatment of sleeping sickness Gambiense sleeping sickness Rhodesiense sleeping sickness Stage I Pentamidine Stage I Suramin Stage II NECT (nifurtimox + eflornithine combination therapy) Stage II Melarsoprol

 Some cures of stage II infections have also been reported, but cere- brospinal fluid drug levels are usually not sufficiently high to guar- antee a reliable trypanocidal effect in the central nervous system. Pentamidine is usually given by deep intramuscular injec- tion, often to outpatients. If hospital care and reasonable moni- toring conditions are available, an intravenous infusion, given in normal saline over 2 h, might be used instead. The main ad- vantage of pentamidine over other drugs is the short treatment course and ease of administration. Adverse effects are related to the route of administration or its dose and are usually reversible (Table 8.8.11.3). Pentamidine is also used as second-line therapy for visceral leishmaniasis and in the prophylaxis and treatment of opportun- istic Pneumocystis jiroveci pneumonia in AIDS patients. Since the start of the HIV pandemic, the cost of pentamidine has been in- creased more than 10-fold by producers, making it unaffordable for health institutions in low-income countries. After an intervention by WHO, pentamidine is now made available for use in HAT as part of a donation programme. Suramin In the early 20th century, the development of suramin, resulting from German research on the trypanocidal activity of various dyes (‘Bayer 205’), was a major breakthrough in the field of tropical medi- cine. For the first time, human African trypanosomiasis, at least in its early stages, became treatable without causing major harm. Even today, suramin is still used to treat stage I HAT, especially rhodesiense. Like pentamidine, it does not reach therapeutic levels in cerebrospinal fluid. Suramin is injected intravenously after dilu- tion in sterile water. Adverse effects depend on nutritional status, concomitant illnesses (especially onchocerciasis), and the patient’s clinical condi- tion. Although life-threatening reactions have been described, ser- ious adverse effects are rare (Table 8.8.11.3). Table 8.8.11.3 Dosage and principal adverse reactions of antitrypanosomal agents Drug Dosage regimen Adverse drug reactions Pentamidine 4 mg/kg body weight intramuscular daily or on alternate days for 7 to 10 injections (3 dose regimen currently under investigation) Hypotensive reaction with tachycardia, dizziness, even collapse and shock, especially after intravenous administration, close monitoring of pulse rate and blood pressure after injection is mandatory Inflammatory reactions at the site of injection (sterile abscesses, necrosis) Renal, hepatic, and pancreatic dysfunction Neurotoxicity: peripheral polyneuropathy Bone marrow depression Suramin Day 1: Test dose of 4–5 mg/kg body weight Pyrexia (very common) Day 3, 10, 17, 24, and 31: 20 mg/kg body weight, maximum dose per injection 1 g Early hypersensitivity reactions such as nausea, circulatory collapse, urticaria Late hypersensitivity reactions: skin reactions (exfoliative dermatitis), haemolytic anaemia Renal impairment: albuminuria, cylinduria, haematuria (high renal tissue concentrations); regular urine checks during treatment are mandatory Neurotoxicity: peripheral neuropathy Bone marrow toxicity: agranulocytosis, thrombocytopenia Melarsoprol New regimen: Treatment-induced encephalopathy Day 1–10: 2.2 mg/kg body weight Pyrexia Neurotoxicity: peripheral motor or sensory polyneuropathy Dermatological reactions: pruritus, urticaria, exfoliative dermatitis

Cardiotoxicity Renal and hepatic dysfunction Eflornithine Most commonly used dosage regimen: Gastrointestinal symptoms such as nausea, vomiting, and diarrhoea 100 mg/kg body weight at 6-hourly intervals for 14 days Bone marrow toxicity: anaemia, leucopenia, thrombocytopenia Alopecia, usually towards the end of the treatment cycle Neurological symptoms such as convulsions Nifurtimox 5 mg/kg body weight 3 times daily for 30 days Abdominal discomfort such as nausea, pains, and vomiting in half of the treated patients, often leading to a disruption of the treatment course Neurological complications: convulsions Impairment of cerebellar function, polyneuropathy Skin reactions NECT Eflornithine: 200 mg/kg body weight at 12-hourly intervals for 7 days; Nifurtimox: 5 mg/kg body weight 3 times daily for 10 days Neurological symptoms and gastrointestinal disorders are the leading adverse reactions, however, much less pronounced compared to the eflornithine monotherapy

section 8 Infectious diseases 1458 Stage II drugs Melarsoprol Until the systematic introduction of the arsenical compound melarsoprol in 1949, advanced trypanosomiasis was virtually un-treatable. Since then, it has remained the most widely used stage II antitrypanosomal drug both for gambiense and rhodesiense infec- tions. It has saved thousands of lives, but has a high rate of dangerous adverse effects. Increasing frequency of relapses and resistance have been reported in some parts of the Democratic Republic of Congo, Angola, Sudan, and Uganda (Fig. 8.8.11.8). Melarsoprol clears trypanosomes rapidly from the blood, lymph, and cerebrospinal fluid. Its toxicity usually restricts its use to stage II disease. It is given by slow intravenous injection; extravascular leakage must be avoided. A new, simpler regimen is based on pharmacokinetic investiga- tions and modelling (Table 8.8.11.3). The most important adverse effect is an acute encephalopathy, provoked around day 5 to 8 of the treatment course in 5 to 14% of all patients. Other adverse re-actions are severe headache, convulsions, rapid neurological de- terioration, or deepening of coma. Characteristically, the comatose patient’s eyes remain open. The overall case fatality under treatment ranges between 2 and 6%, depending on the stage of disease and the quality of medical and nursing care. Simultaneous administra- tion of glucocorticosteroids (prednisolone 1 mg/kg body weight; maximum 40 mg daily) reduces mortality. However, in areas where tuberculosis, amoebiasis, and strongyloidiasis are highly prevalent, their use is problematic. Eflornithine (DFMO) Initially developed as antitumour agent, eflornithine (α- difluoromethylornithine) was introduced in 1980 as an antitry panosomal drug, in the hope that it might replace melarsoprol for treatment of stage II trypanosomiasis. However, exorbi- tant costs and limited availability have restricted its use mostly to melarsoprol-refractory cases of gambiense sleeping sickness. T. b. rhodesiense is much less sensitive, because of a much higher turnover rate of the target enzyme ornithine decarboxylase, and therefore cannot be treated with eflornithine. Eflornithine should be administered slowly over a period of at least 30 min. Continuous 24-h administration is preferable if facilities allow. The range of adverse reactions to eflornithine is wide, their occurrence and intensity increase with the duration of treatment and the severity of the patient’s general condition (Table 8.8.11.3). In 2000 WHO established a public-private partnership with Sanofi which resulted in supply of eflornithine free of charge. The partnership was renewed in 2006 and in 2011. NECT (Nifurtimox eflornithine combination therapy) NECT, a combination treatment of nifurtimox and eflornithine was introduced in 2009. It reduces the duration of treatment of eflornithine to 7 days and the number of IV infusions to 14, com- bined with oral nifurtimox at 5 mg/kg 3-times a day for 10 days. But, unfortunately, it has not been studied in T.b. rhodesiense infection. Nifurtimox is registered for Chagas’ disease (T. cruzi) but not for HAT. As a monotherapy nifurtimox is not very effective for HAT; however, in combination with eflornithine it acts synergistically producing oxidative stress to the parasite. NECT is superior to the eflornithine monotherapy regarding ef-

ficacy and safety. The relapse rate after 18 months was 1.4% com- pared to 5.7% for the monotherapy. Adverse events were lower in the NECT group than in the eflornithine group. Both drugs are provided free of charge by WHO to endemic countries with a kit containing all the material needed for its administration. 50 000 40 000 30 000 20 000 10 000 1940 1943 1946 1949 1952 1955 1958 1961 1964 1967 1970 1973 1976 1979 1982 1985 1988 1991 1994 1997 2000 2003 2006 2009 2012 0 Cases Year Fig. 8.8.11.8 Number of annually reported cases of human African trypanosomiasis. Reprinted from Franco JR et al. (2014). Epidemiology of human African trypanosomiasis. Clin Epidemiol, 6, 257–275 (based on data from the WHO).

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