Nevertheless, limited studies have shown that only ~70% of acute infections are cured by a full course of treatment. Common adverse effects of nifurtimox include anorexia, nausea, vomiting, weight loss, and abdominal pain. Neurologic reactions to the drug may include restlessness, disorientation, insomnia, twitching, paresthesia, polyneuritis, and seizures. These symptoms usually disappear when the dosage is reduced or treatment is discontinued. The recommended daily dosage is 8–10 mg/kg for adults, 12.5–15 mg/kg for adolescents, and 15–20 mg/kg for children 1–10 years of age. The drug should be given orally in four divided doses each day, and therapy should be continued for 90–120 days. Nifurtimox is available from the Drug Service of the Centers for Disease Control and Prevention (CDC) in Atlanta (telephone number, 404-639-3670).

The efficacy of benznidazole is similar or even superior to that of nifurtimox. A cure rate of >90% among congenitally infected infants treated before their first birthday has been reported. Adverse effects include rash, peripheral neuropathy, and rare instances of granulocytopenia. The recommended oral dosage is 5 mg/kg per day for 60 days for adults and 5–10 mg/kg per day for 60 days for children, with administration of two or three divided doses. Benznidazole is generally considered the drug of choice in Latin America.

The question of whether adults in the indeterminate or chronic symptomatic phase of Chagas disease should be treated with nifurtimox or benznidazole has been debated for years. The fact that cure rates in persons with long-established chronic infection are notably inferior to those in patients with acute or recent chronic infection is central to this controversy. No convincing evidence from randomized controlled trials indicates that nifurtimox or benznidazole treatment of adults in the indeterminate or chronic symptomatic phase reduces either the appearance or progression of symptoms or mortality rates. On the basis of results of some observational studies, a panel of experts convened by the CDC in 2006 recommended that adults <50 years old with presumably long-standing indeterminate *T. cruzi* infections—or even with mild to moderate disease—be offered treatment. A large randomized clinical trial (the BENEFIT multicenter trial) designed to assess the parasitologic and clinical efficacy of benznidazole in 2856 adults (18–75 years old) with chronic Chagas heart disease (without advanced lesions) is being performed in Brazil, Argentina, Colombia, Bolivia, and El Salvador, but results will not be available until 2015. In contrast, randomized studies have shown that treatment of children is useful, and the current consensus of Latin American authorities and the CDC panel of experts is that all *T. cruzi*–infected persons up to 18 years old and all adults known to have become infected recently should be given benznidazole or nifurtimox.

The usefulness of antifungal azoles for the treatment of Chagas disease has been studied in laboratory animals and to a lesser extent in humans. To date, none of these drugs has exhibited a level of anti–*T. cruzi* activity that would justify its use in humans. Several newer drugs in this class have shown promise in animal studies and are currently being evaluated in phase 2 clinical trials.

Patients who develop cardiac and/or gastrointestinal disease in association with *T. cruzi* infection should be referred to appropriate subspecialists for further evaluation and treatment. Pacemakers can be useful in patients with ominous arrhythmias. The usefulness of implantable cardioverter defibrillators in persons with Chagas heart disease has not been established and currently is being studied in a prospective randomized trial. Cardiac transplantation is an option for patients with end-stage chagasic cardiomyopathy; more than 150 such transplantations have been done in Brazil and the United States. The survival rate among Chagas disease cardiac transplant recipients seems to be higher than that among persons receiving cardiac transplants for other reasons. This better outcome may be due to the fact that lesions are limited to the heart in most patients with symptomatic chronic Chagas disease.

### PREVENTION

Because drug therapy has limitations and vaccines are not available, the control of *T. cruzi* transmission in endemic countries depends on the reduction of domiciliary vector populations by spraying of insecticides, improvements in housing, and education of at-risk persons. As noted above, these measures, coupled with serologic screening of blood donors, have markedly reduced transmission of the parasite in many endemic countries. Tourists would be wise to avoid sleeping in dilapidated houses in rural areas of endemic countries. Mosquito nets and insect repellent can provide additional protection.

In view of the possibly serious consequences of chronic *T. cruzi* infection, it would be prudent for all immigrants from endemic regions who are living in the United States to be tested for evidence of infection. Identification of persons harboring the parasite would permit periodic electrocardiographic monitoring, which is important to detect incipient heart disease and guide further diagnostic studies and treatment. The possibility of congenital transmission is yet another justification for screening. *T. cruzi* is classified as a Risk Group 2 agent in the United States and a Risk Group 3 agent in some European countries. Laboratory staff should work with the parasite or infected vectors and mammals at containment levels consistent with the risk group designation in their areas.

## SLEEPING SICKNESS (AFRICAN TRYPANOSOMIASIS)

### DEFINITION

Sleeping sickness, or human African trypanosomiasis (HAT), is caused by flagellated protozoan parasites that belong to the *T. brucei* complex and are transmitted to humans by tsetse flies. In untreated patients, the trypanosomes first cause a febrile illness that is followed months or years later by progressive neurologic impairment and death.

### THE PARASITES AND THEIR TRANSMISSION

The East African (*rhodesiense*) and the West African (*gambiense*) forms of sleeping sickness are caused, respectively, by two trypanosome subspecies: *T. b. rhodesiense* and *T. b. gambiense*. These subspecies are morphologically indistinguishable but cause illnesses that are epidemiologically and clinically distinct (Table 252-1). The parasites are transmitted by blood-sucking tsetse flies of the genus *Glossina*. The insects acquire the infection when they ingest blood from infected mammalian hosts. After many cycles of multiplication in the midgut of the vector, the parasites migrate to the salivary glands. Their transmission takes place when they are inoculated into a mammalian host during a subsequent blood meal. The injected trypanosomes multiply in the blood (Fig. 252-2) and other extracellular spaces and evade immune destruction for long periods by undergoing antigenic variation, a process driven by gene switching in which the antigenic structure of the organisms' surface coat of glycoproteins changes periodically.

**TABLE 252-1 COMPARISON OF WEST AFRICAN AND EAST AFRICAN TRYPANOSOMIASES**

| Point of Comparison | West African *(gambiense)* | East African *(rhodesiense)* |
|---|---|---|
| Organism | *T. b. gambiense* | *T. b. rhodesiense* |
| Vectors | Tsetse flies (palpalis group) | Tsetse flies (morsitans group) |
| Primary reservoir | Humans | Antelope and cattle |
| Human illness | Chronic (late CNS disease) | Acute (early CNS disease) |
| Duration of illness | Months to years | <9 months |
| Lymphadenopathy | Prominent | Minimal |
| Parasitemia | Low | High |
| Epidemiology | Rural populations | Workers in wild areas, rural populations, tourists in game parks |

***Abbreviation:*** CNS, central nervous system.

***Source:*** Reprinted with permission from LV Kirchhoff, in GL Mandell et al (eds): *Principles and Practice of Infectious Diseases,* 7th ed. Philadelphia, Elsevier Churchill Livingstone, 2010.