Chagas Disease

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Epidemiology

Chagas disease (American trypanosomiasis) is caused by the protozoan parasite *Trypanosoma cruzi*. It is transmitted to humans by infected triatomine bugs ("kissing bugs"), and less commonly by transfusion, organ transplant, from mother to infant, and, in rare instances, by ingestion of contaminated food or drink.[1-4]

Vector-borne transmission occurs only in the Americas, where an estimated 6 million people have Chagas disease.[5,6] Historically, transmission occurred largely in rural areas in Latin America, where houses built of mud brick are vulnerable to colonization by the triatomine vectors.[4] In such areas, Chagas disease usually is acquired in childhood. In the last several decades, successful vector control programs have substantially decreased transmission rates in much of Latin America.[4,7,8]

Infected triatomine vectors and *T. cruzi*–infected domestic and wild animals are found across the southern half of the United States, and rare cases of autochthonous vector-borne transmission have been documented.[9-11] However, the risk of vector-borne infection within the United States appears to be very low.[12] *T. cruzi* can also be transmitted in blood; screening of blood donations for anti-*T. cruzi* antibodies was introduced in 2007 after the U.S. Food and Drug Administration approved a serological test for that purpose.[13,14]

In people chronically infected with *T. cruzi* as a result of prior infection, profound immunosuppression (e.g., due to advanced HIV) may lead to reactivation of the disease, characterized by parasitemia, which is associated with increased intracellular parasite replication and lack of immunological control of the infection.[15-17]

Clinical Manifestations

Acute Phase. The acute phase of *T. cruzi* infection, which typically goes unrecognized, lasts up to 90 days and is characterized by circulating trypomastigotes detectable on microscopy of fresh blood or buffy coat smears.[2,4] If the portal of infection was the conjunctiva, patients may develop the characteristic Romaña's sign—unilateral painless swelling of the upper and lower eyelids—which usually lasts several weeks. The other symptoms of acute infection are usually limited to a non-specific febrile illness. In a small proportion of patients, however, acute, life-threatening myocarditis or meningoencephalitis may occur.[2,4] At the end of the acute phase, typically 60 to 90 days after infection, parasitemia falls below levels detectable by microscopy, and in the absence of effective antitrypanosomal treatment, *T. cruzi* infection passes into the chronic phase.[2,4]

Chronic Phase. Most patients with chronic *T. cruzi* infection have no signs or symptoms and are said to have the indeterminate form of the disease. Over the course of their lives, 20% to 30% of these patients will progress to clinically evident Chagas disease—most commonly, cardiomyopathy.[2,4] The earliest manifestations are usually conduction system abnormalities, such as right bundle branch block, alone or in combination with frequent premature ventricular contractions, which may develop years to decades after infection.[4,18] Over time, the disease may progress to

higher-grade heart block and complex ventricular arrhythmias. In patients with more advanced cardiomyopathy, poor prognostic factors include congestive heart failure, ventricular aneurysm, and complete heart block; these are associated with short-term mortality, including sudden death.[19] Chagas digestive disease is much less common than cardiomyopathy.[20] Dysphagia is the characteristic symptom of megaesophagus, and prolonged constipation is the most common complaint associated with megacolon.

T. cruzi reactivation during the chronic phase of Chagas disease is characterized by a return to high levels of parasite replication and parasitemia, which are usually detectable by microscopy. Reactivation can occur in individuals on immunosuppressive medications or cancer chemotherapy and in people with HIV.[16,21-25] Even in the absence of symptoms, people with HIV and chronic Chagas disease have significantly higher levels of *T. cruzi* parasitemia than their immunocompetent counterparts.[24] Most cases of clinically apparent reactivation occur with CD4 T lymphocyte cell counts <200 cells/mm^3, a history of prior opportunistic infections, or both.[16]

The clinical features of reactivated Chagas disease in people with HIV differ from those observed in individuals who are immunosuppressed for other reasons. The most common manifestations consist of *T. cruzi* meningoencephalitis, with or without brain abscesses (chagomas).[15,16,26,27] The presentation in people with HIV may be confused with central nervous system (CNS) toxoplasmosis and should be considered in the differential diagnosis of CNS symptoms or mass lesions on imaging. The second most frequently reported manifestation of reactivation in people with HIV is acute myocarditis, sometimes superimposed on pre-existing chronic Chagas heart disease.[16,17] Patients may present with new arrhythmias, pericardial effusion, acute cardiac decompensation, or rapid progression of existing chronic cardiomyopathy.[16,28] Less frequent manifestations of reactivation include skin lesions, erythema nodosum, and parasitic invasion of the peritoneum, stomach, or intestine.[16,28]

Diagnosis

Screening with serological testing is recommended for all individuals who have lived in Mexico or Central or South America for greater than 6 months.[29]

Most persons infected with *T. cruzi* are in the chronic phase and are typically unaware of their infection. Screening for infection to identify persons with the indeterminate or early clinical forms of chronic Chagas disease is important to identify those who might benefit from antiparasitic treatment and counseling regarding potential transmission of *T. cruzi* to others (e.g., blood donation, organ donation). This is particularly important for people with HIV because of the risk of reactivation disease.

Diagnosis of chronic infection relies on serological methods to detect immunoglobulin G antibodies to *T. cruzi*, most commonly enzyme-linked immunosorbent assay (ELISA) and immunofluorescent antibody assay (IFA). No available assay has sufficient sensitivity and specificity to be used alone; a single positive result does not constitute a confirmed diagnosis. Two serological tests based on different antigens (i.e., whole parasite lysate and recombinant antigens) and/or techniques (e.g., ELISA and IFA) should be used for individuals with suspected Chagas. In some cases, the infection status remains difficult to resolve even after a third test, because there is no true gold standard assay for chronic *T. cruzi* infection.[29,30]

Data suggest that the sensitivity of serological assays varies by geographical location, possibly because of *T. cruzi* strain differences and resulting antibody responses.[31,32] Options for *T. cruzi* serological testing in the United States include diagnostic ELISA kits based on parasite lysate or recombinant antigens.[29,33] In general, polymerase chain reaction (PCR) is not a useful diagnostic test for chronic *T. cruzi* infection, as its sensitivity is highly variable.[30,34,35]

In people with HIV and epidemiologic risk factors for Chagas disease, coinfection with *T. cruzi* and reactivation disease should be considered in the differential diagnosis of CNS mass lesions, meningoencephalitis, arrhythmias or heart failure.[16,25,26] The imaging pattern of brain chagoma is similar to that of cerebral toxoplasmosis, although chagomas tend to be larger than *Toxoplasma* lesions.[17,26,27] Computed tomography and magnetic resonance imaging show subcortical hypodense lesions that enhance with contrast or gadolinium. These lesions most often involve brain white matter. Histopathology shows inflammation and the presence of *T. cruzi* amastigotes in glial cells and, less often, in neurons. Cerebrospinal fluid (CSF) typically shows a mild pleocytosis (lymphocyte predominance), increased protein, and *T. cruzi* trypomastigotes.[16,17,26,27] In a case series that included 15 people coinfected with HIV and *T. cruzi* with clinical meningoencephalitis, trypomastigotes were visualized in CSF in 85%.[36]

A definitive diagnosis of reactivation is established by identification of the parasite or its products in tissue, such as on brain biopsy, in CSF, or in blood.[16] In chronically infected patients who are immunocompetent or who have HIV coinfection in the absence of reactivation, trypomastigotes typically are undetectable in the circulating blood.[24] If observed in a coinfected patient, circulating parasites suggest reactivation and the need for treatment.

Testing to identify *T. cruzi* should be considered in all at-risk individuals with suspected reactivation of chronic Chagas disease. Initial assessment can be done by evaluation of a peripheral blood smear. Blood concentration techniques, such as capillary centrifugation, can improve sensitivity.[34] In centrifuged blood, *T. cruzi* trypomastigotes are found just above the buffy coat. Parasites also may be observed in lymph nodes, bone marrow, skin lesions, or pericardial fluid. Hemoculture is somewhat more sensitive than direct methods but takes 2 to 8 weeks to demonstrate parasites. Quantitative PCR assays performed on serial blood specimens that show rising parasite numbers over time provide the earliest and most sensitive indicator of reactivation.[37,38] As such, clinicians should consider obtaining PCR testing in all individuals in whom there is high clinical suspicion and blood and/or tissue tests are negative.

In people with HIV who have suspected CNS Chagas disease, centrifugation and microscopic examination of CSF should be conducted. Few published data exist on PCR of CSF, but it would be expected to have high sensitivity for the diagnosis of reactivation in the CNS.[39]

In the United States, Chagas disease molecular detection (PCR testing for *T. cruzi* DNA) is available at the Centers for Disease Control and Prevention (CDC); consultations and testing requests should be addressed to Parasitic Diseases Hotline for Healthcare Providers (404-718-4745, parasites@cdc.gov, hours: 8 a.m.–4 p.m. ET/Monday–Friday) or through the CDC Emergency Operations Center (770-488-7100) for emergencies after business hours, on weekends, and federal holidays.

Preventing Exposure

Travelers to endemic countries may be at risk of infection with *T. cruzi* if they visit rural areas and stay in rustic lodging. The triatomine vector typically infests cracks in walls and roofing of poor-quality buildings that are constructed of adobe brick, mud, or thatch.[40] Because the insects feed at night, individuals who live in or visit Chagas disease–endemic areas should avoid sleeping in such dwellings or outdoors. Control programs in endemic areas rely on spraying infested dwellings with residual-action insecticide. If sleeping outdoors or in suspect dwellings cannot be avoided, sleeping under insecticide-treated bed nets provides significant protection.[41]

In the United States, all blood donors are screened for Chagas disease when they first donate blood. Universal screening of blood donors has been implemented in 21 Chagas disease–endemic Latin American countries.[42] Although transfusion-acquired cases have been uncommon in the United States, transfusion with infected blood products remains a risk for acquiring Chagas disease. No drugs or vaccines for preventing *T. cruzi* infection are available.

Preventing Disease

All people with HIV with epidemiologic risk factors for Chagas disease should be tested for antibody to *T. cruzi* to detect latent infection.[29,43]

For people living with HIV, a single course of treatment with benznidazole or nifurtimox should be offered to individuals with *T. cruzi* infection who have not been previously treated and who do not have advanced Chagas cardiomyopathy, with a discussion of potential risks and benefits and shared decision making **(BIII).** However, the efficacy of currently available drugs in the chronic phase is suboptimal, there is no useful test of cure, and treated individuals are still considered at risk for reactivation.[32,44] There are no direct studies evaluating interactions between antiretroviral medications and either benznidazole or nifurtimox. However, as benznidazole may be partially metabolized by the cytochrome P450 (CYP) system, medications that inhibit this system may increase benznidazole toxicity and those that induce CYP enzymes may reduce benznidazole efficacy.[43,45]

Although direct data are lacking, optimization of antiretroviral therapy (ART) may help prevent Chagas reactivation in coinfected patients**.** Most symptomatic reactivation cases have occurred in people with HIV who were not virologically suppressed on ART.[16,43]

Treating Disease

Therapy for Chagas disease with benznidazole or nifurtimox is effective in reducing parasitemia and preventing clinical manifestations or slowing progression in patients with acute and reactivated disease.[44,46] These drugs have limited efficacy, however, in achieving parasitological cure. As both drugs are U.S. Food and Drug Administration (FDA)–approved only for children, use for the treatment of adults in the United States is off-label. Individuals with advanced Chagas cardiomyopathy will not benefit from treatment. Consultation with a specialist should be sought. Consultations with experts at the CDC can be addressed to the Parasitic Diseases Hotline for Healthcare Providers (404-718-4745, parasites@cdc.gov).

Benznidazole (commercially available at http://www.benznidazoletablets.com/en) is approved by the FDA for use in children 2 to 12 years of age. The use of benznidazole to treat a patient outside of the

FDA-approved age range is based on clinical diagnosis and decision by a treating physician under practice of medicine. The regimen of 5 to 8 mg/kg/day in two divided doses taken with or without food for 60 days is the recommended treatment **(BIII);** a daily maximum dose of 300 mg is recommended by most experts.[47,48]

Nifurtimox (Lampit®) is also FDA approved for children less than 18 years of age and is available from retail sources.[49,50] Use of nifurtimox to treat a patient outside of the FDA-approved age range is based on clinical diagnosis and decision by the treating physician under practice of medicine. The recommended regimen is 8 to 10 mg/kg/day in three divided doses with food for 60 days **(BIII).**[51]

Treatment of patients outside of the FDA-approved age ranges for either drug is based on clinical diagnosis and decision by the treating physician under practice of medicine. The duration of therapy with either of these agents has not been studied in people with HIV. Mortality is high for symptomatic reactivated *T. cruzi* infection, even in patients who receive chemotherapy.[16,26] Limited data suggest that early recognition and treatment of reactivation may improve prognosis.[16]

Special Considerations with Regard to Starting Antiretroviral Therapy

As with other parasitic infections that localize in the CNS, the decision to initiate ART must be carefully considered in people with HIV and reactivated *T. cruzi* infection involving the brain. Only anecdotal information exists on the consequences of starting ART after a diagnosis of CNS Chagas disease, but there are no cases of Chagas-related immune reconstitution inflammatory syndrome (IRIS) that have been well described. Therefore, there is no known contraindication to starting or optimizing ART in patients with CNS Chagas disease. ART should be initiated in all patients with concomitant *T. cruzi* **(AIII).** In general, as IRIS is not recognized as a common manifestation in the setting of coinfection, treatment of *T. cruzi* does not warrant delay in ART.

Monitoring for Adverse Events

Patients undergoing treatment should be monitored closely because both benznidazole and nifurtimox are associated with significant toxicities.[46]

Benznidazole-associated adverse drug reactions include abdominal symptoms (abdominal pain, nausea, vomiting, diarrhea), reversible peripheral neuropathy, rash, and granulocytopenia. Comprehensive metabolic panel (CMP) and complete blood count (CBC) should be monitored before initiation and during therapy. Co-administration of benznidazole with disulfiram, alcohol, and products that contain propylene glycol should be avoided.

Nifurtimox-associated adverse drug reactions include anorexia, nausea, vomiting, abdominal pain and weight loss, rash, restlessness, tremors, and dose-dependent peripheral neuropathy. Alcohol consumption with nifurtimox should be avoided. CMP and CBC should be monitored before initiation and during treatment with nifurtimox.

The frequency of monitoring CMP and CBC during treatment, though not standardized, is generally every 2 weeks. The adverse effects of both drugs wane when the drugs are discontinued. For more information, refer to the Adverse Drug Reactions table.

As stated above, there are no reports at this time regarding *T. cruzi* infection and IRIS.

Managing Treatment Failure

People with HIV are at risk for clinical manifestations because of intermittent reactivation of chronic infection.[43] Benznidazole and nifurtimox are only partially effective in the chronic phase of *T. cruzi* infection and may be suppressive rather than curative.[44] Because the drugs are toxic and experience with their use in people with HIV is limited, expert advice should be sought.[46] Whether secondary prophylaxis or chronic maintenance therapy should be used in people with HIV with latent Chagas disease is unclear, particularly when potent ART is used.

There are no current recommendations for monitoring for reactivation after treatment. *T. cruzi* antibodies may persist after treatment. Reactivation after treatment is diagnosed based on compatible clinical symptoms and identification of the parasite in blood or CNS fluid/tissue by microscopy or PCR. Although no efficacy data are available, retreatment with benznidazole or nifurtimox is recommended for people with HIV and *T. cruzi* reactivation who fail to respond or who reactivate again after initial antitrypanosomal therapy **(AIII).**

Special Considerations During Pregnancy

Anyone who has lived in endemic areas should be screened for Chagas disease, particularly if pregnant, to identify maternal infection and possible risk of infection in their offspring.. See the CDC resource for congenital Chagas disease for more information.

Between 1% to 10% of infants of mothers with *T. cruzi* are born with acute *T. cruzi* infection.[52] Most congenital *T. cruzi* infections are asymptomatic or cause non-specific signs; laboratory screening is required for detection of these cases.[53] In a small proportion of patients, congenital infection causes severe morbidity, including low birthweight, hepatosplenomegaly, anemia, meningoencephalitis, and/or respiratory insufficiency, with high risk of mortality.[52,54] Limited data suggest that the rate of congenital transmission is higher for women with HIV than in immunocompetent women.[16,55] Infants with HIV and concomitant *T. cruzi* also may be more likely to have symptoms, especially neurologic symptoms.[56,57]

Minimal data are available on the potential reproductive toxicity of benznidazole and nifurtimox, although both drugs have been associated with increased detection of chromosomal aberrations in children being treated for Chagas disease.[58,59] Benznidazole crosses the placenta in rats.[60] Due to the toxicity and limited experience with use of these drugs in pregnancy, treatment of acute *T. cruzi* infection during pregnancy should only be undertaken in consultation with a specialist in this area, and treatment of chronic disease should be considered only after completion of the pregnancy and breastfeeding. In cases of symptomatic reactivation of *T. cruzi* infection during pregnancy, ART should be initiated **(AIII)** as initial treatment. Only two cases of treatment of Chagas disease in pregnancy with benznidazole have been reported in people with HIV.[61,62] One infant was born with a low birthweight.[62] All infants born to women with *T. cruzi* should undergo appropriate testing for congenitally acquired *T. cruzi* infection and be treated promptly if infection is confirmed.[63,64] Refer to the Opportunistic Infection Drugs During Pregnancy table for additional information.

Recommendations for Preventing and Treating Chagas Disease (American Trypanosomiasis)

Preventing Manifestations of Chagas Disease

- All people with HIV who have epidemiologic risk factors for Chagas disease should be tested for antibody to *T. cruzi* using at least two serological tests based on different antigens (e.g., whole parasite lysate and recombinant antigens) and/or techniques (e.g., ELISA and IFA).

Indication

- Individuals with epidemiological risk factors for Chagas disease who have tested positive for antibody to *T. cruzi*, have not been previously treated, and do not have advanced Chagas cardiomyopathy

Therapy

- A single course of benznidazole or nifurtimox is recommended by some experts (doses and duration same as for treatment of acute or reactivated infection).
  - Benznidazole 5–8 mg/kg/day PO in 2 divided doses for 60 days (BIII) (commercially available at http://www.benznidazoletablets.com/en). Most experts recommend a daily maximum of 300 mg.
  - Nifurtimox (Lampit®) 8–10 mg/kg/day PO in 3 divided doses for 60 days (BIII) (commercially available through retail sources)

Note: Efficacy of both therapies is suboptimal, and treated patients are still at risk of reactivation.

Treating Acute or Reactivated *T. cruzi* Infection

Indication

- Individuals with acute or reactivated *T. cruzi* infection as manifested by presence of parasitemia should be treated (AII).

Therapy

- Benznidazole 5–8 mg/kg/day PO in 2 divided doses for 60 days (BIII) (commercially available at http://www.benznidazoletablets.com/en). Most experts recommend a daily maximum of 300 mg.
- Nifurtimox (Lampit®) 8–10 mg/kg/day PO in 3 divided doses for 60 days (BIII) (commercially available through retail sources)
- Initiation or optimization of ART is recommended for all people with HIV with concomitant *T. cruzi* (AIII).

Note: Treatment is not recommended for patients with advanced chagasic cardiomyopathy.

Key: ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; ELISA = enzyme-linked immunosorbent assays; IFA = immunofluorescence assays; PO = orally

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