Chagas Disease (American Trypanosomiasis)

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Updated: Nov 10, 2014

Background

Chagas disease, also known as American trypanosomiasis, is caused by infection with the protozoan parasite Trypanosoma cruzi. The organism *T. cruzi* and infection in humans were first described in 1909 by the Brazilian physician Carlos R. J. Chagas. *T. cruzi* is found mostly in blood-sucking triatomine insects (kissing bugs) and small mammals in a sylvatic cycle that is enzootic from the southern and southwestern United States to central Argentina and Chile. *T. cruzi* infection in humans occurs in a spotty distribution throughout the range of the sylvatic cycle.\(^1\)

New cases of vector-borne *T. cruzi* infection usually occur in persons who live in primitive houses in areas where the sylvatic cycle is active. The living quarters are invaded by infected triatomines, which become domiciliary. Infected insects take blood meals from humans and their domestic animals and deposit parasite-laden feces. The parasites are then transmitted via contact with breaks in the skin, mucosal surfaces, or the conjunctivas. Transmission can also occur congenitally, via blood transfusion and organ transplantation, and by ingestion of food and drink contaminated with feces from infected bugs.

*T. cruzi* infection is life-long. A minority of persons with long-standing *T. cruzi* infection develop the serious cardiac and gastrointestinal problems that characterize chronic symptomatic Chagas disease.

The parasite

*T. cruzi* is a member of the family Trypanosomatidae in the order Kinetoplastida and belongs to a special section called Stercoraria. The infective forms of *T. cruzi* are contained in the feces of the insect vectors and gain entry into its mammalian hosts through contamination. This mechanism of transmission contrasts with that of the two subspecies of African trypanosomes that cause human disease, *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, which are transmitted via the saliva of their vectors, and with the mechanism by which the nonpathogenic trypanosome found in the Americas, *Trypanosoma rangeli*, is transmitted to its mammalian hosts.

As with other parasites that infect both mammalian and insect hosts, the life cycle of *T. cruzi* is complex (see image below).

The *T. cruzi* life cycle consists of 3 main developmental forms. Epimastigotes are an extracellular and noninfective form of the parasite found in the midgut of insect vectors, where they multiply by binary fission. As epimastigotes (depicted in the first image below) move to the hindgut, they differentiate into metacyclic trypomastigotes (depicted in the second image below), which are nondividing forms resistant to mammalian complement that have the capacity to infect mammalian cells. They then enter local cells through breaks in the skin, mucous membranes, or the conjunctivas and transform into the third morphologic form, amastigotes. Amastigotes multiply intracellularly until the host cell is overwhelmed, at which point they transform into bloodstream trypomastigotes.
Chagas disease (American trypanosomiasis). The trypomastigote is the infective flagellated form of the parasite found in the blood of the mammalian hosts (blood trypomastigote) and in the hindgut of vectors (metacyclic trypomastigote). Image courtesy of Peter Darben, MD.

Chagas disease (American trypanosomiasis). The epimastigote form of Trypanosoma cruzi is the multiplying stage of the parasite that grows in the gut of the insect vector and also in cell-free culture medium as shown here. Image courtesy of Peter Darben, MD.

As the host cells rupture, the trypomastigotes are released into the lymphatics and bloodstream, through which they spread to distant sites and invade new host cells. See image below.

Trypanosoma cruzi trypomastigotes in a mouse blood smear (Giemsa, x625). Courtesy of Dr. Herbert B Tanowitz, New York, NY.

This process continues asynchronously for the life of the host. Small numbers of trypomastigotes may be ingested in blood meals taken by uninfected triatomines. The trypomastigotes transform into epimastigotes in the midgut of these insects, thus completing the cycle.

*T. cruzi* can also be transmitted when mammalian hosts ingest infected insects, and this mechanism of transmission may play a major role in maintaining the sylvatic cycle.

Numerous biological, biochemical, and molecular studies have shown that the population of *T. cruzi* is highly diverse. Although *T. cruzi* is a diploid organism in which some genetic exchange may occur in insect vectors, its genetic and phenotypic diversity is thought to result from the clonal multiplication of the epimastigote and amastigote forms. The current consensus is that *T. cruzi* can be divided into 6 discrete taxonomic units (DTUs: Tcl through TcVI). The strains in each DTU show variability in geographic, epizootic, epidemiologic, and pathogenic characteristics.

**Vectors of *T. cruzi***

Triatomines, which transmit *T. cruzi*, belong to the family Reduviidae in the order
Hemiptera. Reduviidae has 22 subfamilies, including the Triatomiinae. Although the vectors of \( T \) \( cruzi \) are occasionally referred to as reduviids, this term is not appropriate since the vast majority of the species in the family Reduviidae are phytophagous or insectivorous and do not transmit the parasite.

All triatomine species are able to transmit \( T \) \( cru z i \) to humans, but only a handful become domiciliary to any great extent and are important as \( T \) \( cru z i \) vectors. Many more triatomine species are involved in the widespread sylvatic cycles. Triatomines have 5 nymphal stages (instars), all of which can harbor and transmit \( T \) \( cru z i \).

The three vector species most important in the transmission of \( T \) \( cru z i \) to humans include \textit{Triatoma infestans}, \textit{Rhodnius prolixus} (see image below), and \textit{Triatoma dimidiata}. Historically, \textit{T infestans} has been by far the most important, as it has been the primary vector in the sub-Amazonian endemic regions. Since the early 1990s, under the aegis of the Southern Cone Initiative (SCI), which is supported by the World Health Organization (WHO) and the Pan American Health Organization (PAHO), Chagas disease control programs in Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay have focused on eliminating domiciliary \( T \) \textit{infestans}.

These efforts have been widely successful, so much so that Uruguay, Chile, and, most recently, Brazil have been declared transmission-free by the PAHO.

Major progress in vector control has also been achieved in Argentina, Paraguay, and Bolivia. Programs similar to the SCI have been implemented in the Andean nations and Central America, where \( R \) \textit{prolixus} is typically found. The range of \( T \) \textit{dimidiata} is similar but also extends far into Mexico. Other domiciliary species occupy more restricted areas and play less important roles in the transmission of \( T \) \textit{cru z i} to humans. The sylvatic species can also colonize human dwellings and thus present a potential risk for transmission.

Mammalian hosts of \textit{T cru z i}.

\( T \) \textit{cru z i} infection has been found in more than 100 mammalian species throughout the range mentioned above, which includes the southern and southwestern United States. Mammals typically involved in sylvatic cycles of transmission include opossums, armadillos, raccoons, monkeys, wood rats, and coyotes, among many others.

Pets such as dogs and cats can become infected in enzootic regions, likely as they eat parasitemic prey or ingest infected insects. It is of interest that Carlos Chagas observed \( T \) \textit{cru z i} in the blood of wild marmosets and a domestic cat before he discovered the parasite in the blood of his first infected patient, Berenice. In some situations, dogs have been shown to be an important link in the maintenance of the domiciliary cycle and consequent transmission to humans.

Livestock have occasionally been found to be infected with \( T \) \textit{cru z i}, but the parasite is not known to affect the health of livestock. Birds, amphibians, and reptiles are naturally resistant to \( T \) \textit{cru z i} infection; however, in some situations, birds may be important sources of blood meals for triatomines.

The modes of transmission of \textit{T cru z i} to humans.

Historically, most transmissions of \( T \) \textit{cru z i} to humans have resulted from the contamination of vulnerable surfaces (eg, breaks in the skin, mucosae, and the conjunctivas) with the feces of infected vectors. However, as noted, vector-borne transmission has been reduced markedly in many endemic countries. Transfusion transmission was a major public health problem in endemic countries for decades, but, as accurate serologic assays for \( T \) \textit{cru z i} infection were developed and screening of blood donors became mandatory and were implemented throughout the endemic range, this problem has been all but eliminated.

Not surprisingly, \( T \) \textit{cru z i} can also be transmitted via transplantation of organs obtained from persons with chronic infection, and occasional reports of this in Latin America and in the United States have appeared.

The rate of congenital (transplacental) transmission from mothers with chronic \( T \) \textit{cru z i} to their newborns has been studied extensively.

http://emedicine.medscape.com/article/214581-overview#showall
Trypanosoma cruzi infection to their newborns is 1%-15%.\[^{22, 23}\]^\[2\] To date, no measures have been defined to reduce or eliminate this form of transmission.\[^{24, 25, 26}\]^\[2\] As transmission by vectors and through transfusion of contaminated blood have been reduced, the proportion of new T cruzi infections that result from congenital transmission has increased. Nonetheless, the overall number of instances of congenital transmission certainly has decreased as seroprevalence rates have fallen.

In contrast to Toxoplasma gondii, vertical transmission of T cruzi is possible with successive pregnancies. Transmission of T cruzi via breast milk appears to be extremely rare.\[^{27}\]^\[2\] Several instances of transmission of T cruzi to groups of people via ingestion of food or drink presumably contaminated with the feces of infected vectors have been reported.\[^{28, 29, 30, 31, 32, 33}\]^\[2\] Finally, the facility of producing infective forms of T cruzi in the laboratory has resulted in numerous accidental transmissions in this context.\[^{34}\]^\[2\]

**Pathophysiology**

An inflammatory lesion caused by T cruzi that may appear at the site of entry in patients with acute Chagas disease is called a chagoma.\[^{35}\]^\[2\] Histologic changes may include interstitial edema, lymphocytic infiltration, and reactive hyperplasia of adjacent lymph nodes due to intracellular parasitism of muscle and other subcutaneous tissues. When parasitized host cells rupture, trypomastigotes are released and can often be detected by microscopic examination of anticoagulated blood. As the infection spreads systemically, muscles, including the myocardium, and various other tissues become parasitized.\[^{36}\]^\[2\]

Acute myocarditis, consisting of patchy areas of necrosis and infected cells, may develop (see image below).\[^{37, 38}\]^\[2\] The pseudocysts occasionally seen in sections of infected tissues are intracellular aggregates of amastigotes. The patent parasitemias of the acute illness may be accompanied by lymphocytosis, and transaminase levels may be elevated. The cerebrospinal fluid may contain parasites.\[^{39}\]^\[2\]

The heart is the most commonly affected organ in persons with chronic Chagas disease.\[^{40}\]^\[2\] Autopsy may reveal marked bilateral ventricular enlargement, often involving the right side more than the left, in the heart of patients who die of chagasic heart failure (see image below). The ventricular walls are often thin, and mural thrombi and apical aneurysms may be present. In addition, diffuse interstitial fibrosis, widespread lymphocytic infiltration, and atrophy of myocardial cells may all be present.
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T cruzi parasites are rarely found during microscopic examination of stained sections of myocardial tissue; however, in numerous studies, T cruzi -specific polymerase chain reaction (PCR) assays have demonstrated parasites in areas of focal inflammation.[41, 42, 43, 44] Pathologic changes in the conduction systems of chronic chagasic hearts are also common and often correlate with dysrhythmias.[45] Chronic inflammatory lesions and dense fibrosis frequently involve the right branch and the left anterior branch of the bundle of His, but lesions may also be found in other segments of the conduction system.

Salient features on gross examination of the colon or esophagus in patients with chronic chagasic gastrointestinal disease (megadisease) include dilatation and muscular hypertrophy of the affected organs (see images below).[46, 47] Focal inflammatory lesions with lymphocytic infiltration are visible on microscopy. The number of neurons in the myenteric plexus is often markedly reduced, and periganglion and intraganglion fibrosis with accompanying Schwann cell proliferation, along with lymphocytosis, are present. In most patients with megadisease, the functional effects of this parasympathetic denervation are limited to the esophagus or colon, but clinically manifest dysfunction of the ureters, biliary tree, and other hollow viscera has been reported.
Air-contrast barium enema of a Bolivian patient with chronic Chagas disease and megacolon. The markedly increased diameters of the ascending, transverse, and sigmoid segments of the colon are readily apparent.

The pathogenesis of cardiac and gastrointestinal lesions of chronic Chagas disease has been a focus of debate for decades.\(^{48, 49, 50}\) During the last 20 years, however, convincing evidence has shown that low levels of parasites in chronically affected tissue, detectable with molecular methods, provokes a chronic inflammatory response that eventually leads to the pathologic changes observed microscopically and organ dysfunction.\(^{43, 51}\)

### Epidemiology

#### Frequency

**United States**

Despite the presence of the sylvatic cycle of *T. cruzi* transmission in the southern and southwestern United States, only 23 cases of autochthonous transmission of the parasite have been reported.\(^{37, 52, 53}\) Although some cases of *T. cruzi* infection probably go unnoticed or unreported, autochthonous acute Chagas disease is rare in the United States. This concept is supported by the extreme rarity of *T. cruzi* infection among US blood donors who were not born in or who have not traveled extensively in endemic countries. The rarity of vector-borne transmission of *T. cruzi* to humans in the United States is likely due to the overall sparsity of vectors and the generally higher housing standards, which help prevent the vectors from becoming domiciliary.

In contrast, the epidemiology of chronic *T. cruzi* infection in the United States has changed markedly in the last few decades owing to the large number of people from endemic countries who have moved to the United States. According to one recent estimate, 23 million persons from endemic countries now live in the United States, 300,000 of whom have chronic *T. cruzi* infection.\(^{54, 55}\) Approximately two thirds of these immigrants from endemic countries are from Mexico, where the overall prevalence of *T. cruzi* infection is 0.5%-1%.\(^{56}\)

Five cases of transfusion-associated transmission of *T. cruzi* were reported in the United States prior to the implementation of donor screening in 2007,\(^{57, 58}\) all of which occurred in immunocompromised patients.\(^{59}\) Two additional such cases were found through trace-back studies after screening started.\(^{60}\)

Two tests are currently being used to screen US blood donors for Chagas disease: the Ortho *T. cruzi* ELISA Test System (Ortho Clinical Diagnostics, Rochester, NY)\(^ {61, 62}\) and the Abbott Prism Chagas assay (Abbott Laboratories, Abbott Park, IL).\(^ {63}\) Donor samples positive in either of the two screening assays generally undergo confirmatory testing in the Chagas RIPA (performed by Quest Diagnostics, Inc., Chantilly, VA)\(^ {64}\) or the Abbott Enzyme Strip Assay (ESA) Chagas.\(^ {65, 66}\)

The data accumulated to date indicate that about 1 in every 13,000 US blood donors is infected with *T. cruzi* (ie, repeat reactive in the Ortho or Abbott screening assays and positive in the Chagas RIPA or the Abbott ESA), which is consistent with estimates by groups familiar with the epidemiology of *T. cruzi* in the United States prior to the initiation of screening. No instances of transfusion transmission of *T. cruzi* in the United States are known to have occurred since donor screening was implemented.

Five recipients of organ transplants from 3 donors with *T. cruzi* infection developed acute Chagas disease in the United States, one of whom died of the illness.\(^ {20, 21}\)

**International**

*T. cruzi* is found only in the Americas, except in isolated cases in which infected persons have carried the parasites to other regions (eg, the Far East, Australia, Europe).\(^ {67, 68, 69, 70, 71}\) The PAHO estimates that, in 2006, 7.7 million persons had *T. cruzi* infection in the 21 endemic countries, which had a total population of
532 million.[72] The PAHO also estimated that there were approximately 41,200 new vector-borne cases of T cruzi infection per year and that 14,400 infants were born with congenital Chagas disease annually.

According to PAHO estimates at that time, the following are the countries most affected by Chagas disease: Bolivia (6.8% prevalence); Argentina (4.1%); El Salvador (3.4%); Honduras (3.1%); Paraguay (2.5%); Guatemala (2%); Ecuador (1.7%); French Guyana, Guyana, and Surinam (1.2%); Venezuela (1.2%); Nicaragua (1.1%); Brazil (1%); and Mexico (1%).

As noted above, in recent years, the epidemiology of T cruzi infection has improved markedly in many endemic countries, as blood bank and vector-control programs have been implemented. Because of the success of programs directed at domiciliary vector programs, prevalence rates in younger age groups have been decreasing in many areas.[73, 74, 75, 76] All endemic countries have statutory or regulatory mandates for screening donated blood for T cruzi, and, with a few notable exceptions, particularly Mexico,[54, 77, 78, 79] effective universal screening has been implemented.[16]

In the author’s view, the enormous progress made in controlling Chagas disease in recent decades clearly indicates that the obstacles hindering the complete elimination of T cruzi transmission to humans are primarily economic and political. In this context, no additional major advances, such as a more detailed understanding of the pathogenesis of Chagas disease,[80, 81] further genetic analyses,[4, 82] novel diagnostic approaches, or breakthroughs in vaccine development,[83] are necessary for its completion. Other investigators take an opposing view regarding the application of high-technology approaches to the problem of Chagas disease.[84]

**Mortality/Morbidity**

Approximately 12,000 deaths attributable to Chagas disease occur annually, typically due to heart disease,[85, 86, 87, 88] or, much less frequently, megadisease or meningoencephalitis.[89] In persons with chronic T cruzi infection, mortality is primarily due to the rhythm disturbances and congestive heart failure that result from the chronic inflammatory cardiomyopathy due to the persistence presence of parasites in the heart tissue.[90] Embolization of intraventricular clots to the cerebrum and lungs can also contribute to mortality.

Individuals with severe megaesophagus who do not receive medical attention can die of malnutrition and/or chronic aspiration pneumonitis. Megacolon (depicted in the image below) can also result in death, usually when volvulus develops and is not resolved surgically.

![](image)


**Race**

T cruzi infection does not have a racial predilection.

**Sex**

T cruzi infection does not have a sexual predilection.

**Age**

Morbidity during the acute phase of Chagas disease is more pronounced in children than in adults. The gastrointestinal and cardiac manifestations of chronic T cruzi infection become apparent many years or even decades after initial infection and
thus occur almost exclusively in adults.

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Disclosure: Received salary from Goldfinch Diagnostics Inc. for equity owner; Received royalty from Quest Diagnostics Inc. for licensed technology; Received royalty from Abbott Laboratories, Inc. for licensed technology.

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Disclosure: Nothing to disclose.

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Disclosure: Nothing to disclose.

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37. Ochs DE, Hnilica VS, Moser DR, et al. Postmortem diagnosis of autochthonous acute chagasic myocarditis
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