

Chagas disease: from Latin America to the world

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Abstract: Migratory flows have globalized Chagas disease and have contributed to change its epidemiology. Additionally, Chagas disease has a great impact on the affected people as well as on the economy of their countries. However, till now, this disease remains a neglected disease. Historically, very few resources have been invested to study Chagas disease or to provide care to the millions of affected people. In Latin America, the endemic countries still have several challenges ahead, which include care for the affected people, the effective control of vertical transmission, or the maintenance of vector control. In nonendemic countries where the disease is emerging, care for patients and the control programs for blood banks, organ transplant, and mother-to-child transmission should be the priorities.

Keywords: Chagas disease, *Trypanosoma cruzi*, migration, benznidazol, globalization

Introduction: biology and epidemiology of Chagas disease

Chagas disease (CD), caused by the parasite *Trypanosoma cruzi* (*T. cruzi*), is the third most common parasitic infection worldwide, the most important in Latin America and is an emerging disease in Spain, the US, and other nonendemic countries.¹ Up to now, and because endemic populations affected were mainly rural and marginalized, CD has been considered a neglected disease.² The global economic burden of this infection is calculated to be \$7.19 billion per year, similar to or worse than other well-known diseases like rotavirus or cervical cancer.³

T. cruzi, the parasite that causes CD, is highly diverse and has a complex life cycle involving around 125 triatominae species and more than 100 mammal species,⁴ showing a patchy distribution.⁵ Besides, *T. cruzi* is a heterogeneous species with different biological characteristics.⁶

The parasite has the capability to express different antigens at different stages of differentiation, causing varying responses within hosts. *T. cruzi* has the capability to evade antigen presentation through major histocompatibility complex class I and to produce products that interfere with immune response modulation and activation.⁷ Resistance against infection could be regulated by the genetic characteristics of the host, but the persistence of the infection is due to additional factors depending on both the parasite and the host.⁸

In most cases, the immune response of the host is not enough to eradicate the parasite. Therefore, a vaccine in order to reinforce immune response to the parasite has been proposed, but it is still in the early stages of development.

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The parasite plays a fundamental role in the genesis and development of lesions in the host, inducing cell lysis, an inflammatory response, and fibrosis. The inflammatory reaction is intense during the acute phase, then lower, but maintained, in the chronic phase of the infection.⁹ The initial inflammatory response is a result of the rupture of infected cells that release a great amount of proinflammatory trypanomastigotes and parasitic molecules, dead parasites, and cellular waste.¹⁰ Cellular lesions primarily affect muscle cells (myocytolysis) and nerve cells (autonomic neuronal denervation)^{11,12} producing megaviscera. Recent results show that cardiac and digestive lesions are preferably observed in patients with few regulatory T-lymphocytes (CD4+CD25+h) capable of limiting cytotoxic mechanisms that depend on CD8+ T-cells.^{12,13} Fibrosis develops more intensely in chronic Chagas heart disease than in any other etiology, as a poorly vascularized collagen neof ormation of difficult regression.

Although several mechanisms of autoimmunity have been described as a cause of pathophysiological changes in patients with CD,^{14,15} there is no conclusive evidence that autoimmunity plays a role in its pathogenesis.^{16,17}

Regarding clinical stages of the disease, after the acute clinical phase, in which only a low percentage of the infected people have enough clinical symptoms to be detected and treated, the infection becomes chronic. People are usually asymptomatic for many years. However, 30%–40% of the chronically infected people develop symptoms several years after infection. The development of clinical symptoms is gradual and paucisymptomatic at first. The heart, the digestive tract, and, to a lesser extent, the central nervous system (CNS) are the main involved organs or systems presenting clinical disease.^{18,19} The main clinical symptoms affecting infected people are described in Tables 1 and 2.

The chronicity of the infection is one of the key factors that explain the spread of the disease beyond the Americas. Moreover, the slow development of symptoms years after the infection and the nonspecificity of these symptoms make CD difficult to be diagnosed in early stages of the infection.

The epidemiology of CD has been traditionally related to migration flows,²⁰ which firstly started from rural to urban areas in endemic countries, were later followed by migrations to mainly the US and Spain,²¹ with more than 22 million and 2 million people, respectively.^{21,22} Blood banks control, programs of vector control with the use of insecticides, and the increasing detection of oral transmission outbreaks have recently contributed to modify the epidemiology of CD.^{23–26} Moreover, epidemiological changes are currently underway in Europe due to the economic crisis that pushes Latin American

Table 1 Signs and symptoms associated with chronic cardiological Chagas disease

Cardiological alteration	Symptom related
Bradyarrhythmias or tachyarrhythmias	Palpitations Syncope Presyncope Fainting Sudden death
Heart failure	Effort dyspnea Hepatic congestion: pain in the right hypochondriac region Pulmonary congestion: orthopnea, paroxysmal nocturnal dyspnea
Venous and systemic thromboembolic events	Pulmonary or systemic emboli Cerebrovascular accident (generally ischemic)
Microvascular (or esophageal) abnormalities	Precordial or retrosternal pain

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migrants living in Spain and Italy to move to other European countries with better job opportunities.²⁷

Globally, it is estimated that 8–10 million of people are infected by *T. cruzi* and that around 90–100 million people are estimated to be at risk of infection.²⁸ Moreover, around 12,500 deaths a year can be attributable to CD.²⁵ In Europe, it is estimated that there are between 68,000 and 123,000 patients infected with *T. cruzi*, but until 2009 only 4,290 cases were reported.^{21,29} In the US there are about 300,000 people infected with *T. cruzi*.²² The number of people affected by *T. cruzi* in other countries ranges from 140 in Australia to 12,000 in England.^{21,29,30}

Table 2 Signs and symptoms associated with chronic digestive Chagas disease

Esophageal alterations	Colon alterations
<ul style="list-style-type: none"> • Dysphagia: in relation to solids/liquids; changes with heat/cold; location of dysphagia • Regurgitation: active (after ingestion) or passive (in advanced cases, generally in decubitus) • Retrosternal chest pain • Odynophagia • Nocturnal cough • Sialorrhoea • Parotid gland hypertrophy 	<ul style="list-style-type: none"> • Constipation • Changes in bowel habit • Straining at stool • Incomplete evacuation sensation
	Gastric/duodenal alterations
	<ul style="list-style-type: none"> • Dyspepsia • Pyrosis • Bloating • Satiety sensation • Epigastric pain (eventually)

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The spread and globalization of *T. cruzi* infection and its introduction to nonendemic countries oblige the recipient countries to attend several challenges of public health concern, mainly referred to the care of infected people and the control of transmission.

Transmission, diagnosis, and management

The transmission of *T. cruzi* to humans can occur through several ways: by vector transmission (the main form of intradomiciliary transmission), oral transmission (contaminated food and drinks), blood transfusion, organ transplants, mother-to-child transmission, and accidental infection in laboratories. Among them, only vector and oral transmission are restricted to traditionally endemic areas.

- **Vector transmission:** Vector transmission is a result of depositing infected metacyclic trypomastigotes found in the droppings of triatomines on the cracked skin and/or mucous membranes of human beings or animals. The parasite goes through the host's tissues reaching peripheral blood and is spread by the host.
- **Oral transmission:** Another transmission way, restricted to endemic areas, is the ingestion of food or drinks contaminated with metacyclic trypomastigotes forms coming from droppings of infected Triatominae or by the triatomine itself.³¹
- **Blood transmission:** Historically considered as the second major route of *T. cruzi* infection, this way of transmission (whole blood or blood compounds) is possible in both endemic and nonendemic countries. The risk of transmission through blood transfusion varies due to a number of factors such as the immune status and age of the recipient, the strain of the parasite, the amount of blood transfused, and the number of transfusions received.^{32,33}
- **Organ transplantation:** A common practice implemented in the last decades, is also a potential way of *T. cruzi* transmission in both endemic and in nonendemic countries that receive Latin American migration.
- **Maternal–fetal transmission:** Infection and congenital CD is due to the transmission of *T. cruzi* from a mother with the parasite to her fetus through transplacental and/or transmembrane blood.^{34,35}
- **Other transmission ways:** Laboratory accidents and other such ways of transmission, have minor epidemiological relevance.

The diagnosis of *T. cruzi* infection is based on epidemiological risk, clinical features, and laboratory testing. Following

World Health Organization (WHO) recommendations,³⁶ the diagnosis of Chagas' is based on:

- History compatible with the epidemiology of the disease, regarding possibility of having acquired the infection.
- Laboratory diagnosis: individuals are considered to be infected when they have a positive result in parasitological tests or two positive results with two serologic techniques that employ different antigens.

Antibody response starts at the end of the first month after infection, and the number of circulating parasites, that have been multiplying during this period, decrease. In the acute stage of the infection, the parasite is easy to detect in peripheral blood and the diagnosed methods proposed are based on the parasite detection.³⁷ Micromethod and Strout are the main concentration methods used for *T. cruzi* diagnosis. Diagnosis in the chronic stage of the disease is based on serological techniques detecting IgG antibodies against *T. cruzi*, because the parasite load after the acute phase of the disease decreases exponentially³⁸ and the peripheral parasitemia is intermittent and scarce. Following the current international criteria, in the chronic stage of the disease at least two serological methods using different antigens must have positive results to establish a diagnosis.³⁶ Even if different serological tests have shown to be useful for the diagnosis of the chronic stage of the disease, ELISA (enzyme-linked immunosorbent assay) tests have proven the highest sensitivity, and several ELISA kits which employ recombinant proteins are highly sensitive and specific.³⁹

Molecular techniques like polymerase chain reaction (PCR)⁴⁰ have proven to be highly useful in clinical trials and have demonstrated a high sensitivity to be useful in the diagnosis and monitoring of newborns and for the control of reactivation in transplant recipients.^{41–44}

It is estimated that every year 2% of chronically infected people start to develop heart or digestive tract complications.⁴⁴ Regarding the diagnosis of the organ involvement in case of chronic stages of the disease, specific studies of cardiac and digestive organs are necessary. An electrocardiogram, echocardiography, and chest X-Ray are the basis of cardiologic involvement diagnosis. Other studies as 24-hour Holter monitoring, electrophysiologic study, ergometry, or cardiac catheterization could be employed following the symptomatology of each patient. Radiological tests such as abdominal X-ray, barium swallow, and barium enema are used to determine if there are digestive complications.

The management of CD should be focused in two aspects: the antiparasitic treatment in order to eradicate or

diminish the parasite burden and the management of organ complications.

Following WHO recommendations, antitrypanosomal treatment is recommended where *T. cruzi* infection is diagnosed by parasitological and/or serological methods,³⁶ in the absence of contraindication.⁴⁵ There are two drugs accepted for *T. cruzi* infection treatment: benznidazole (BZD) and nifurtimox (NFX). Treatment with these drugs provides cure rates of almost 100% in children under 12 months⁴⁶ and around 60% in people with chronic recent infection.⁴⁷ The efficacy in later chronic stages of the disease is still unclear due to the lack of early biomarkers of therapeutic efficacy, however, several studies show a reduction of clinical complications in treated patients⁴⁸ or are underway trying to show more conclusive results.⁴⁹

Moreover, a recently published study shows that fertile women previously treated with BZD, have a lower probability to transmit *T. cruzi* than the nontreated women.⁵⁰

The regime of BZD in children should be indicated with an 8–10 mg/kg daily dose in two or three divided doses for 60 days, and for adults, with a 5 mg/kg daily dose. NFX should be prescribed at a dose of 15 mg/kg daily in three divided doses for 60–90 days for children and 8–10 mg/kg daily for adults. Both drugs must be administered after meals. BZD is the most used drug, due to its widespread availability.

Both drugs have common adverse drug reactions (ADRs) and cause dermatological, digestive, neurological (most frequent with NFX), articular, and general symptoms like asthenia, anorexia, and fever.^{51–53} Only 5% of the ADRs are severe, and the mild and moderate ADRs could be well managed with symptomatic treatment. In order to better manage the presence of ADRs, a close follow-up of patients under treatment should be performed.

The need for better tolerated and efficacious drugs is one of the main priorities in CD. Ketoconazole and allopurinol, among others, have been tested in patients with CD without success.⁵⁴

Today, new drugs as posaconazole (POS), pro-vacuonazole, or fexinidazole have been recently tested or are currently under investigation.^{55,56} Until now, these drugs have shown that they are not useful as unique drugs for the treatment of CD at the doses proposed.

Regarding advances in the development of a therapeutic vaccine, recent studies in murine models have shown that vaccine-based immunostimulation might offer a rational alternative to reprogram the immune response in order to

preserve and even recover tissue injury in Chagas' heart disease.^{57,58}

Monitoring and surveillance, risk estimation, and management

Even if laboratory diagnosis is well established, there is a lack of laboratory tests to confirm parasitological cure or response to treatment. In patients treated with BZD or NFX, seroconversion measured by conventional serological test, that takes several years to occur in the chronic stage of the disease, is currently the gold standard for evaluating efficacy of drugs against *T. cruzi*.^{48,59} Several biomarkers of response to treatment are currently being investigated in order to assess early response to treatment and therapeutic efficacy. These biomarkers could be used in clinical trials with new drugs or combinations of drugs and for monitoring treated patients.^{60–62}

On the other hand, the early diagnosis of heart or intestinal damage leads to early management and control of the clinical features derived from CD. For this purpose, several biomarkers (myocardial damage as diastolic dysfunction, natriuretic peptides, and troponins^{63,64}) and certain complementary techniques (cardiac magnetic resonance^{65,66} or esophageal manometry^{67–69}) have been proposed in selected cases.

Less than 1% of infected people receive specific treatment against *T. cruzi*. It is important to reinforce the message that cardiac or digestive events are due to the persistence of the parasite in these body tissues. Moreover, in nonendemic countries, education of health professionals on this new, emerging, and neglected disease, is necessary to improve the diagnosis and therefore the treatment. For this purpose, several clinical guidelines have been published.^{41,70–72}

Status of vector control, prevention, and prospects for controlling the spread of Chagas disease

During the last decades, vector control has been reinforced with excellent results⁷³, and, currently, the challenge is to give continuity to vector control measures in order to avoid the possibility of resurgence of vector-borne transmission in regions where it is already successfully controlled. The situation in the US deserves a specific comment. Although in 27 states of the country eleven species of triatominae have been detected, and many of them are parasitized by *T. cruzi*, the risk of transmission of the parasite to humans is very low.⁷⁴ Only few autochthonous human cases of CD have been reported in the US. This is possibly due to the higher standard of housing construction and the low level of contact between kissing bugs and humans.

Several outbreaks of orally transmitted *T. cruzi* have been described in the last years. Measures of continuous insecticide application together with hygiene education with community participation have been introduced in order to better control vector-borne reinfestation and transmission, including measures to prevent oral transmission.^{74–77}

The control of vertical (mother-to-child) transmission is another important step in the prevention of new cases in both endemic and traditionally nonendemic countries. However, only in few endemic countries specific programs for controlling vertical transmission are in place, still being one of the most important challenges in Latin America.^{78–80} In 2004, the Pan American Health Organization established a guideline for the diagnosis and treatment of congenital CD.⁸¹

Every year between 20–183 and 63–115 children in Europe and the US, respectively, are born infected with *T. cruzi*.^{22,29} In one study, the risk of mother-to-child transmission was estimated to be 7.3% in Spain.⁸² However, there is no specific program to control vertical transmission in the US, and only few regions have implemented control programs in maternity wards in Europe.⁸³

Due to the high efficacy of specific *T. cruzi* treatment in newborns (close to 100%) and the cost-effectiveness of these control programs,⁸⁴ they should be implemented in all the affected countries to screen pregnant women coming from endemic areas, with the objective to give early treatment to the infected newborns.

There are no studies to assess the risk of transmission through organ transplants, but some cases of transmission through this pathway have already been reported.⁸⁵ To reduce the risk of infection through transplants, several clinical guidelines have been published.⁴³

Moreover, in Europe, some national transplant organizations (Italy, Spain, and the UK) have included specific directives regarding the control of *T. cruzi* transmission through organ transplantation in their national guidelines.⁸³ Also, the risk of *T. cruzi* reactivation is of concern in CD patients who are immunosuppressed due to organ transplant.⁸⁶

Control programs in blood banks have achieved good results in endemic countries.⁸¹ Several studies have assessed the risk of transmission in maternity wards and blood banks in nonendemic countries. Regarding blood transmission, studies in Spain, the US, and other countries have shown a risk of transmission ranging from 0.62% to 5%.^{79–82,87–91} Universal blood donation screening for *T. cruzi* began in 2005 in Spain and in 2007 in the US. Up to now, in Europe, only four more countries (France, Switzerland, UK, and Sweden) have implemented clear and effective measures to

control risk of CD via blood transfusion. In the US, systematic screening for people at risk has been mandatory since 2010. The measures to control blood transmission in other countries like Australia and Japan have been mainly based on questionnaires to assess *T. cruzi* transmission risk.

Overall, for the control of *T. cruzi* transmission in both endemic and nonendemic countries, it is mandatory to modify public health policies in blood banks, maternity wards, and in the transplant programs.

Conclusion

Nowadays, CD is still a neglected disease and a public health problem in both endemic and nonendemic countries. Health systems worldwide should be prepared to give response in order to avoid new cases of the infection by preventive measures, and to have better tools to manage patients at different stages of the disease. Global collaboration and research on new tools to improve diagnosis, treatment, and control measures should be supported and reinforced. Several initiatives have started to define priorities and milestones to improve the situation of neglected CD patients.^{92,93} In 2012, a community of international partners endorsed the London Declaration on Neglected Tropical Diseases,⁹² demanding coordinated efforts to eliminate or control 10 neglected tropical diseases, including CD.

In 2013, The Global Chagas Disease Coalition was launched.⁹⁴ This is an open collaborative alliance that aims to facilitate the access to existing tools for the affected individuals in order to improve their condition. It also calls for a new R&D agenda and for strengthening control programs in endemic and nonendemic countries.

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Disclosure

The authors report no conflicts of interest in this work.

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