Chagas diseases

https://doi.org/10.56238/sevened2024.007-052

Isadora Max Amaral[1], Ana Eliza Machado[2], Lígia Braz Benfica do Nascimento[3], Sarah dos Santos Oliveira[4], Janaina Sousa Campos Alvarenga[5] and Ângela Cardoso Alvarenga[6]

ABSTRACT

Introduction: Chagas disease, also known as American trypanosomiasis, is a slowly progressing chronic condition that mainly affects the heart muscle and the smooth muscle of the digestive tract. The World Health Organization recognized the disease in 2005 as a neglected tropical disease, which contributed to raising international awareness. Aim: To provide a more comprehensive overview of Chagas disease, exploring specific characteristics in order to combat misinformation about this public health condition. Etiological agent: Trypanosoma cruzi is a protozoan of the Trypanosomatidae family, unicellular, with an elongated "C" shaped cell and a single flagellum at the anterior end. Vector: The vectors of Chagas' disease are triatomine insects - which are nocturnal and have a life expectancy of 1 to 2 years - also known as barbers. The most epidemiologically relevant genera are Panstrongylus, Triatoma and Rhodnius. Evolutionary forms: The different forms (trypomastigote, epimastigote and amastigote) of Trypanosoma cruzi play specific roles in the parasite's life cycle, involving transmission, reproduction and infection in hosts. Forms of contamination: Cont amination in Chagas disease can be via the vector, through the feces that are eliminated at the time of the bite, vertical transmission, oral transmission, blood transfusion, organ transplantation and transmission through laboratory accidents. Biological cycle: The parasite's life cycle is complex and involves invertebrate hosts (barbers) and different species of wild and domestic mammals, including man. Clinical manifestations: This is a chronic disease. In the initial, acute phase, most patients are asymptomatic and then progress to the indeterminate form of the disease, which can last for decades. Years later, the patient may present in chronic stages, the cardiac form; with cardiopathy associated with myocarditis and fibrosis that results in heart failure, blood clot formation and cerebrovascular accidents; or the digestive form with alterations such as megacolon and/or megaesophagus, which may be associated with gastrointestinal disorders, Diagnosis: The diagnosis, in the acute phase is made from the direct parasitological examination on a blood slide. In the chronic phase, the disease is rarely detected, as most individuals are asymptomatic Treatment: Treatment consists of the use of drugs such as Benznidazole and Nifurtimox. Prophylaxis: With regard to the prevention of Chagas disease, vector control measures such as the application of long-lasting insecticides in homes and peridomiciliary structures are essential. In addition, improving the quality of domestic structures, serological screening of blood components, mosquito screens on doors and windows are also measures used. Conclusion: Chagas disease represents a significant public health challenge due to the chronic cases of the disease, which are complex and manifest themselves in different ways. It is essential to emphasize the importance of updating information and consulting health professionals in order to properly manage this condition.

Keywords: Chagas Disease, Trypanosomiasis, Trypanosoma cruzi, Triatomines.

[1] Medical student at PUC Minas.
[2] Medical student at PUC Minas.
[3] Medical student at PUC Minas.
[4] Medical student at PUC Minas.
[5] Dr. in Parasitology, Professor of Medicine at PUC Minas.
[6] Dr. in Parasitology, Professor of Medicine at the University of Itaúna, MG.

INTRODUCTION

Chagas disease, also known as American Trypanosomiasis, is a chronic disease of slow evolution, which mainly affects the heart muscle and the smooth muscles of the digestive tract. This pathology was discovered by Carlos Chagas, a Brazilian scientist, in 1909, while investigating a malaria epidemic in Minas Gerais. From this perspective, it is an endemic parasitic disease in rural and urban areas in a large part of the Americas, from the south-central region of the United States to the south of Argentina, where it represents an important public health problem, since, according to the World Health Organization, there are about 6 to 7 million individuals infected with *Trypanosoma cruzi*. etiological agent of the disease.

In 2005, Chagas disease was recognized by the WHO as a neglected tropical disease and, as a result, facilitated the recognition of the pathology as a public health problem in the international scenario, the fight against misinformation, and the political commitment related to American trypanosomiasis.

ETHIOLOGICAL AGENT

Or *Trypanosoma cruzi*, protozoan of the family *Trypanosomatidae*, presents an elongated, flagellated cell and heteroxenic biological cycle. It has different strains and groups, known as discrete typing units (DTU), which have a wide diversity of mammalian hosts and worldwide distribution. In this panorama, the description of seven DTUs in the Brazilian territory is evidenced, however, little is known about their distribution in nature, hosts, reservoirs and risk for human disease.

The life cycle of *T. cruzi* is complex, since the parasite has four stages of development in its hosts: blood amastigote and trypomastigote in mammalian hosts; and metacyclic epimastigote and trypomastigote in the insect vector. The amastigotes and trypomastigotes (metacyclic and blood) forms are responsible for causing infection in their hosts.

VECTOR

The vectors of Chagas disease are triatomine insects, predominantly hematophagous, popularly known as kissing bugs and belonging to the family *Reduviidae*subfamily *Triatominae*, where all 154 species are potential vectors of protozoan transmission *Trypanosoma cruzi*. However, the genera with significant epidemiological importance are *Panstrongylus*, *Triatoma* and *Rhodnius*.

In Brazil, more than 62 species of triatomines have been catogized, and 05 of them have direct participation in the household transmission of the disease: *Triatoma infestans*, *Triatoma brasiliensis*, *Triatoma pseudomaculata*, *Triatoma sorida* and *Panstrongylus megistus*.

These insects are nocturnal and have a life expectancy of approximately 01 to 02 years. Females are capable of producing 100 to 200 eggs per year and hatching occurs about 18 to 25 days after laying.

In addition, both males and females of these insects feed on blood, and females are exclusively hematophagous, needing blood for the maturation of their eggs. Transmission of the protozoan can occur effectively in the younger stages of these insects, with first-instar nymphs already being able to transmit *Trypanosoma cruzi*. Figure 1 shows the development cycle of these insects.

Figure 1 – Photograph of the evolutionary cycle of *Rhodnius* sp.

Source: Authors' personal collection.

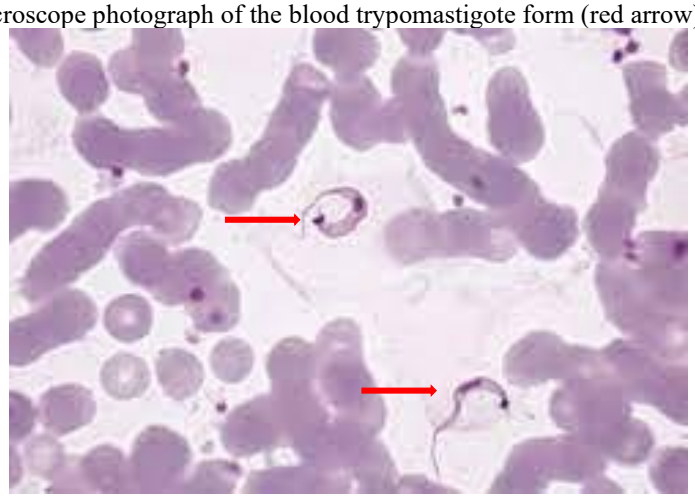
EVOLUTIONARY FORMS

Trypanosoma cruzi is a flagellate protozoan with the presence of a single flagellum and a kinetoplast, an organelle that contains mitochondrial DNA and is located near the flagellum. During its life cycle, *T. cruzi* takes on three distinct forms, depending on the host it is in. In mammals there are the intracellular amastigotes and blood trypomastigotes forms, while in invertebrates, such as kissing bugs, the metacyclic epimastigotes and trypomastigotes forms occur.

The trypomastigote form is an elongated cell, with a centralized nucleus and kinetoplast located in the anterior region of the cell. It has a flagellum that emerges from the posterior region of the cell, adhered to the cell membrane, with a free portion. They are highly mobile and do not reproduce. It is the infective form of the protozoan, found in the intestine of the insect vector and in the blood of vertebrate hosts, presenting significant importance for the dissemination and

establishment of infection in the host. Figure 2 shows the photo of the trypomastigote form in the blood of a vertebrate host.

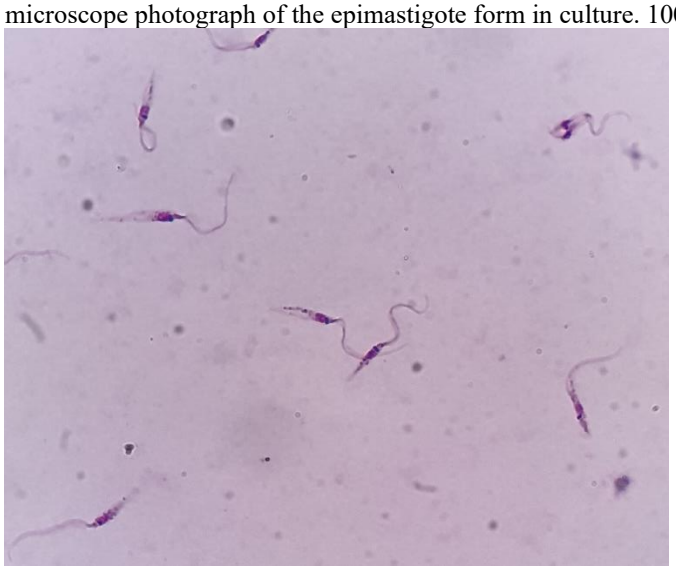
Figure 2 – Optical microscope photograph of the blood trypomastigote form (red arrow). 100X magnification.



Source: Authors' personal collection.

The epimastigote form is found only in the insect vector. The kinetoplast is located next to the nucleus, in the anterior region, and the flagellum has a larger free part. It has high mobility and is the form that reproduces in the digestive tract of the insect vector. Figure 3 shows the photo of the epimastigote form.

Figure 3 – Optical microscope photograph of the epimastigote form in culture. 100X magnification.

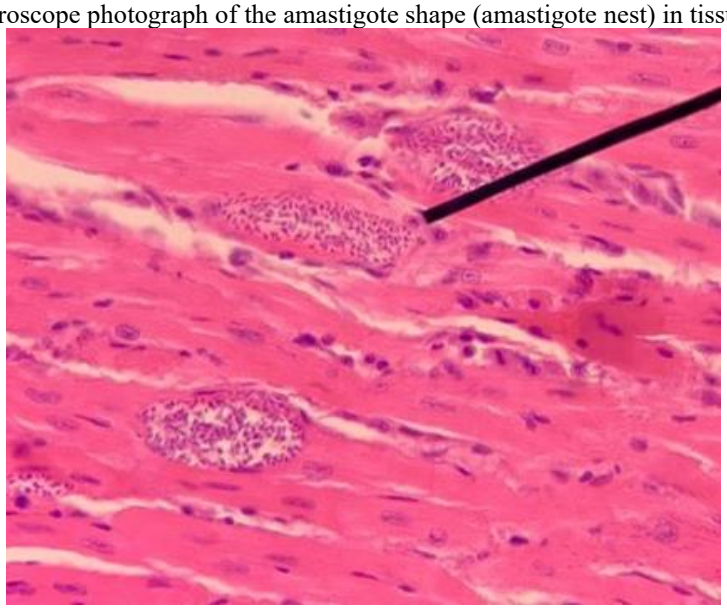


Source: Authors' personal collection.

The amastigote shape has a spherical or oval shape. It is found only in vertebrate hosts. It has a nucleus and a kinetoplast, the flagellum being reduced to a small flagellar pouch. It is the form that reproduces within the cells of vertebrate hosts, forming amastigote nests with tropism for cells of the heart muscle and the smooth muscle of the digestive tract. This evolutionary form contributes

directly to the clinical manifestations of Chagas disease, which may include damage to the heart and gastrointestinal tract. Figure 4 shows a photo of an amastigote nest in the tissue of a vertebrate host.

Figure 4 – Optical microscope photograph of the amastigote shape (amastigote nest) in tissue. 40X magnification.



Source: Authors' personal collection.

FORMS OF CONTAMINATION

Chagas disease is endemic in 21 Latin American countries, stretching from the southern United States to northern Argentina and Chile. Historically, this disease was more common in rural regions of Latin America, where residents of infested homes often came into contact with vectors carrying the parasite, with vector transmission being the main way Chagas disease spread for a long time.

VECTORIAL

The main route of transmission of the parasite is through infected triatomine insects. The trypomastigote form is widely found in the feces of these insects. The triatomines defecate on the host's skin during or shortly after the blood meal, allowing the microorganism to enter the body through the bite wound. The parasite can also penetrate through the eye or mucous membranes if the bite is close to these places.

VERTICAL

Congenital transmission can occur through women who have been infected since birth, perpetuating the cycle of the disease in the absence of the vector. The determining factor in the risk of vertical transmission is the level of parasitemia in the mother; women who test negative on polymerase chain reaction (PCR) tests have a very low likelihood of transmitting the infection to their babies. Other factors that increase the risk of congenital transmission include a younger

maternal age and the presence of HIV infection, probably due to the association with higher parasite loads.

As for the transmission of Chagas disease through breastfeeding, the risk is currently unknown. However, mothers with acute or reactivated Chagas disease should not breastfeed. Breastfeeding is considered safe for mothers with chronic Chagas disease. In these cases, it is recommended to stop breastfeeding if the nipples are cracked or bleeding, and it is advisable to use other forms of feeding for the baby.

ORAL

Oral transmission occurs when individuals consume food or beverages contaminated by infected triatomines or their feces. The main foods associated with oral transmission include fresh açaí, guava juice, and sugarcane juice. Effective control of oral transmission depends on the continued maintenance of vector control and the implementation of good hygiene practices in the preparation of food and beverages. It is important to note that acute morbidity in orally transmitted infections appears to be more severe compared to patients infected by vector-borne transmission.

BLOOD TRANSFUSION

Transmission by blood transfusion carries a high risk when it comes to platelet transfusions, compared to other blood components. Although this form of transmission has been most frequently reported in the United States, since rigorous screening of blood supply began, no cases of transfusion transmission have been recorded. In Brazil, with the control of blood banks, this form of transmission has little relevance today.

ORGAN TRANSPLANTATION

Patients who receive an organ from a donor infected with *Trypanosoma cruzi*, even if they were not originally infected, are at risk of developing an acute infection with the protozoan. Infection rates after transplantation from an infected donor are higher in heart recipients. Therefore, it is critical to establish close follow-up of the recipient after an infected organ donor has been identified.

LABORATORY ACCIDENTS

High-risk incidents involve injuries resulting from needlestick accidents or contact of ocular mucous membranes with the blood of laboratory animals known to be infected with *Trypanosoma cruzi*. Professionals working in laboratories should take protective measures, including the use of safety equipment to prevent needlestick injuries and exposure of the face, particularly the eyes. In addition, people who have experienced high-risk exposures should undergo monitoring, which

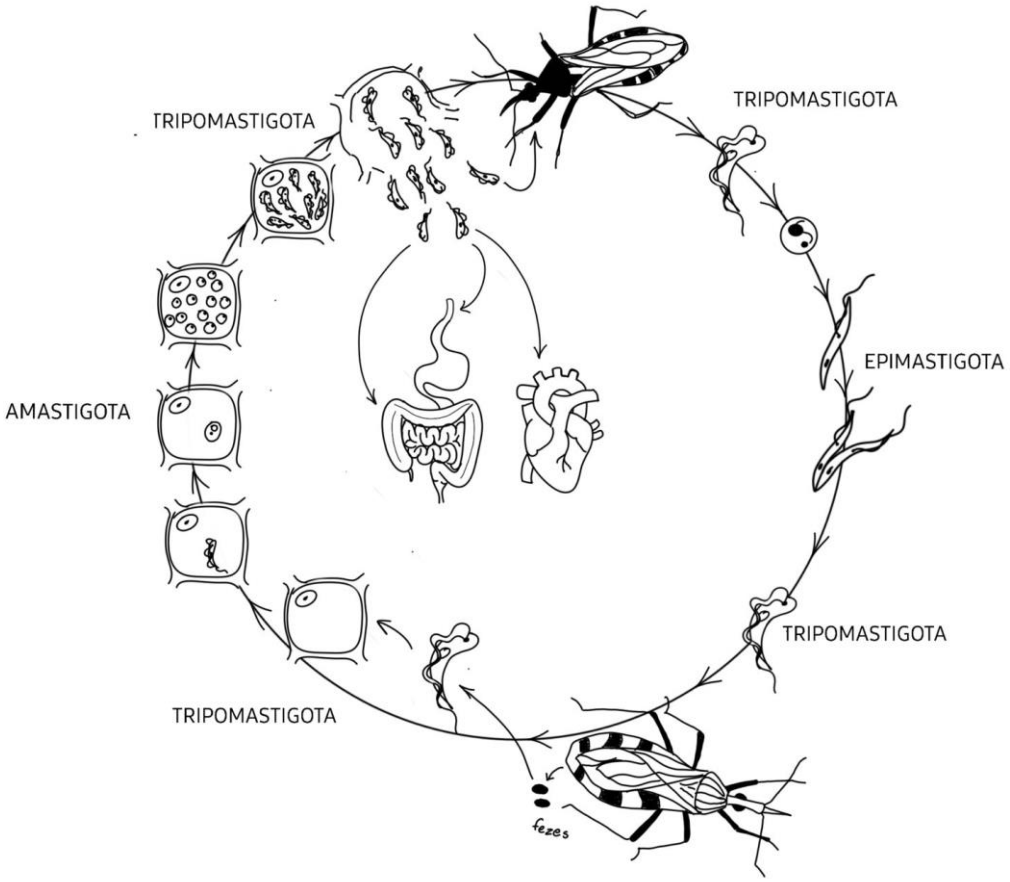
includes PCR testing of weekly blood samples over the course of four weeks, as well as serological testing in the fourth and eighth week after the incident.

BIOLOGICAL CYCLE

The life cycle of *T. cruzi* is heteroxenous, alternating between invertebrate hosts, which are the vectors of the parasite, and a wide variety of mammalian hosts. Figure 5 shows a schematic drawing of the biological cycle of *Trypanosoma cruzi*. When an insect vector becomes infected by ingesting the blood of infected animals during the blood meal, the trypomastigote forms of the protozoan undergo a transformation in the stomach, giving rise to the epimastigote forms. These adhere to the surface of the midgut and hindquarters, where they multiply abundantly. Next, the epimastigotes migrate to the hindgut, reaching the rectum, where they transform into metacyclic trypomastigotes, which are eliminated in the feces and urine of the insect vector. These forms are able to infect a variety of cells in the vertebrate host, using components of its cell surface as well as host cells.

Once the infective forms are deposited on the skin of mammalian hosts, they face the first barriers of the innate immune system, such as the skin and mucous membranes, which act as physical barriers and surround the complement system. In the vertebrate host, trypomastigotes infect cells and differentiate into amastigotes, an intracellular form of proliferation. Subsequently, the amastigotes transform into trypomastigotes, which rupture the host cells and enter the bloodstream, which can infect new host cells or be ingested by kissing bugs during a new blood meal. Inside the insect vector, the parasites transform into epimastigotes, starting a new cycle.

Figure 5 – Schematic drawing representative of the biological cycle of *Trypanosoma cruzi*.



Source: Prepared by the authors.

CLINICAL FORMS

The acute phase of Chagas' infection may be asymptomatic or the patient may present with low, continuous, prolonged fever, myalgias, asthenia, edema of the face or lower limbs, lymph node hypertrophy, hepatomegaly, splenomegaly, general discomfort and inflammation at the site of infection, in cases of vectorial transmission. At this stage, the most frequently affected organ is the heart, and some individuals may develop severe and occasionally lethal cases of myocarditis. A striking feature of this phase is high blood parasitemia, with a large number of circulating trypomastigote forms. Most of those infected go through the acute phase of the infection asymptomatically and then progress to the indeterminate chronic phase.

The indeterminate chronic phase lasts from 10 to 40 years or more and is characterized by the total absence of clinical manifestations and alterations in exams, such as x-rays and electrocardiograms. These patients are diagnosed accidentally, for example when they apply for blood donation.

Years or decades after infection, 10% to 30% of patients may progress to the chronic phase and manifest one of the two main clinical forms: heart disease, associated with myocarditis and

fibrosis, which results in heart failure, blood clot formation, and cerebrovascular accidents; and digestive disorders, such as megacolon and/or megaesophagus, which may be associated with gastrointestinal disorders such as regurgitation, malnutrition, and severe constipation.

The establishment of an immune response that results in inflammation in the affected tissues during the acute phase of *Trypanosoma cruzi* infection is essential for the control of the parasite and for maintaining the balance in the parasite/host relationship, as observed in most patients with Chagas disease.

CARDIAC SHAPE

Chronic Chagas heart disease is the most common symptomatic manifestation of Chagas disease and represents an important source of morbidity and mortality. Chronic myocardial aggression is predominantly triggered by the continued persistence of the parasite and the unfavorable immune response to this persistent infection.

Distinguishing features of chronic Chagas' heart disease include severe inflammation and fibrosis of the heart, complex ventricular arrhythmias associated with disturbances in the formation and conduction of atrioventricular and intraventricular electrical stimulation, high incidence of sudden death and thromboembolic phenomena, along with right ventricular dysfunction and the formation of ventricular aneurysms.

CLINICAL MANIFESTATIONS OF CHRONIC CHAGAS' HEART DISEASE

The clinical manifestations of chronic Chagas' heart disease can be grouped into three syndromes: arrhythmic, heart failure, and thromboembolic syndrome. These syndromes can occur alone or in combination in the same patient, and can also be associated with conditions such as megaesophagus and/or megacolon.

ACUTE CHAGASIC HEART DISEASE

Especially in the Legal Amazon region, there is a systematic record of cases of acute chagasic heart disease, both isolated and in outbreaks and familial microepidemics. In these cases, the main form of contamination is oral, involving food contaminated with triatomine feces. The clinical presentation varies and differs from classic acute chagasic carditis (vectorial), especially due to the absence of evidence of a gateway (such as inoculation chagoma) and the involvement of community or family groups in outbreaks, without a preferred age group of infection or specific severity.

The clinical manifestations of acute orally transmitted disease are variable, ranging from asymptomatic cases to severe situations that can progress to severe heart failure, cardiac shock and,

in extreme cases, death. It can also manifest as a nonspecific infectious syndrome, presenting with prolonged fever, usually lasting more than three weeks.

Trypanosoma cruzi-infected *individuals* who are also exposed to immunosuppressants or who have other concomitant conditions, such as neoplasms and other infections, especially HIV, may experience reactivation of Chagas disease. In about 30% to 40% of cases of Chagas disease reactivation in individuals co-infected with HIV, the heart appears to be involved. However, isolated myocarditis does not appear to be a common occurrence. Cardiac involvement usually manifests as acute myocarditis, with diffuse or focal organ involvement. Clinically, presents with signs or symptoms of heart failure (such as tachycardia, edema, and hepatomegaly) or severe arrhythmias. Some patients exhibit only electrocardiographic changes, while in others, myocarditis is only confirmed by histopathological examination in endomyocardial biopsy specimens, revealing acute myocarditis with marked inflammatory infiltrate, focal damage to cardiac fibers, and the presence of a large number of amastigote forms of the parasite. In cases where there is already previous cardiac involvement (due to chronic Chagas' heart disease), the reactivation of Chagas disease may overlap with the decompensation of the preexisting heart condition, making it complex to determine the cause of the condition, which can be attributed to the reactivation of Chagas disease, HIV-related myocarditis, or a combination of both conditions.

DIGESTIVE FORM

The digestive form of Chagas disease, although it can affect several organs of the gastrointestinal system, manifests itself clinically, for the most part, through changes in the esophagus and large intestine, resulting in conditions known as megaesophagus and megacolon, respectively. The combination of megaesophagus and megacolon is observed in approximately 92% of cases requiring surgical intervention, and the triad of megaesophagus, megacolon, and heart disease occurs in about 65% of cases.

DIGESTIVE MANIFESTATIONS IN THE ACUTE PHASE OF CHAGAS DISEASE

The clinical manifestations in the acute phase of Chagas disease, related to the digestive system, are usually subtle and difficult to identify, with practically imperceptible symptoms. However, there are case reports of gastrointestinal bleeding in situations of oral transmission, and in rare vector-borne cases, symptoms such as dysphagia may occur.

DIGESTIVE MANIFESTATIONS IN THE CHRONIC PHASE OF CHAGAS DISEASE

The digestive manifestations in the chronic phase of Chagas disease are concentrated in the esophagus and colon and basically include dysphagia and constipation, resulting from chronic

changes in these organs that can lead to the development of megaesophagus and/or megacolon. However, due to the damage that the disease causes in the autonomic nervous system throughout the gastrointestinal tract, anatomical and functional changes can also occur in organs such as the salivary glands, stomach, extrahepatic bile ducts, duodenum, small intestine, large intestine and even organs that are not part of the gastrointestinal system, such as the ureter.

DIAGNOSIS

Acute Chagas infection should be suspected in individuals who have been in endemic areas. However, *T. cruzi* infection is rarely detected in the acute phase due to its brief duration and the existence of few or no symptoms.

In the acute phase, parasitemia is high. Motile trypomastigotes can be observed by light microscopy with fresh blood preparations with anticoagulant. The level of parasitemia decreases within 90 days after infection, and is undetectable by microscopy in the chronic phase. Thus, the technique of choice for diagnosis at this stage is the direct parasitological examination, with a blood slide and search for the parasite.

Polymerase Chain Reaction (PCR) is a diagnostic tool that is also sensitive in the acute phase. Generally, positive PCR assays appear days to weeks before circulating Tripomastigotes are detectable on peripheral blood smears. However, the high cost of the technique and the need for specialized labor make its use unfeasible in the routine of the Brazilian public health system.

In the chronic phase of Chagas disease, most individuals are asymptomatic or have cardiac or gastrointestinal symptoms. The diagnosis of chronic Chagas infection requires serological methods to detect IgG antibodies against *T. cruzi,* which is most commonly done by enzyme-linked immunosorbent immunosorbent assay (ELISA) and immunofluorescent antibody assay (IFA). These two assays do not have sufficient sensitivity and specificity to be used in isolation, so they are used in parallel to increase diagnostic accuracy.

TREATMENT

The approach to the management of Chagas disease varies according to the stage of the disease. The only drugs with proven efficacy against the protozoan to be used in humans are Benznidazole and Nifurtimox, the latter of which is not marketed in Brazil. Benznidazole has activity against trypomastigotes and amastigotes of *T. cruzi,* is rapidly absorbed by the gastrointestinal tract and has a mean half-life of 12 hours and the duration of therapy with the drug usually lasts 60 days. Laboratory tests such as complete blood count, bilirubin, serum creatinine should be performed prior to initiation of treatment, and blood count should be repeated every 2 to 3 weeks during treatment.

Adverse effects include dermatitis, peripheral neuropathy, angioedema, and bone marrow suppression.

The indication for treatment with benznidazole varies according to the stage of the disease, the age of the patient, and the presence of comorbidities. Both drugs are contraindicated for pregnant women, patients with severe renal or hepatic impairment.

PROPHYLAXIS

Public health interventions to address Chagas disease can be categorized as: primary prevention, secondary prevention (early detection and treatment to prevent sequelae), and tertiary prevention (medical and surgical management to prevent sequelae). Thus, primary prevention should be focused on the prevention of infection and includes vector control, screening of blood donors, prenatal care, use of repellents and curtains, installation of screens on doors and windows, cleaning of yards, care and hygiene in food processing, among others.

Transmission by domestic vectors can be reduced through the application of long-lasting insecticides in human dwellings and peridomiciliary structures. In addition, improving the quality of domestic structures is also a control mechanism, as it eliminates Triatomine hiding places and decreases colonization by this vector.

REFERENCES

1. Aparecida, P., Darlene. (2012, outubro 25). Caracterização biológica e molecular de cepas de Trypanosoma cruzi isoladas durante o surto de doença de Chagas agudo em Santa Catarina [Dissertação de mestrado].

2. Dias, J. C. P., et al. (2016). II Consenso Brasileiro em Doença de Chagas, 2015. Epidemiol. Serv. Saúde, 25(n. esp), 7-86. Disponível em <http://scielo.iec.gov.br/scielo.php?script=sci_arttext&pid=S1679-49742016000500007&lng=pt&nrm=iso>.

3. Doenças de Chagas - Secretaria da Saúde. Disponível em: <https://www.saude.go.gov.br/biblioteca/7585-doen%C3%A7as-de-chagas>.

4. José Antonio Marin-Neto et al. (2023). Diretriz da SBC sobre Diagnóstico e Tratamento de Pacientes com Cardiomiopatia da Doença de Chagas, 120(6).

5. Paulo, S. Guia de triatomíneos do Estado de São Paulo. Disponível em: <https://www.saude.sp.gov.br/resources/sucen/homepage/downloads/arquivos-de-chagas/guia_dos_triatomineos_do_estado_de_sao_paulo_final.pdf>.

6. Portal da Doença de Chagas – Portal de informações sobre Doença de Chagas da Fiocruz. Disponível em: <https://chagas.fiocruz.br/>.

7. UpToDate. (2023). Chagas disease: chronic Trypanosoma cruzi infection. Disponível em: <https://www.uptodate.com/contents/chagas-disease-chronic-trypanosoma-cruzi-infection?search=diagn%C3%B3stico%20cr%C3%B4nico%20chagas&source=search_result&selectedTitle=1~18&usage_type=default&display_rank=1>.

8. UpToDate. (2023). Chagas disease: antitrypanosomal drug therapy. Disponível em: <https://www.uptodate.com/contents/chagas-disease-antitrypanosomal-drug-therapy?search=doen%C3%A7a%20de%20chagas&source=search_result&selectedTitle=7~83&usage_type=default&display_rank=7>.

9. UpToDate. (2023). Chagas disease: epidemiology, screening, and prevention. Disponível em: <https://www.uptodate.com/contents/chagas-disease-epidemiology-screening-and-prevention/print?search=doen%C3%A7a%20de%20chagas&source=search_result&selectedTitle=3~83&usage_type=default&display_rank=3>.

10. UpToDate. (2023). Chagas disease: acute and congenital Trypanosoma cruzi infection. Disponível em: <https://www.uptodate.com/contents/chagas-disease-acute-and-congenital-trypanosoma-cruzi-infection?search=Chagas%20disease:%20Acute%20and%20congenital%20Trypanosoma%20cruzi%20infection&source=search_result&selectedTitle=1~82&usage_type=default&display_rank=1>.