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I LATIN AMERICAN GUIDELINE FOR THE DIAGNOSIS AND TREATMENT OF CHAGAS' HEART DISEASE

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I Latin American Guideline for the Diagnosis and Treatment of Chagas' Heart Disease

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We used the following definitions for degree of recommendation and level of evidence:

Class of recommendation

Class I: Conditions for which there is conclusive evidence, or, if not, there is consensus that the procedure is safe and useful/effective.

Class II: Conditions for which there is conflicting evidence and/or divergent opinions about the procedure's safety and usefulness/effectiveness.

Class IIa: Weight or evidence/opinion in favor of the procedure. Approved by most professionals.

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Level of Evidence

Level A: Data derived from multiple significantly sized randomized trials, consistent and/or robust meta-analysis of randomized clinical trials.

Level B: Data derived from less robust meta-analysis, grounded on a single randomized trial or nonrandomized (observational) trials.

Level C: Data derived from consensual opinions of experts.

Note that the levels of evidence classified as B or C may not be interpreted as weak recommendations. There are many consensual recommendations; thus having class of recommendation I, level of evidence C (expert opinions). On the other hand, some indications considered controversial (class of recommendation II) may be grounded on randomized controlled trials (level of evidence A).

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Presentation

The description of the life cycle of Chagas' Heart Disease by the Brazilian scientist Carlos Chagas, published in "Memórias do Instituto Osvaldo Cruz", entitled "**Nova tripanosomiaze humana. Estudos sobre a morfolojia e o ciclo evolutivo Schizotrypanum cruzi n. gen. n SP., agente etiológica de nova entidade mórbida no homem**" has celebrated its 100-year anniversary in 2009.

Given the relevance and significance of this fact for the Brazilian and international Medicine, the Executive Board of Sociedade Brasileira de Cardiologia (SBC) proposed that this date be celebrated producing a guideline on the diagnosis and treatment of the Chagas' Heart Disease.

Looking at the overall current scenario for the Chagas' Heart Disease, a relevant pidemiological issue in several South American and North American countries, including countries in Europe and other continents, SBC chose to invite the South American and Inter-American Societies of Cardiology to prepare together this document and, on account of that, the I Latin American Guideline for the Diagnosis and Treatment of Chagas' Heart Disease was outlined.

The guideline was prepared with an editorial board made up of Brazilian and Latin American cardiologists. The cardiologists participating in the joint effort have recognized expertise and qualifications in the subject, which is substantiated by a number of papers published in reference scientific journals nationally and internationally. Furthermore, they were supported by a large group of cardiologists, having similar qualifications, and integrating and forming working groups.

SBC intends that the scope of this objective be widened, in concert with the Latin American Cardiology Societies, so as to reflect the international scientific knowledge and thereby gain acceptance, recognition and application by cardiologists of the countries involved.

The Brazilian, South American and Inter-American Societies of Cardiology, in addition to the editors and the entire group of professionals cooperating in the drafting of this guideline expect that its development and disclosure contribute to an enhanced coping and regulating of the behavior towards prevention, diagnosis and treatment of all forms of Chagas' Heart Disease.

Jadelson Andrade

1. Introduction and epidemiology

The 100th anniversary of the discovery of Chagas disease (CD) is celebrated with the publication of the first Latin American Guideline for the Management and Treatment of CD, and with homage paid to Carlos Chagas (Figure 1). With his geniality, he described the disease, from its etiology to its clinical findings, including its major mode of transmission and epidemiology. Differently from what Carlos Chagas did, the clinical-epidemiological presentation of an infectious disease usually motivates the search for its causative agent and mode of transmission, such as happened with *Mycobacterium tuberculosis*, discovered by Robert Koch in 1882.

At the end of 1907, already a physician at Instituto Oswaldo Cruz, where he entered in 1906, three years after graduating at the Rio de Janeiro Medical School, currently known as Medical School of the Rio de Janeiro Federal University, Carlos Chagas and Belisário Penna were designated by Oswaldo Cruz to control the outbreak of malaria in Lassance, a village in the state of Minas Gerais, close to the margins of the São Francisco river, where malaria hindered the work at the camping site of the Central do Brasil Railroad. Right after arriving at Lassance, the railroad engineer Cantarino Mota made Carlos Chagas aware of an insect that lived in the crevices of the mud walls of the thatched-roof houses. The insects emerge at night, when the inhabitants are sleeping, and tend to feed on blood on people's faces, being known as "barbers"[1]. Carlos Chagas initiated then an investigation that showed his brilliant innate talent as a researcher. He found protozoa in the intestine of those hematophagous insects, which he sent to the Instituto Oswaldo Cruz. There those insects infected experimental animals, which became ill, and, in their blood, a new species of parasite was identified, being named *Trypanosoma cruzi* (*T. cruzi*) after Oswaldo Cruz. The human disease was characterized on April 23rd, 1909, when the *T. cruzi* was identified in the blood of a 2-year-old girl with an acute febrile disease, called Berenice. That was the first case of acute CD described, whose patient survived. In that same year, Carlos Chagas disseminated his discovery, describing the disease cycle in brief notes in the *Brasil Médico* and in the *Archiv fur Schiffs-und Tropen Hygiene*, followed by an extensive article, in Portuguese and German, published in the *Memórias do Instituto Oswaldo Cruz,* entitled "*Nova tripanosomiaze humana. Estudos sobre a morfolojia e o ciclo evolutivo do Schizotrypanum cruzi n. gen., n sp., ajente etiolojico de nova entidade morbida do homem*[2]".

Figure 1 - *Carlos Justiniano Ribeiro Chagas (1879 - 1934), Brazilian physician and scientist, in his laboratory at Instituto Oswaldo Cruz (*). (*)Wikipedia: the free encyclopedia. Carlos Chagas. [Access on August 24, 2010]. Available at: http://pt.wikipedia.org/wiki/carlos chagas.*

From the identification of the new disease in 1909 until Carlos Chagas' death in 1934, he dedicated himself to widen the knowledge on the American trypanosomiasis. The village of Lassance became a permanent site for the study of that and other rural endemic diseases. In 1912, Oswaldo Cruz received federal government funding to map the geographic distribution of the disease, to equip a small hospital in that railroad station, and to begin simultaneously at Manguinhos the construction of a hospital aimed at studying the cases referred from that site. The continuation of the research in Lassance and at the Instituto Oswaldo Cruz allowed Chagas to develop a complete study on the essential features of the new trypanosomiasis. Chagas counted on several researchers from Manguinhos to help him with that task, mainly Gaspar Vianna, Arthur Neiva, Eurico Villela, Magarinos Torres, César Guerreiro, Astrogildo Machado, Evandro Chagas and Emmanuel Dias.

Finishing his cycle of direct contribution on CD, Carlos Chagas has published a review article[3] approaching the epidemiology and etiopathogenesis of the disease, with emphasis on its congenital transmission, then described by Gaspar Vianna, one of his collaborators. It is worth noting the description of clinical forms with a rare lethal outcome or remission in the acute phase, as well as the progression to heart failure (HF) and/or sudden death (SD) in the chronic forms. Sudden death, as a primary event in that disease progression, was frequently registered in endemic areas, affecting apparently healthy individuals; HF, however, characterized the clinical form that served as a base for the clinical and pathological recognition of that disease. In addition, atrial, ventricular and atrioventricular arrhythmias, common in that condition, were described in details, the latter as variable bundle-branch block. That review article carefully recorded arterial and venous pulse by use of direct technique, and later by use of electrocardiogram (ECG), a then incipient technique, better mastered by the cardiologist Eurico Villela.

Of the speculations about not granting the Nobel Prize to Carlos Chagas, two aspects are worth noting: first, the lack of massive support of the Brazilian scientific and academic community to the indications; and, second, the fact that the disease was is restricted to Latin American countries, which are not within the colonial interests of European nations and the United States of America. Nevertheless, History has paid homage to the scientific contribution of Carlos Chagas, who should remain as a paradigm of scientist, physician and sanitarian for Brazilians and the rest of the world[4].

1.1. Epidemiological aspects in Brazil

Since its description, the attempt to control CD transmission in Brazil has proved to be a challenge. In the 1970's, there were intense efforts and political and social pressures as organized acts of campaigns to control the disease. However, it was only in 1991 that the development of the Subregional Initiative for CD Control by the Southern Cone Countries boosted that control[5].

Organized and coordinated campaigns to control the triatomine vector and the transmission via transfusion, with greater strictness in blood banks, have provided a significant reduction in new cases. In June 2006, the World Health Organization (WHO) issued the certificate of elimination of CD transmission via the wild vector *Triatoma infestans (T. infestans)* to Brazil [6]. This, somehow, represents the disease eradication, because isolated outbreaks in different Brazilian states and registration of sporadic acute cases continue to occur. The reduction in transmission is confirmed by comparing 1975-1985 data, approximately 4,500,000 infected individuals, with data from 30 years later, estimated 1,900,000, in 2005[7]. A survey conducted by the Brazilian Ministry of Health, assessing the result of the Southern Cone program for that disease control, evidenced that, from 1975 to 1995, 89% of the potential transmissions were prevented, thus avoiding approximately 2,339,000 new cases and 337,000 deaths. That assessment has also shown the cost-effectiveness of the CD control program, evidencing that, for each US$ 1.00 spent, US$ 17.00 were saved[8,9]. With better control of the vectorial and transfusional modes of transmission, the oral mode has gained relative importance, as seen in the following outbreaks: 2005, in the states of Santa Catarina and Pará; 2006, in the states of Ceará and Pará; and 2007, in the states of Pará and Amazonas. In the Amazon region, the number of acute cases has increased, from less than 10 in 1968 to almost 100 in 2007. This has mainly occurred as isolated outbreaks usually with oral transmission, or, less frequently, via isolated nondomiciliary vectors, or still via human exposure to vectors in the wild[10,11]. Because of that increase in the number of cases in the Amazon region, a specific program (AMCHA) was created in 2004 to map and detect the disease transmission[12].

A serological inquiry performed with schoolchildren from 7 to 14 years of age, in 1994-1997, revealed a 0.05% seroprevalence[13]. In 1999, for that same age group, the prevalence of *T. cruzi*-infected individuals was 0.04%. In 2005, the screening of Brazilian blood banks showed 100% assessment of the samples regarding a possible *T. cruzi* infection, with only 0.21% seropositivity[14].

Thus, in Brazil, permanent surveillance is required, as well as the continuity of control programs for other modes of transmission, whose results will be assessed in the medium and long run.

1.2. Epidemiology of Chagas disease in Latin America and the rest of the world

Chagas disease is crossing the borders of countries historically known as its major sources.

The exodus of millions of Latin Americans to more developed countries has been decisive to the fact that over 100,000 chronically infected individuals are now living in the United States. In addition, other cases of *T. cruzi* infection were associated with blood transfusion and transplantations in the United States of America, Canada and several European countries, where screening for CD in donors was not performed until recently[15].

In the United States of America, the concern about CD has increased to a point that it is now considered a prevalent disease and an important differential diagnosis in several clinical settings[16]. A recent analysis with immigrants (data from the PEW Hispanic Center and US Department of Homeland Security) estimates that 300,000 individuals have *T. cruzi* infection, and between 30,000 and 45,000 have clinical disease. Similarly to classically endemic countries, in the United States of America, most individuals with *T. cruzi* infection have neither signs nor symptoms of chronic CD, being considered as having the indeterminate form[17]. Since 2007, comprehensive screening of blood and organ donors have been federally enforced in the United States of America, contributing to increase the visibility of CD[18].

In Spain, where most immigrants come from Bolivia, whose CD prevalence is between 20% and 40%, a recent communication has revealed that, in the past two years, the CD prevalence among Bolivian pregnant women at a Spanish hospital was 17.7%, with a vertical transmission rate of 1.4%[19].

Thus, new epidemiological, socioeconomic and political problems have been recently arisen created, resulting from CD globalization, due to legal and illegal migration from endemic to non-endemic countries, mainly the United States of America, Canada, Spain, France, Switzerland, Italy, Japan, Asian emerging countries and Australia (Figure 2)[20]. Compounding those problems, the following issues are worth noting: the risk for transfusional and congenital transmission; the need for medical care; difficulties in CD diagnosis due to the lack of experience of physicians in recognizing the disease pathology; and need for additional control at blood banks in countries with little experience in the topic. Such epidemiological aspects differ from those in endemic countries. In the Americas, the CD epidemiological characteristics can be distributed in the following groups of countries according to the transmission cycle and the transfusion and vector control programs (Figure 3)[21]:

Group I - Argentina, Bolivia, Brazil, Chile, Ecuador, Honduras, Paraguay, Peru, Uruguay and Venezuela have domestic, peridomiciliary and wild transmission cycles, with a high prevalence of human infection and predominance of chronic Chagas cardiopathy (CCC).

Group II - Colombia, Costa Rica and Mexico have domestic and peridomiciliary transmission cycles, and CCC.

Group III - El Salvador, Guatemala, Nicaragua and Panama have domestic, peridomiciliary and wild transmission cycles, with deficient clinical information.

Group IV - Antilles, Bahamas, Belize, Cuba, United States of America, Guyana, French Guiana, Haiti, Jamaica and Suriname have wild transmission cycles and scarce clinical information[21].

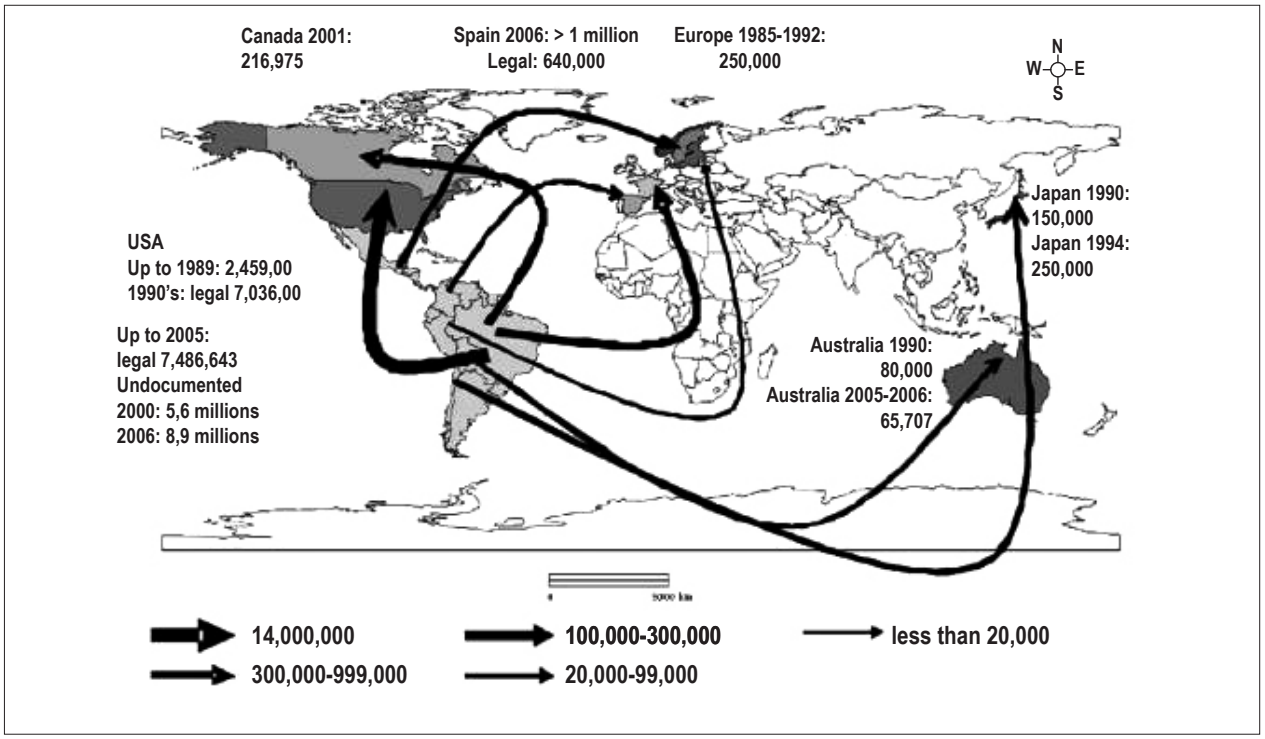

Figure 2 - *Globalization of Chagas disease. Potential number of emigrants from countries with T. cruzi infection (*). (*) Adapted from Schmunis G. The globalization of Chagas disease. ISBT Science Series. 2007;2(1):6-11.*

Figure 3 - *Distribution of Chagas disease in the Americas (*). (*) Coura JR, Dias JCP. Epidemiology, control and surveillance of Chagas disease: 100 years after its discovery. Mem. Inst. Oswaldo Cruz. 2009;104(Supl.1):31-40.*

1.3. Control measures for disease transmission

An overview of CD allowing the definition of comprehensive preventive strategies has been provided by a cross-sectional epidemiological survey individually conducted in 15 Latin American countries since the 1980s. The results have shown that the original endemic areas with domiciliary vectorial transmission to humans comprised 18 countries with the highest *T. cruzi*-infection rates, infested with *T. infestans* (Southern Cone countries) and *Rhodnius prolixus* (Andean and Central American countries), which are the best adapted triatomine species to the human household[22].

The most effective means to interrupt the transmission of *T. cruzi* infection have also been indicated: 1) implementation of vector control activities in the household aimed first at reducing, and, then, at eliminating the *T. cruzi* vectorial transmission; and 2) development and implementation of policy for blood screening for human use to prevent CD transfusional transmission.

In 1975, the program to control CD vectorial transmission was initiated in Brazil. This consisted of insecticide spraying in the houses and around them, aiming at interrupting the domestic and peridomiciliary transmission cycles involving vectors, and animal and human reservoirs. In addition, sanitary educational measures have been adopted and a monitoring system involving the local community members has been established. In Brazil, those programs proved effective to eliminate the *T. infestans* domiciliary vector, the most important vector from the epidemiological viewpoint[23]. At the beginning of the program, 711 municipalities had *T. infestans*-infested houses. A significant reduction in the number of *T. infestans*-infested houses was observed: from 166,000 insects collected in the control program in 1975 to only 6,111 insects collected in 1999. The mean infestation rate dropped to 1 insect to every 10,000 houses investigated, a figure significantly lower than the minimum required for disease transmission[21,22]. The prevalence of human *T. cruzi* infection at young age groups can also be considered a control index of disease transmission. As previously reported, for in the age group of 7-14 years, in 1999, a 0.04% positivity rate was observed, representing a 99.8% reduction as compared with 18.5% observed in 1980[14]. In 2007, the results of 94,000 serological tests in samples of 0 to 5 years indicated 0% positivity rate.

2. Pathogenesis and pathophysiology of chronic Chagas cardiopathy

Chronic Chagas cardiopathy is essentially a dilated cardiomyopathy, in which chronic inflammation, usually mild and continuous, causes progressive tissue destruction and extensive heart fibrosis. Several mechanisms contribute to the pathogenesis of the cardiac lesions and consequent installation of the pathophysiological disorders, according to recent reviews[24-28].

2.1. Cardiac dysautonomia

Several independent *postmortem* studies with chagasic patients and experimental models of *T. cruzi* infection have evidenced neuronal depopulation, predominantly of the cardiac parasympathetic system[29]. Such pathological changes are accompanied by cardiac dysautonomia, confirmed by several researchers with varied methods of functional assessment. They precede the appearance of ventricular dysfunction, being found even in the indeterminate and digestive forms of the disease[24,30,31]. As a consequence of those functional disorders of the cardiac autonomic regulation, chronic chagasic patients can be deprived of the vagal inhibitory control normally exerted on the sinus node and other cardiac structures. In addition, they can become incapable of rapid chronotropic adjustments in response to physiological stimuli, such as posture changes and physical exercise, mediated by the vagal system[24,30]. Furthermore, the implication of loss of cardiac parasympathetic control in mechanisms of SD in CCC would be a plausible pathophysiological hypothesis. Although to a lesser extent, structural and functional changes of the cardiac sympathetic system, such as at the ventricular level, also occur in association with myocardial contractility and perfusion disorders[32]. Circulating antibodies, capable of interfering with receptors of both sympathetic and vagal systems, are likely to affect pathophysiologically the cardiac autonomic behavior and to modulate electrophysiological properties involved in the mechanisms of malignant arrhythmias[33]. However, the role played by those antibodies in the genesis of myocardial changes is still unclear, and not correlated with ventricular contractility dysfunction[34].

Briefly, although morphological and functional changes of the cardiac autonomic system are detected in some chronic chagasic patients, they vary in intensity and do not correlate directly with the degree of ventricular depression. Thus, the "neurogenic theory", as understood on pioneer studies[29], does not convince to explain myocardial destruction in CCC[24].

2.2. Microcirculatory disorders

Experimental models of *T. cruzi* infection have evidenced microvascular changes, such as the formation of microthrombi associated with microcirculatory spasm, endothelial dysfunction and increased platelet activity[35]. Such microcirculatory disorders might result from the inflammation directly related to *T. cruzi* or mediated by immune injury[36]. Those microcirculatory changes are considered to amplify the inflammatory effects and to cause myocardial ischemia[24]. Several patients with CCC manifest angina-like symptoms, have electrocardiographic changes suggestive of ischemia and various myocardial perfusion defects[32,37]. Their epicardial coronary arteries are usually angiographically normal, but can react abnormally to vasodilating or vasoconstricting stimuli[37,38]. It has been postulated that such microcirculatory changes cause hypoperfusion in myocardial areas relatively devoid of coronary branches (zones of marginal perfusion or "watersheds"), being associated with the formation of aneurysms in the apical and posterior basal left ventricular (LV) walls[39].

Similarly to the "neurogenic theory", the "microvascular hypothesis" still requires more convincing clinical support, but, despite not being an independent pathogenic mechanism of CCC, it can potentiate chronic myocardial inflammation.

2.3. Immunopathological mechanisms

There is experimental evidence that, after the intense myocarditis of the acute phase of CD, when parasitemia and tissue parasitosis are controlled by immune mechanisms, inflammation subsides and persists focally at low intensity during the indeterminate form of disease[40]. It has been postulated that the balance and relative pathological stability of that the indeterminate form, in which the immune mechanism should be essentially modulated in the protective direction, are disrupted by still obscure factors, when inflammation, necrosis and fibrosis become more intense, diffuse and progressive[24-27,39,41]. Several factors can determine the stability or instability of the process: parasite load, parasite strain or tissue tropism, duration of infection, and genetic components of the host. The existence of proper immunoregulatory mechanisms are believed to be crucial in differentiating individuals who control their infection without developing important tissue damage (through limited inflammatory response) from those progressing to severe disease, with intense inflammation, necrosis and reactive fibrosis.

There is unequivocal evidence that autoimmune pathogenic reactions occur in CCC, through molecular mimicry, polyclonal activation and other mechanisms[24-27,42]. It is not clear whether the autoimmunity-dependent injury to cardiac structures is decisive for the installation of the characteristic lesions of CCC. Despite the current knowledge limitation, the theory that the immune system reaction to *T. cruzi* infection is actually a "two-edged sword" and plays as fundamental role in the chronic phase of chagasic myocarditis is supported by an extensive body of experimental and clinical evidence[24-27,39-41].

2.4. Inflammation and tissue injury dependent on the parasite presence

In the chronic phase of CD, the classical histologic methods used to emphasize the absence or paucity of parasites in the hearts of *T. cruzi*-infected experimental animals or humans[29]. With more sensitive techniques [immunohistochemistry or polymerase chain reaction (PCR)], the persistence of parasites in myocardial inflammatory foci has been evidenced[43,44]. In addition, a reduction in the parasite load due to trypanocidal treatment in experimental animals and humans has been observed to attenuate or halt the progression of chronic myocarditis[45,46]. In contrast, *T. cruzi* reinfections or its multiplication during immunodepression exacerbate the inflammatory manifestations and CCC course[47,48].

Based on that evidence, there is an emerging consensus that the essence of CCC pathogenesis resides on the inflammation directly dependent on the parasite persistence and consequent adverse immune reaction elicited by it[24-28,49]. This rescues the notion that, even in its chronic phase, the cardiopathy is essentially an infectious inflammatory process, requiring testing whether in that phase the trypanocidal treatment alters the natural history of CCC.

There is substantial evidence that the cytokines produced by *T. cruzi*-infected patients and animals can modulate the gene and proteomic expression of myocardial cells and other cardiac tissue components[50]. Polymorphism of genes related to innate immune response and to cytokine production can influence the course of the pathogenetic process of CCC.

2.5. Pathophysiology of chronic Chagas cardiopathy

The cardiac injury in CD results from fundamental changes (inflammation, necrosis and fibrosis) caused directly or indirectly by *T. cruzi* in the specialized conducting tissue, contractile myocardium and intramural nervous system.

The frequent impairment of the sinus node, atrioventricular node and bundle of His due to inflammatory, degenerative and fibrotic changes can cause sinus node dysfunction and various types of varied atrioventricular and intraventricular blocks. The right bundle branch and the left anterior superior fascicle are more vulnerable and frequently affected because they are more individualized structures. Inflammatory foci and areas of fibrosis in the ventricular myocardium, especially in the posterior-lateral and inferior-basal regions, can produce electrophysiological changes, favoring the appearance of reentry. That is the major electrophysiological mechanism of malignant ventricular tachyarrhythmias, which cause SD even in patients with neither HF nor severe LV dysfunction.

Another consequence of the myocardial lesions is the biventricular dysfunction characteristic of CCC. Initially, there is regional impairment, similar to that which occurs in cardiopathy due to coronary obstruction, but, gradually, generalized dilation and hypokinesia develop, conferring the hemodynamic pattern of dilated cardiomyopathy on CCC.

Since the earliest phases, dyssynergia or ventricular aneurysms predispose to thromboembolic complications. In advanced stages, global dilation, venous stasis and atrial fibrillation are additional factors that propitiate the formation of thrombi and consequent pulmonary and systemic embolism, such as in the central nervous system[51]. That aspect confers on CCC, in addition to the predominant characteristic of causing malignant arrhythmias and refractory HF, the characteristic of essentially causing embolic complicationssm.

3. Clinical presentation and classification

According to its course, CD should be classified into two phases: acute and chronic. The acute phase can be due to primary infection or reactivation of the chronic phase. The chronic phase can have four clinical forms: indeterminate; cardiac; digestive; and mixed (cardiac and digestive impairment in the same patient). The cardiac form can occur with or without global ventricular dysfunction (usually called arrhythmogenic form). The chronic phase can also be classified into stages of cardiac impairment (A, B, C and D), according to international recommendations adapted to the chagasic etiology[52].

Stage A comprises patients with the indeterminate form, with neither current nor previous HF symptoms and with normal ECG and chest radiography (XR) findings.

Stage B comprises patients with structural cardiopathy, who never had HF signs or symptoms. This stage contemplates two clinical situations: B1 and B2. Stage B1 comprises patients with electrocardiographic changes (conduction disorders or arrhythmias) and no ventricular dysfunction, who can have mild echocardiographic changes (regional contractility abnormalities), but normal global ventricular function. Stage B2 comprises patients with global ventricular dysfunction and reduced LV ejection fraction (LVEF).

Stage C comprises patients with current or previous HF symptoms and ventricular dysfunction [NYHA functional class (FC) I, II, III and IV].

Stage D comprises patients with HF symptoms at rest, refractory to maximized clinical treatment (NYHA FC IV), requiring specialized and intensive interventions.

That classification is simple, operational and consistent, allowing international understanding and comparison with other etiologies (Chart 1).

3.1. Acute phase

After the initial infection, the acute phase of CD lasts 6-8 weeks. The clinical findings are similar to those of other types of myocarditis, with systemic manifestations of fever, disproportional tachycardia, splenomegaly and edema. Inflammation can be observed at the site the parasites penetrate the skin. If the entrance site is the ocular region, conjunctivitis can occur accompanied by unilateral eyelid swelling and preauricular satellite adenopathy (Romaña's sign). The ECG can reveal sinus tachycardia, low-voltage QRS complexes, prolonged PR and/or QT interval, and alteration of ventricular repolarization. Ventricular arrhythmias, atrial fibrillation and right bundle-branch block can be observed, indicating worse prognosis[53]. When the disease transmission is congenital, hepatosplenomegaly, jaundice, cutaneous hemorrhage and neurological signs can supervene associate, especially in premature neonates. Other rarer conditions, such as oral contamination and laboratory accident, can lead to the acute form of disease[54,55].

The acute phase is most frequently detected in children. If untreated, 5% to 10% of symptomatic patients die during that phase, due to acute HF or meningitis, SD being rare.

The acute phase can also result from the reactivation of a previously established infection in its chronic phase. Immunosuppressive conditions can cause parasite proliferation, necrotic or tumoral lesions in the brain and esophagus, and myocarditis aggravation[56]. This has been frequently observed in HIV coinfection, particularly with CD4 counts lower than 200/mL, and in organ transplantation[57]. Acute myocarditis and/or esophagitis have been observed with exacerbation of previous cardiopathy and congestive HF (CHF). After cardiac transplantation and in the presence of fever, myocarditis and cutaneous lesions, differentiating reactivation from rejection can be difficult[58].

3.2. Chronic phase

After the initial acute phase, three clinical conditions can occur: indeterminate form; cardiac form without ventricular dysfunction; and cardiac form with ventricular dysfunction. This new classification should be preferred rather than the one previously used, which defined independent congestive and arrhythmic forms. Ventricular dysfunction, the major prognostic marker, is worth noting. Those clinical forms usually occur after the latency period of several decades that characterizes the indeterminate form[59].

Given the current wide availability of echocardiography (ECHO), its performance should be considered as part of the initial assessment of patients with positive serology and whenever there are changes in the clinical or electrocardiographic findings. For patients with electrocardiographic changes, ambulatory ECG (Holter monitoring) should be considered at the initial assessment and later whenever warranted by the symptoms require (Table 1).

3.2.1. Indeterminate form

By definition, patients with the indeterminate form of CD have positive *T. cruzi* serology and/or parasitological tests, but neither symptoms, nor physical signs; in addition, they have no evidence of organic lesion (cardiac and extracardiac) on ECG and chest XR, and on any other radiological imaging study (esophageal and colon)[60-62]. However, more strict and sophisticated tests (ECHO, autonomic assessment, exercise testing, Holter monitoring, myocardial scintigraphy, magnetic resonance imaging, cardiac catheterization, and endomyocardial biopsy) can evidence some changes, usually mild and with no prognostic value established in any study[61,63-66]. Because such patients have chagasic infection, they are believed to be at an increased risk for developing HF and regional contractility abnormalities, and, thus, for progressing to the cardiac form of the disease.

The indeterminate form can last 30-40 years, and 30%-40% of the patients will eventually develop the cardiac form of CD[62,67].

Chart 1 – Clinical classification of left ventricular dysfunction in chagasic cardiopathy

Acute phase	Chronic phase				
	Indeterminate form	Cardiac form with no ventricular dysfunction	Cardiac form with ventricular dysfunction		
	A	B1	B2	C	D
Patients with findings compatible with acute Chagas disease	Patients at risk for developing CHF. They have positive serology, neither structural cardiopathy nor CHF symptoms. No digestive changes	Patients with structural cardiopathy, evidenced by electrocardiographic or echocardiographic changes, but with normal global ventricular function and neither current nor previous signs and symptoms of CHF	Patients with structural cardiopathy characterized by global ventricular dysfunction, and neither current nor previous signs and symptoms of CHF	Patients with ventricular dysfunction and current or previous symptoms of CHF (NYHA FC I, II, III or IV)	Patients with refractory symptoms of CHF at rest, despite optimized clinical treatment, requiring specialized interventions

Table 1 – Recommendations and levels of evidence for performing cardiological tests in the initial assessment of chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
I	12-lead ECG	C
	Posteroanterior chest XR	C
IIa	Doppler echocardiography	C
	Holter monitoring in patients with altered resting ECG	C

The other patients will remain asymptomatic during their entire life, maintaining the immune balance between the parasite and the host[68]. The gradual appearance of electrocardiographic or echocardiographic changes marks the beginning of the chronic cardiac form[69].

3.2.2. Cardiac form without ventricular dysfunction

Most commonly, arrhythmic manifestations coexist with congestive findings. Some patients, however, can have a form of chagasic cardiopathy characterized only by arrhythmias and intraventricular and atrioventricular conduction disorders, with normal ventricular function. Although malignant ventricular arrhythmia is more common among patients with concomitant ventricular dysfunction, it can also occur among those with preserved ventricular function, being an important prognostic marker[70].

Arrhythmia-related symptoms include palpitations, dizziness, lipothymia and syncope. Syncope in chagasic cardiopathy can be due to both episodes of ventricular tachyarrhythmias and to sinus node dysfunction and atrioventricular blocks (AVB) with asystole[71]. Sudden death is the major cause of death, has a proteiform multiple mechanism (ventricular tachycardia or fibrillation and asystole) and is associated with multiple scar areas in the myocardium[59,70].

Chronotropic incompetence can result from degeneration of the conduction system and autonomic dysfunction, causing symptoms related to intolerance to physical exercise, even in the presence of normal ventricular function[30,72].

3.2.3. Cardiac form with ventricular dysfunction

Chronic HF usually installs at least 20 years after the original infection. At that stage, the clinical findings depend on the expression of three frequently coexisting disorders: HF, arrhythmias and thromboembolism. The most frequent clinical presentation is biventricular HF, with predominance of symptoms related to serious higher impairment of the right ventricle function (jugular venous stasis, hepatomegaly, ascitis and lower limb edema), associated with ventricular and atrial arrhythmias and atrioventricular and intraventricular conduction disorders[73,74].

Patients usually complain of weakness rather than of dyspnea, which can be partially explained by their lower blood pressure levels as compared with those of other HF etiologies and by the concomitance or preponderance, in some cases, of right ventricular (RV) dysfunction. Several patients complain of chest pain, usually as like atypical angina, possibly due to microcirculation abnormalities caused by the inflammatory process[75]. The clinical exam reveals significant cardiomegaly with impulsive and diffuse *ictus cordis*, murmurs of mitral and tricuspid regurgitation and split of the second cardiac sound.

Dilated ventricles with apical aneurysms, in addition to the high prevalence of atrial fibrillation at more advanced stages, are important sources of mural thrombi, causing systemic and pulmonary thromboembolic phenomena[76]. Cerebral vascular accidents (CVA) are more common in chagasic HF than in HF of other etiologies, being CD a risk factor for CVA[77]. The prognosis worsens as congestion progresses and arrhythmias become more difficult to control[78-80].

4. Clinical diagnosis, differential diagnosis and prognosis of chronic chagasic cardiopathy

4.1. Clinical diagnosis of CCC

As previously mentioned, CCC can manifest as HF, thromboembolic events, ventricular arrhythmias and SD[80]. Its diagnosis is based on positive epidemiology, anamnesis, physical exam, electrocardiographic and radiological changes and serological tests[81-83]. The major symptomatology is HF with progressive dyspnea, fatigue and asthenia. Symptoms of right HF, such as edema, increased abdominal volume and epigastric discomfort, can appear early, but are more frequent at advanced stages of disease, accompanied by low cardiac output symptoms, such as intolerance to exertion. Suggestive history of arrhythmic events (bradyarrhythmia or tachyarrhythmia) with palpitations, presyncope and syncope is frequent[79,84,85]. Thromboembolic events, mainly CVA, can be the first manifestation of CCC, and originates mainly from intracavitary thrombi[84]. Angina of atypical character is frequent, results from ischemia in the absence of angiographically detectable coronary obstruction, and is explained by inflammatory changes, thrombosis and other coronary microcirculation disorders[32,37,75]. The physical exam can evidence global cardiomegaly, murmurs of mitral and tricuspid regurgitation and presence of the third cardiac sound. Low cardiac output signs, such as hypotension and filiform pulse, are detectable in some individuals, unlike signs of the less conspicuous pulmonary congestion, due to the important RV dysfunction[73,86,87].

4.1.1. Serological tests (Table 2)

Because of the low parasitemia in the chronic phase of CD, parasitological tests are not used, and the serological tests based on the detection of antibodies against *T. cruzi* should be routinely used to establish the etiology of the cardiopathy[81].

The serological diagnosis of *T. cruzi* infection is confirmed, or excluded, by using at least two serological tests of different principles, which should confirm the existence of anti-*T. cruzi* antibodies[81]. Quantifying the concentration of antibodies is desirable. The most commonly used and useful serological tests are the conventional ones: enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence (IIF) and indirect hemagglutination (IHA). When those three tests are performed, concordance between them is obtained in more than 98% of the sera[88,89]. Each test has different characteristics regarding sensitivity and specificity: ELISA and IIF have sensitivity greater than 99.5%, but lower specificity (97%-98%), while the IHA tests have lower sensitivity (97%-98%) and higher specificity (99%)[90-93]. The use of two serological tests prevent false-positive or false-negative results, with ethical and legal connotations[81,89-94].

4.1.2. Complementary tests (Table 3)

4.1.2.1. Electrocardiography

Electrocardiographic changes are frequently the first indicators of CCC. Initially, the changes are characterized by transient or fixed atrioventricular conduction delays, right bundle-branch conduction delays, ventricular repolarization changes and ventricular ectopies[95,96]. With disease progression, mainly when global or regional contractility disorders appear, the changes on ECG become outstanding, with relevant prognostic implications[69,97].

In CCC, complete right bundle-branch block associated with left anterior hemiblock is the most frequently found abnormality change (> 50% of the patients)[69,95,96]. Impairment of the left bundle branch or of the left posterior fascicle is rare. Variable grades of AVB are commonly described in several studies[69,95-98]. More advanced AVBs result from extensive lesions of the atrioventricular node and bundle of His, and can be the first manifestation of the disease. Dysfunction of the sinus node can cause episodes of sinoatrial block, with bradycardia or ectopic atrial tachycardia. Atrial flutter and fibrillation occur late and usually after the installation of severe ventricular dysfunction, as in other cardiopathies[99,100].

Table 2 – Recommendations and levels of evidence for performing serological and parasitological tests in the etiological assessment of patients suspected of having *T. cruzi* infection

Recommendation class	Indications	Level of evidence
I	Use of two serological tests of different principles to confirm the etiological diagnosis in the chronic phase of disease (IIF, IHA and ELISA)	C
III	Use of the Machado Guerreiro reaction	C

Table 3 – Recommendations and levels of evidence for performing complementary tests for the diagnosis and prognosis of patients with chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
I	12-lead ECG for the periodical diagnostic assessment of chagasic patients	C
	Chest XR for the periodical diagnostic assessment of chagasic patients	C
	Doppler echocardiography for the complementary diagnostic and prognostic assessment of CCC patients	C
	Holter monitoring for the assessment of arrhythmias and prognostic stratification of CCC patients	C
	Cardiopulmonary test for functional assessment, risk stratification and help in indicating cardiac transplantation for patients with advanced HF	C
	Cardiac catheterization to assess coronary artery anatomy in patients with typical angina and important risk factors for coronary disease or very positive test for ischemia	C
IIa	Doppler echocardiography for the assessment of patients with the indeterminate form	C
	Right cardiac catheterization to assess pulmonary vascular resistance in candidates for cardiac transplantation with noninvasive evidence of pulmonary hypertension	C
	Cardiac catheterization to assess apical or inferobasal aneurysm if aneurysmectomy or percutaneous ablation of arrhythmogenic circuits is proposed	C
III	Cardiac catheterization as routine indication in chagasic patients with atypical pain	C

Polymorphic ventricular extrasystoles are common in the presence of ventricular dysfunction. Complex ventricular arrhythmias, such as non-sustained or sustained ventricular tachycardia (NSVT and SVT, respectively), can even occur in patients with no HF; however, they usually occur in more advanced cases, and their coexistence indicates worse prognosis[69,79,85,97].

4.1.2.2. Chest radiography

In advanced phases, severe global cardiomegaly usually contrasts with mild or absent pulmonary congestion. It is worth noting that, due to the frequent and intense RV impairment and tricuspid regurgitation, the enlarged right cavities can stand out on chest XR. Systemic venous congestion, and pleural and pericardial effusion frequently accompany the signs of cardiomegaly.

4.1.2.3. Echocardiography

Echocardiography allows assessing regional and global LV contractility, RV impairment, presence of apical or submitral aneurysms, intracavitary thrombi and diastolic function changes[74,101]. In large case series, even in the indeterminate phase of the disease, ECHO can show segmentary contractility changes in the inferior or apical LV wall in 10%-15% of the patients, and apical aneurysm can be detected in 40%-60% of the patients with CCC[74,101,102]. Systolic dysfunction has also been detected by using tissue Doppler imaging. The systolic shortening and diastolic stretching velocities, even in patients with normal ECG, can show prolonged isovolumetric contraction times in both ventricles[103-106]. Thus, a normal ECG reading does not exclude the presence of functional damage to the myocardium[103,105-107]. Studies with pharmacological stress have reported a reduction in the inotropic and chronotropic response to dobutamine infusion, including biphasic contractile response[72]. Finally, stress ECHO can induce complex ventricular arrhythmias even in patients at the early phases of cardiopathy[108].

It is worth noting that, although some patients with the indeterminate form can have diastolic or systolic function changes, usually mild, on ECHO, several case series have documented the usually excellent prognosis of patients with that form of CD[14,62,68,82,109].

The classical echocardiographic aspect of advanced CCC is that of large dilation of the atrial and ventricular cavities, with diffuse biventricular hypokinesia, which is more not so marked than in ischemic cardiomyopathy or in those of other etiologies[63,74]. In addition, atrioventricular valve regurgitation secondary to the dilation of valvar rings is observed. Despite the predominance of diffuse contractile deficit, ventricular aneurysms detected on ECHO in 47%-67% of the patients are characteristic of CCC, being associated with a higher thromboembolic risk (apical position) and with malignant ventricular arrhythmias (basal inferior or posterior lateral wall)[102]. Intramural thrombi can be visualized on ECHO also in atria, especially in the presence of atrial fibrillation. All those echocardiographic aspects are relevant to the prognosis of patients with CCC[74,101,109].

4.1.2.4. Cardiac magnetic resonance

In CCC, myocardial fibrosis is a constant and intense substrate associated with disease progression and poor prognosis due to the high risk of SD and ventricular arrhythmias[39,70]. Cardiac magnetic resonance imaging can identify early cardiac involvement, by detecting delayed enhancement areas that indicate fibrosis, thus allowing a more accurate stratification of the stages of disease severity[110]. The extent of fibrosis correlates directly with the stage of disease and functional class FC, and inversely with the LVEF, contributing to the prognostic stratification of CCC[110].

4.1.2.5. Nuclear medicine

Assessing the biventricular function on nuclear angiocardiography with ^{99m}Tc is an alternative to ECHO, mainly to assess RV ejection fraction and the conditions of contractile synchronization of both ventricles, which have prognostic value[63,86]. Myocardial perfusion scintigraphy shows segmental perfusion deficits in as much as 30% of patients with CCC and angina, but with normal coronary angiography, indicating coronary microcirculation changes, and myocardial fibrosis, disorders that correlate with the progressive deterioration of ventricular function[75,111].

4.1.2.6. Dynamic electrocardiography (Holter)

Dynamic electrocardiography is indicated to assess the chagasic patient with syncope, which can be due to ventricular bradyarrhythmia or tachyarrhythmia[112,113]. Both can coexist in the same patient, the most severe being SVT and advanced AVB. In retrospective and prospective series, as well as in a systematic review, NSVT has also been proved to predict worse prognosis[79,85,112,113].

4.1.2.7. Exercise test and cardiopulmonary test

Exercise and cardiopulmonary tests, although of limited usefulness to clarify chest pain in chagasic patients, are useful to detect exertion-induced arrhythmias in CCC and to establish their prognosis[108,112]. The cardiopulmonary test with direct measurement of oxygen consumption (VO_2) shows high mortality in one year for patients with VO_2 lower than 12 mL/kg/min, being also used as an auxiliary method to indicate cardiac transplantation (CT).

4.1.2.8. Electrophysiological study

The electrophysiological study (EPS) allows the investigation of sinus function and AV conduction, being also indicated to clarify syncope of undetermined origin after noninvasive assessment, in patients with resuscitated SD[112,113]. It is not indicated for risk assessment in patients with preserved systolic function or with NSVT. It is also indicated to map refractory ventricular tachycardia for possible ablation of arrhythmogenic foci[113].

4.1.2.9. Cardiac catheterization

Cardiac catheterization in CCC should only be indicated in special situations, such as some patients with typical angina and classical risk factors for coronary disease, or with a large

ischemic area evidenced on noninvasive tests. It should not be indicated in chagasic patients with atypical pain and no coronary risk factors[37]. The recommendation for cardiac catheterization in patients requiring CT is discussed further ahead in this document.

4.2. Differential diagnosis of CCC

There are no pathognomonic manifestations for CCC by either clinical or complementary tests. In most cases, the serological confirmation of the disease in a patient with HF clinical syndrome is diagnostic[68,79,81]. On ECG, right bundle-branch block associated with left anterior hemiblock is highly suggestive of CCC in patients from endemic areas[95,98], while left bundle-branch block makes the chagasic etiology less likely. According to some researchers, LV apical aneurysm, sparing the septum, would be a "marker of the disease"[74,102]. In addition to changes in LV segmentary mobility, finding prominent RV impairment, which is less frequent in ischemic and hypertensive cardiopathies, contributes to the diagnosis of CCC[63,86,87]. The presence of precordial pain, usually similar to atypical angina, in patients with suggestive epidemiology, even in the presence of perfusion defects on myocardial scintigraphy, supports the chagasic etiology in the differential diagnosis[24,75,111]. Under such circumstances, the positive serology should be confirmed rather than referring patients to coronary cineangiography, which usually reveals no angiographically detectable coronary obstruction.

4.3. Prognosis of chronic chagasic cardiopathy

Chronic chagasic cardiopathy is almost always progressive, its prognosis depending on the phase and clinical form of disease[79,80,85]. In the acute phase, 90% of the cases have cardiac impairment, which is usually benign in more than 90% of the cases. The prognosis is usually inversely proportional to the patient's age, being more severe in children with myocarditis or severe encephalitis[114].

In the indeterminate form, electrocardiographic changes appear in 2.0% of the patients every year[61,82,101]. Although several researchers have described mild changes in the LV systolic and diastolic function of patients with the indeterminate form[72,74,105-108], and despite the speculation whether those disorders might identify patients who will later progress to the cardiac form of disease, two observations should be considered: usually those studies have not met the strict criteria for including only patients with the indeterminate form (for example, a barium enema has not been performed to rule out the presence of colopathy)[115]; although preliminary research has suggested that early changes in regional LV contractility of chagasic patients with normal ECG indicate further deterioration of global LV function[116], no study has proved the importance of any abnormality for prognostic stratification in that phase of the disease[61]. Thus, a benign prognosis and survival similar to that of individuals without CD should be considered for the indeterminate form of CD[61,62,81,82,100,117].

Several observational case series have shown a worse outcome for patients with CCC as compared to those with other cardiomyopathies[118,119]. Several pathophysiological factors contribute to that difference, but several studies have reported LV contractility dysfunction as an independent prognostic predictor when assessed via both cardiomegaly on chest XR and LVEF or ventricular diameter[79,85,109,118-120].

In 2006, for patients with CCC assessed with different noninvasive methods, a risk score was described using six prognostic factors identified via multivariate analysis and long-term follow-up[79]. The following variables showed independent prognostic value: NYHA FC III or IV (5 points); cardiomegaly on XR (5 points); left ventricular dysfunction on ECHO (3 points); NSVT on Holter (3 points); low-voltage QRS complex (2 points); and male gender (2 points). Based on the Rassi score[79], weighted on the prognostic significance of the variables, patients at low risk (score 0 to 6 points) showed 10% mortality, while those at intermediate risk (score 7 to 11 points) showed 44% mortality, and those at high risk (score 12 to 20 points) showed 84% mortality in a 10-year follow-up[79].

A systematic review of studies on prognosis comprising 3,928 patients has identified the following independent prognostic variables: LV systolic dysfunction; NYHA FC III/IV; and cardiomegaly on chest XR[85]. The combination of ventricular dysfunction with the presence of NSVT on Holter monitoring increases the risk for death during follow-up on average 2.14 times[79,85]. The presence of ventricular arrhythmia in patients with HF increases their chance of SD[79, 85,119,120]. Those algorithms can stratify prognosis in a simplified and logical way by using clinical parameters and methods available at most cardiology services in Brazil[79,85]. In CCC, as in other cardiopathies, other variables, such as FC, RV dysfunction, ventricular diameter, LVEF, VO_2, duration of exercise, and brain natriuretic peptide (BNP) level, can affect the prognosis[78,86,119-122] (Figure 4).

5. Etiological treatment of Chagas disease

The etiological treatment of CD is controversial, especially regarding its indication in the late chronic phase. Currently, only two confirmed trypanocidal drugs are available (only one in Brazil), confirming the lack of interest of the pharmaceutical industry in developing new drugs over several decades. No definitive studies assessing the parasiticide treatment effect on the natural history of the disease have been conducted, and the context of uncertainty is compounded by the lack of tests that assure the complete eradication of the parasite and confirm the cure of the disease. The following items are intended to reinforce concepts approached in previous chapters of this guideline.

5.1. Parasite participation

5.1.1. Acute phase

The presence and amount of parasites bear a direct relationship to the severity of myocarditis. However, even with no parasiticide treatment, more than 90% of acute cases recover from the infection with no apparent immediate sequelae.

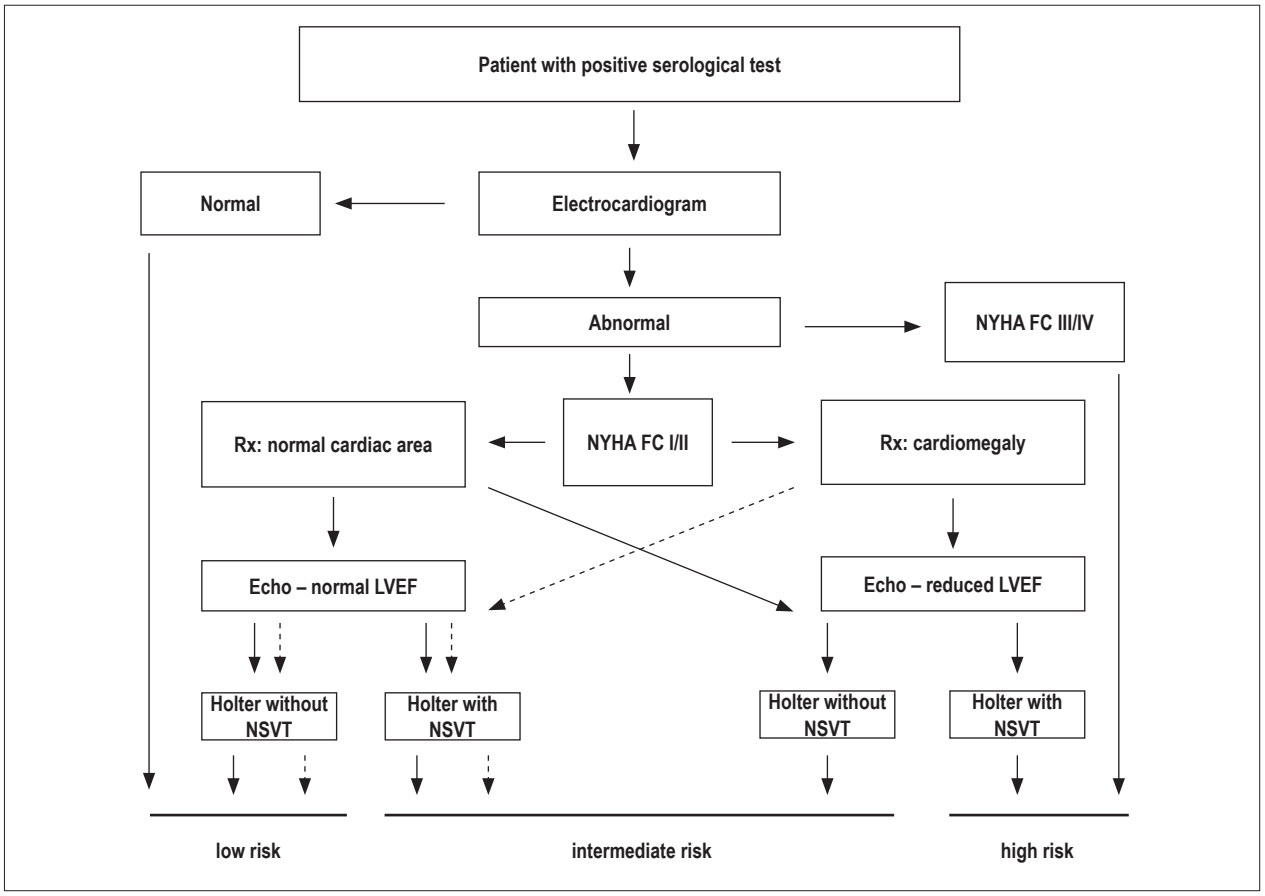

Figure 4 – *Algorithm for risk stratification in chronic chagasic cardiopathy (*). (*)Adapted from Rassi A Jr, Rassi A, Rassi SG. Predictors of mortality in chronic Chagas disease. Circulation. 2007;115:1101-8.*

5.1.2. Chronic phase

The importance of lymphocytic myocarditis in the progression to HF could be identified by use of endomyocardial biopsy in patients with different clinical forms. Studies have shown the topographic association of *T. cruzi* antigens and DNA with myocarditis foci, suggesting that the presence of the parasite is fundamental to the perpetuation of the inflammatory process. However, inflammation severity is disproportionally intense as compared to the paucity of *T. cruzi* elements[123].

5.2. Trypanocidal drugs

5.2.1. Nifurtimox (nitrofuran)

Nifurtimox was described in 1965 (Lampit, by Bayer, no longer available in Brazil), but its mechanism of action has not been completely clarified. The tablet contains 120 mg of active substance. The recommended dose is 15 mg/kg/day for children and acute cases, and 8-10 mg/kg/day for adults, for 60 days, the daily dose being divided into three. The drug has gastrointestinal absorption, is metabolized in the liver (cytochrome P450) and excreted preferentially by the kidneys. Its side effects comprise anorexia (the most severe and frequent), abdominal pain, nauseas, vomiting and weight loss.

5.2.2. Benznidazole (nitroimidazole)

Benznidazole was developed by Roche in 1971 under the commercial name of Rochagan, being currently produced by the Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE). The tablets have 100 mg of active substance. It has gastrointestinal absorption, preferentially renal excretion, and half-life of 12 hours. Its recommended dose is 10 mg/kg/day for children and acute cases, and 5 mg/kg/day for chronic cases, for 60 days, the daily dose being divided into three or two administrations. The recommended maximum dose is 300 mg/day. For adults weighing more than 60 kg, the total dose should be calculated, and the duration of treatment prolonged beyond the 60 days to complete the total dose required. Thus, a 65-kg patient will receive 300 mg/day for 65 days; a 70-kg patient will receive that daily dose for 70 days; and a 80-kg patient will receive the maximum dose of 300 mg/day for 80 days. For patients over that weight, the daily dose of 300 mg for the maximum period of 80 days should be used. The most frequent side effect is exantemous urticarial dermatitis, which occur in up to 30% of the patients, usually already at the end of the first week of treatment. They respond well to anti-histamines or, more effectively, to small oral doses of corticosteroids. In the presence of fever and lymph node enlargement, the drug should be interrupted suspended.

Other side effects include polyneuropathy (usually at the end of the 60-day treatment), with pain and/or tingling in the lower limbs, and anorexia (much less intense than that of Nifurtimox). Significant leukopenia and agranulocytosis are rare, but, in their presence, the treatment should be interrupted. Lymphomas have been reported in rabbits and rats treated with benznidazole, but not in thousands of patients treated by several authors for several decades.

Those drugs are contraindicated during pregnancy and for patients with kidney or liver failure[124-127].

5.3. Indication for etiological treatment in CD (Table 4)

A WHO bulletin[127] has authorized the trypanocidal treatment to all chagasic patients as long as prescribed by a physician with experience in managing the drug, and who can diagnose and treat possible side effects, as well as ensure post-treatment follow-up[128]. There are two types of indication for the trypanocidal treatment[81,129,130].

5.3.1. Consensual indications

5.3.1.1. Acute phase for all patients, regardless of the mode of transmission

In most acutely infected patients, the disease is not diagnosed due to the unspecificity of symptoms and signs in that phase; nevertheless, treatment should be performed in all cases and as soon as possible, regardless of the mode of transmission, except for the presence of pregnancy, which contraindicates the etiological treatment[81,114,131,132].

5.3.1.2. Chronic phase in children

A Brazilian randomized, placebo-controlled study, assessing 130 chagasic children, aged between 7 and 12 years, receiving either benznidazole (7.5 mg/kg/day for 60 days) or placebo, has reported that, after a three-year follow-up, the IIF reactions of 37 out of the 64 children treated (58%) and only three out of the 66 on placebo (5%) were negative ($p < 0.001$). That favorable effect on the host-parasite ratio was maintained after a six-year follow-up[133,134]. In another independent case series in Argentina, 106 chagasic children, aged between 6 and 12 years, have been randomized for benznidazole or placebo for four years. The authors have reported that the serology (ELISA) for *T. cruzi* of 62% of the children treated and none of those on placebo were negative ($p < 0.01$)[134]. Based on those results, and even with no evidence that the treatment changes the prognosis in a clinically relevant way, all chagasic children should be treated early.

5.3.1.3. Accidental contamination

Treatment should be initiated as soon as the accident is characterized as bearing a high risk for infection transmission. The following are characterized as bearing high risk: accidents caused by cutting and piercing instruments and objects or by mucosal contact, during the manipulation of material containing live parasites, such as samples for culture, vectors and infected laboratory animals, samples from patients suspected of having high parasitemia and autopsy specimen. Benznidazole, at the dose of 7-10 mg/kg, should be maintained for at least ten days. In the presence of high parasite load, the treatment should extend for at least 30 days. When contact with blood of a chronic patient (low risk) is involved, drug prophylaxis is not routinely indicated, serological monitoring being recommended[81,128].

5.3.1.4. Reactivation

Reactivation of CD (disease exacerbation in a chronic patient) can occur in pharmacologically immunosuppressed patients or those with HIV coinfection. The specific conventional treatment for 60-80 days is indicated in such situations, depending on the patient's clinical condition. When there is no symptom, but the parasitemia is persistently high, trypanocidal treatment has been indicated, although long follow-up periods are required to better assess the efficacy of that approach[81,128].

5.3.2. Nonconsensual indications

5.3.2.1. Late chronic phase and indeterminate form in young individuals

The WHO and the Pan American Health Organization (PAHO)[127] have disclosed concepts about the etiological treatment, and have recommended its implementation in countries with poor CD control. Treatment in the late chronic phase is aimed at reducing the parasitemia, preventing the appearance or progression of visceral lesions and interrupting the chain of transmission. Treatment in that phase is indicated to patients with the indeterminate form and mild cardiac and

Table 4 – Recommendations and levels of evidence for the etiological treatment of chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
I	Acute phase	B
	Chronic phase in children	B
	Accidental contamination	C
	Reactivation in chronic phase	C
III	Advanced cardiac form	C

digestive forms[81,132]. The indication of trypanocidal treatment for chronic chagasic patients with the indeterminate form is a public health policy in some South American countries, and has been a primordial recommendation based on seminars conducted by the North American Centers for Disease Control and Prevention as soon as serological tests have become mandatory for blood and organ donors, through federal decision, in the USA[133]. Despite the lack of proof that the etiological treatment of the indeterminate form changes the natural history of disease (randomized studies with that outcome have not been published), it is worth noting that the results of observational and randomized studies in children (favorably changing surrogate outcomes) have been considered sufficient to support the recommendation, aimed at preventing the installation of cardiopathy[134-141].

The indication for trypanocidal treatment in patients with established CCC remains controversial. Several researchers support that treatment based on the following: a) experimental evidence by several researchers that the etiological treatment attenuates the progression of cardiomyopathy[45,418]; b) observational studies in humans, although not "definitive", but with clinically relevant outcomes, have reported a possible positive impact on the natural history of the disease, even in the non-advanced phase of CCC[46,81,126,132,133,141]; and c) the relative paucity and low severity of the side effects, as compared with the potential benefit of short-term treatment (usually two months). In an attempt to solve the dilemma, and considering the opposite risks of alpha or beta errors, an ongoing international, multicenter, randomized, double-blind, placebo-controlled investigation, the BENEFIT study, assesses the six-year clinical outcome of patients with CCC treated with benznidazole or placebo[49].

The results of the BENEFIT study will be strategic for the management of chagasic patients with manifest cardiopathy. The editors of this guideline have not reached a consensus regarding the recommendation class and level of evidence of the indication of treatment for those patients. While some editors have suggested that treatment of the non-advanced cardiac form receives recommendation class IIa with level of evidence B, and that the indeterminate form in young adults receives recommendation class IIa with level of evidence C, other editors have suggested recommendation class IIb, and are waiting for the results of the investigations to yield a definitive recommendation.

5.4. Criteria for infection cure

Laboratory follow-up of treated patients in both the acute and recent or late chronic phases is aimed at assessing the presence of parasites and antitrypanosoma antibobies[142]. Parasitological tests (xenodiagnosis, blood culture, PCR) are useful only when *T. cruzi* is found, which means therapeutic failure. Negative parasitological results are insufficient to assure infection cure. The antibody tests involve serological tests. Positive results (presence of antibodies) do not necessarily mean unsuccessful trypanocidal treatment; however, persistently negative results (over many years) mean cure[143,144]. With therapeutic success, there is progressive decline of antibody titers, until the serological tests become negative. Those titers decline, reaching values observed in the non-infected population in various time frames, which depend on the time the treatment is performed. In cases treated during the acute phase (regardless of age), antibody titers decline in the first year, becoming negative in less than five years. In children (12-14 years) or adults treated within the first years following infection, antibody titers decline in the first five years, becoming negative usually in ten years from treatment. In adults treated later, the curve of antibody titers shows inflexions after 10-20 years, and those titers become negative after 30 years or more[132]. Although not yet totally accepted, the proposed conceptual advance is to consider significant decreases in anti-*T. cruzi* antibody titers to have the same meaning as their absence. The serological tests should be repeated annually until persistently negative results are obtained[88,145,146] (Table 5).

Control with parasitological tests after treatment is unnecessary, because they will be valid only when showing therapeutic failure. If available, they can be indicated annually[147].

5.5. Clinical managements for patients with the indeterminate form

As already mentioned, the indeterminate form is characterized by seropositivity for anti-*T. cruzi* antibodies, absence of symptoms and physical signs, no changes on ECG and chest, esophageal and colon radiological tests (normal barium enema required to characterize the patient as having that disease form, even with normal bowel habits)[115]. Because the prognosis of those patients compares to those of the non-chagasic population, neither restrictions to normal life nor indication for absence from work should exist[131]. Restriction to activities that threaten the patient's or a third party's life is arguable[82]. Chagasic pregnant women and those breast-feeding should receive the same instructions as non-chagasic women under the same conditions; however, special attention should be paid to newborns, aiming at the early diagnosis of congenital transmission. Whenever possible, parasitological tests with blood samples of the newborns should be performed. When positive, the trypanocidal treatment should be initiated; when negative or when the parasitological test is unavailable, the serological test (IgG) should be performed from the 6th to the 9th month

Table 5 – Recommendations and levels of evidence for the indication of tests as healing criteria in chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
IIa	Serological control	B
IIb	Parasitological control	B

of life (when maternal antibodies are no longer present). When the serological test is positive, the trypanocidal treatment should be initiated, and, when negative, the child should be considered not infected[81]. For patients with the indeterminate form, clinical assessment and annual or biannual ECG are recommended[129].

Redefinition of the indeterminate form has been proposed, excluding the barium enema for asymptomatic chagasic patients (or replacing it with abdominal ultrasound) and requiring normal ECHO and no ECG changes; however, the proposal has not been well received[115].

6. Treatment of ventricular dysfunction and heart failure

In addition to parasite infection control, as seen in the etiological treatment chapter, CCC management consists of treating the different clinical manifestations of the disease, i.e. ventricular dysfunction and HF, thromboembolic phenomena and rhythm disorders (Table 5).

6.1. Ventricular dysfunction and heart failure

Similarly to other cardiopathies, the treatment of chagasic HF is based on the routine combination of three types of drugs: diuretics; angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB); and adrenergic beta-blockers (BB)[148].

However, although CD is an important cause of HF in Latin America, patients with CD and HF have not been included in large studies assessing those drugs to treat HF. Thus, their real efficacy and tolerability in patients with CCC have not been scientifically established, and their use have been extrapolated empirically from the results obtained for HF of other etiologies.

6.1.1. Renin-angiotensin-aldosterone system blockade

The renin-angiotensin-aldosterone system blockade plays a fundamental role in adverse cardiac remodeling and ventricular dysfunction progression of HF[149]. Several studies have shown the benefit of the chronic administration of ACEI[150,151] or ARB[152] to the treatment of patients with HF, in both LV remodeling and morbidity and mortality reduction. However, almost none of those studies, except for some small ones, have enrolled patients with CCC[153].

In an experimental study with mice, the use of captopril has reduced myocarditis and fibrosis in the acute phase of CCC[154]. A clinical study including 17% of patients with CCC and assessing the action of captopril on the FC of 115 patients with HF has shown the benefit of that blockade, but has not separated the effects according to the etiologies[155]. Another study with 42 patients with HF and CD has shown that the increase in enalapril dose up to the maximum recommended was well tolerated and improved the quality of life, in addition to reducing BNP levels and the radiological cardiothoracic index[156].

The use of ACEIs in CCC is recommended to all patients with ventricular dysfunction, from NYHA FC I up to FC IV. When ACEIs are not tolerated, the use of ARBs is recommended, supported by extrapolation from studies on HF of other etiologies[157].

Regarding the aldosterone blockade, the use of spironolactone and eplerenone after myocardial infarction has proved beneficial in terms of morbidity and mortality of patients with HF[158,159]. The largest randomized, double-blind and placebo-controlled study assessing spironolactone in the chronic phase of HF has included etiologies other than ischemia, such as CD (some patients with CCC)[159]. That study has evidenced the benefit of that drug to patients in NYHA FC III-IV. However, the analysis of a subgroup of chagasic patients has not been conducted and would not have practical value, because it was not prespecified and the sample size was very small. An experimental study with spironolactone has suggested some benefit to survival and myocardial fibrosis reduction in *T. cruzi*-infected hamsters[160]. That drug is indicated to patients with LV systolic dysfunction, LVEF $\leq$ 35%, and NYHA FC III/IV HF.

6.1.2. Beta-adrenergic blockade

Several studies have shown that, in ischemic cardiopathy and dilated cardiomyopathy with systolic dysfunction, HF treatment with adrenergic BBs, in addition to renin-angiotensin-aldosterone system blockers, is effective in improving the quality of life, reducing symptoms and the need for hospitalizations, and in increasing survival[161-166].

As exposed in the chapter on pathogenesis, there are peculiar aspects of the pathophysiology of CCC involving the autonomous nervous system[29-34,167,168]. There is evidence that CCC has the characteristic of being a cardioneuropathy model because of its important parasympathetic denervation, which precedes the installation of LV systolic dysfunction. In addition, the circulation of antibodies against β-1 adrenergic and M-2 muscarinic receptors, which can be implicated in the perpetuation of the HF process, has been demonstrated. The characteristic adrenergic activation installed with ventricular dysfunction and intensified with HF progression can be more exacerbated in chagasic patients than in patients with other cardiopathies. This can contribute to accelerate the harmful process of ventricular remodeling, to induce arrhythmias and to increase the risk for SD.

Table 5 – Recommendations and levels of evidence for the indication of tests as healing criteria in chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
IIa	Serological control	B
IIb	Parasitological control	B

Thus, extrapolating the indication of BB to treat chagasic patients with ventricular dysfunction, based on studies of other HF causes, seems logical. Considering the high frequency of bradycardia in CCC (due to sinus node dysfunction, sinus node denervation and several AV blocks), it is worth noting that physicians are considerably afraid of aggravating that condition by using BB. Thus, in the BENEFIT study, which has enrolled approximately 1,800 patients with CCC (80% in NYHA FC I and II), only 32% were treated with BB[49].

However, although scarce, there is direct evidence that the use of BBs is beneficial to treat HF, specifically that of chagasic etiology. A randomized, double-masked, place-controlled study with 42 patients with CCC and LVEF < 45% has reported that the use of carvedilol, added to enalapril and spironolactone, has caused the following: significant improvement in the Framingham score and quality of life; significant reduction in the cardiothoracic index and BNP circulating levels; and a 2.8% increase in LVEF[156]. In the randomized, double-masked CHARITY study, in its final phase, the use of bisoprolol in chagasic patients with HF is being compared with the use of placebo (ClinicalTrials.gov, NCT00323973)[169]. Extrapolating the recommendations regarding the treatment of patients with HF of other etiologies[148], carvedilol, bisoprolol or metoprolol succinate should be used to treat chagasic patients with previous or current HF symptoms and/or signs, and LVEF ≤ 45%. The daily dose should be slowly titrated, aiming at avoiding heart rate < 50/min at rest. Those drugs can also be indicated even in the absence of HF symptoms and signs, when there is LV dysfunction or remodeling. Those drugs are contraindicated to patients with bradycardia ≤ 50 bpm or AV conduction disorders (PR > 280 ms).

6.1.3. Hydralazine and nitrate

Extrapolating from the V-HeFT-II and A-HeFT studies, the combination of hydralazine and nitrate is recommended to treat chagasic patients of any ethnicity in NYHA FC II-III with contraindication to ACEI or ARB (progressive renal failure or hyperkalemia). In addition, extrapolating from the A-HeFT study, those drugs are recommended to Afro-descendants in NYHA FC III-IV already on optimized therapy based on ACEI or ARB[170,171].

6.1.4. Digitalis

Digitalis has been used in HF treatment for the longest time. Of all drugs with a positive inotropic action and tested for prolonged use, it was the only that did not increase mortality as compared with placebo (digitalis was even with placebo, but reduced the number of hospitalizations due to HF)[172]. Despite the lack of evidence in chagasic patients, and recognizing that its inhibitory action on the sinus node and the atrioventricular junction can be potentiated by the association with other drugs, such as BB and amiodarone, the use of digoxin can be justified in chagasic patients with symptomatic LVEF ≤ 45% (NYHA FC II-IV HF), mainly when the ventricular frequency is elevated in the presence of atrial fibrillation[173].

6.1.5. Diuretics

As in other etiologies of HF, diuretics should be used in chagasic patients to relieve congestive symptoms and signs. In a meta-analysis of several studies, those drugs have evidenced a mild effect of mortality reduction, being also useful to modulate the beneficial responses to other drugs, such as neuro-hormonal antagonists, whose effects depend on sodium balance[174]. The association of thiazides with loop diuretics is more effective in more advanced HF stages. Thiazides inhibit sodium resorption mainly in the distal convoluted tubule and are mild diuretics, but are not effective when creatinine clearance is lower than 30 mL/min. Loop diuretics, of which furosemide is the most used in Brazil, inhibit sodium, potassium and chlorine resorption in the ascending limb of Henle's loop, have a rapid action, short period of action (4-6 hours) and cause abundant diuresis, and can be intravenously administered. There is no reason to consider that the effect of diuretics in patients with CCC differs from that in cardiomyopathies of other etiologies[81,175].

6.2. Prevention of thromboembolic events

Some series have reported an annual incidence of thromboembolic phenomena of 1%-2% in patients with CCC[176,177], higher (60%) in the subgroup with chronic HF. In those series, apical LV aneurysm and LV mural thrombosis have been observed in 23% and 37% of the patients, respectively. In *postmortem* studies, thrombosis of the apical LV aneurysm has been described in up to 99% of the cases[178]. Among patients with HF, the prevalence of thrombosis of the right cardiac chambers (53%) exceeds that of the left chambers (43%)[178]. Pulmonary thromboembolism is rarely seen in patients without manifest HF, but can affect 37% of those with HF. In 85% of the cases, it associates with mural thrombosis of the right chambers[179].

Systemic thromboembolism affects mainly the brain, can be the first clinical manifestation of the disease, and associates with mural thrombosis and apical LV aneurysm[176]. A case-control study has reported the following independent risk factors of cerebral thromboembolism: HF; arrhythmias on ECG; female sex; and apical LV aneurysm[77]. Table 6 shows the indications for anticoagulation.

In 2008, the *Arquivos Brazileiros de Cardiologia* published an article on the development of a score derived from a prospective cohort of 1,043 patients to assess the risk of cardioembolic CVA in CCC and to implement its prevention. The reported incidence of that event was 3.0% or 0.56%/year. The presence of LV systolic dysfunction contributed with 2 points, whereas apical aneurysm, primary change of ventricular repolarization on ECG and age > 48 years contributed with 1 point each. By use of risk-benefit analysis, warfarin would be indicated for patients scoring 4-5 points (in this subgroup, the incidence of CVA is 4.4% *versus* 2.0% of severe bleeding per year). In the subgroup scoring 3 points, the event and bleeding rates with oral anticoagulation are equivalent, and either acetylsalicylic acid or warfarin could be indicated. For patients scoring 2 points, with low incidence of

CVA (1.22% per year), either acetylsalicylic acid or no prophylaxis would be recommended. Patients scoring 0-1 point, with event incidence close to zero, do not require prophylaxis[51].

6.3. Treatment of the acute phase cardiopathy

Mortality in the acute phase is lower than 10% of the cases with established diagnosis, and usually results from meningoencephalitis, severe HF, and, more rarely, SD[10,180,181]. In most patients, the acute phase passes unnoticed. When signs and symptoms of myocarditis are present, the treatment should be similar to that recommended for myocarditis of other etiologies[181,182], and consists of circulatory support and conservative measures. After In the presence of hemodynamic stabilization, the treatment should meet the recommendations for the chronic management of ventricular systolic dysfunction and HF (Table 6).

6.4. Treatment of decompensated chronic heart failure

Decompensated HF secondary to CD causes 3% of the hospitalizations in the Brazilian Unified Health Care System (SUS), accounting for 33,684 hospitalizations in 2007, at the approximate cost of R$ 2,300,000.00[175].

Table 6 – Recommendations and levels of evidence for the treatment of heart failure in chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
	Renin-angiotensin-aldosterone system blockers	
I	ACEI or ARB (if intolerant to the former) to patients with LV systolic dysfunction, LVEF < 45% and FC I/II/III/IV HF	C
	Spironolactone to patients with LV systolic dysfunction, LVEF < 35% and FC III/IV HF	B
IIb	Spironolactone to patients with LV systolic dysfunction, LVEF < 35% and FC II HF	C
	Beta-blockers	
IIa	Carvedilol, bisoprolol or metoprolol succinate to patients with LV systolic dysfunction, LVEF < 45% and FC I/II/III/IV HF	B
	Hydralazine and nitrate	
I	Patients of any ethnicity with LV systolic dysfunction, LVEF < 45% and FC II-III HF with contraindication or intolerance to ACEI and ARB (progressive renal failure or hyperkalemia)	C
IIa	Patients with LV systolic dysfunction, LVEF < 45% and FC III-IV HF as an addition to optimized therapy	C
	Diuretics	
I	Patients with congestive signs and symptoms (FC II-IV HF)	C
III	Patients with asymptomatic LV systolic dysfunction (FC I HF) or hypovolemic	C
	Digitalis	
IIa	Patients with LV systolic dysfunction, LVEF < 45% and sinus rhythm or AF, symptomatic, despite optimized therapy	C
III	Patients with LV systolic dysfunction, LVEF < 45% and AF, asymptomatic, to control high heart rate	C
III	Asymptomatic patients with sinus rhythm	C
	Patients with EF ≥ 45% and sinus rhythm	C
	Vasoactive amines	
I	Noradrenaline and dopamine in cardiogenic shock	C
	Intravenous inotropic drugs	
I	Dobutamine in cardiogenic shock	C
IIb	Levosimendan in patients with SBP > 90 mmHg	C
	Oral anticoagulation	
I	Atrial fibrillation - With systolic dysfunction - With CHADS2 ≥ 2	 C C
	Mural thrombosis	C
	Previous embolic cerebrovascular accident	C
IIa	IPEC/FIOCRUZ score ≥ 4[51]	B
IIb	LV apical aneurysm (without thrombosis)	C

The hemodynamic profile of chagasic patients with decompensated HF is that of HF due to LV systolic dysfunction. It is characterized by an increase in atrial pressures and in ventricular filling pressures, and a reduction in cardiac output, with an increase in systemic and pulmonary vascular resistances[81]. There is no evidence of cardiac decompensation caused by isolated LV diastolic dysfunction in chagasic cardiomyopathy. Patients with decompensated HF experience an improvement in symptomatology with the use of furosemide at conventional doses[183]. Spironolactone has a beneficial effect on the neurohormonal profile of patients with mild to moderate HF, mainly when associated with ACEI[155]. Thus, that drug might also be useful to treat chagasic patients with decompensated HF.

The intravenous use of sodium nitroprusside considerably relieves the symptoms of chagasic patients with decompensated HF, reducing pulmonary capillary pressure, ventricular filling pressures and atrial pressures, making the treatment of the most severe cases of decompensated HF more effective attractive[184].

The use of ACEI has a favorable impact on the neurohormonal profile of chagasic patients with decompensated HF, particularly when used after digitalization, which, acutely, has a clear hemodynamic effect[185,186].

In extreme cases of decompensated HF (cardiogenic shock or pre-shock), intravenous noradrenaline seems to improve the short-term prognosis of patients[184]. Recently, the usefulness of levosimendan has been suggested[188] in chagasic patients who developed cardiogenic shock due to chagasic acute myocarditis.

6.5. Chagasic cardiopathy and co-morbidities

6.5.1. Diabetes mellitus

The risk factors for atherosclerosis should be properly controlled, regardless of the positivity of CD serological tests, because the patients are at the same risk of those with negative serology[189,190]. In addition, diabetes mellitus is by itself a risk factor for the development of HF[191]. Diabetes mellitus can lead to the impairment of the epicardial coronary arteries and of the microcirculation, which, in patients with CD, have already been previously affected. Recent studies have shown that *T. cruzi*-infected diabetic rats die at a higher rate, and have a change in the metabolism of adipose cells, suggesting that, although very initially, inflammation in that tissue could be related to the development of cardiopathy[192].

Two particularities of the treatment of diabetic patients with CCC and HF are worth noting: the use of thiazolidinediones and of metformin. Regarding the former, rosiglitazone, when used to FC I/II patients, caused fluid retention, although there was no change in LVEF, requiring drug adjustment for compensation[193]. Thus, it is contraindicated to FC III and IV patients. Regarding metformin, it should be carefully used in the more advanced phases of HF of chagasic etiology, in which the renal function impairment is more frequent and intense, because of the higher likelihood of developing metabolic acidosis.

6.5.2. Thyroid disorders

Approximately 30% of the patients with HF have some thyroid dysfunction, with reduced T3 levels, which can be related to the severity of that syndrome. A complicating factor in HF of chagasic etiology is the high prevalence of supraventricular and mainly complex ventricular arrhythmias. One of the few drugs studied and with somehow favorable results in that population of patients is amiodarone, which is known to cause thyroid dysfunction (both hyperthyroidism and hypothyroidism) and can affect up to 64% of the patients[194]. However, the benefits of amiodarone should be opposed to the risk of thyroid dysfunction. Periodical monitoring of the thyroid function in chagasic patients on amiodarone is recommended. In patients on amiodarone and with symptomatic thyroid hypofunction, such as bradycardia aggravation, hormone replacement should be carefully performed.

6.5.3. Systemic arterial hypertension

Some studies have shown that patients with CD and systemic arterial hypertension are older and have cardiopathy more often than hypertensives with negative serology[195], although the clinical-laboratory characteristics are similar in both groups. In the follow-up of patients with in the indeterminate form, systemic arterial hypertension was the most frequently found comorbidity, contributing to ventricular dysfunction[196]. Arterial hypertension control in patients with positive serology has to be as effective and careful as that in patients with negative serology, and the combination and choice of drugs are similar.

6.5.4. CCC and coronary artery disease

Until a few decades ago, chagasic patients were mainly rural workers, at low risk for obstructive coronary artery disease. With the increasing urbanization of the chagasic population, mainly from 1980 onwards, they have been exposed to the same risks of non-infected individuals. Thus, the prevalence of atherosclerotic disease as a cause of acute myocardial infarction is similar in chagasic and non-chagasic patients[197]. The notion that the prevalence of non-obstructive atherosclerotic disease (minimal lesions), or even apparently normal epicardial coronary arteries, is higher in chagasic patients who already had acute myocardial infarction is controversial[37,189].

It is worth noting the difficulty of establishing the differential diagnosis in chagasic patients with precordial pain, which can be intense and disabling. The ECG can evidence changes compatible with coronary artery disease (repolarization anomalies, Q waves, and fibrosis) or that hinder its correct interpretation (AVBs). In addition, those patients often have perfusion disorders. Thus, many several chagasic patients are referred for coronary angiography, which, most of the time, evidences angiographically normal coronary arteries[37].

As a general rule, chagasic patients with obstructive coronary artery disease should receive the same treatment of patients without *T. cruzi* infection.

7. Treatment of arrhythmias and conduction disorders in chagasic cardiopathy

7.1. Mechanisms and substrate of arrhythmias and conduction disorders in chagasic cardiopathy

Arrhythmias and conduction disorders can occur in both the acute phase and CCC[28,198]. The acute phase is usually asymptomatic, but, similarly to other types of myocarditis, arrhythmias and AVB can occur during the acute infection, being markers of poor prognosis[28]. Most arrhythmias and conduction disorders occur during the chronic phase, being direct consequences of the chronic fibrosing myocarditis triggered by *T. cruzi*[28,198], with formation of scars and aneurysms[24,28,198]. Those myocardial scars, focal or scattered spread across the ventricles, contribute to the genesis of reentry ventricular arrhythmias[199-201]. In addition, the cardiac excito-conduction tissue is frequently damaged, leading to sinus node dysfunction and disorders of the atrioventricular and intraventricular conduction[28,198]. In addition to the repairing and reacting fibrosis, damage to the cardiac nervous endings, especially the parasympathetic ones, occurs, a phenomenon that has been associated with an increase in the number of ventricular ectopies, myocardial electrical instability and SD in patients with CCC[24,28,198]. Changes in the density and function of connexins could also contribute to the genesis of arrhythmias and conduction disorders present in the disease[202].

Arrhythmias in chagasic patients can cause disabling symptoms and SD[70,203-205]. Ventricular arrhythmias are the most frequent and can manifest as isolated ectopies or repetitive forms[206]. The SVT is the most common potentially fatal reentry arrhythmia in patients with CCC and segmentary contractile changes, even when the global systolic function is preserved[24,28,198-200]. The arrhythmogenic substrate of that disease is complex, with LV subendocardial, transmural and epicardial scars, which can also affect the right ventricle[200,201-207]. Because of that anatomical complexity, the subendocardium or subepicardium (approximately 55% of ventricular tachycardias), or both (transmural circuits), can participate in the reentry circuits of CCC, explaining the presence of episodes of SVT with multiple morphologies[200,201,207].

7.1.1. Mechanisms of rhythm changes in chagasic cardiopathy

1. *Acute phase* - myocarditis (rare)
2. *Chronic phase* - the invariably present substrate comprises:

   Subendocardial, subepicardial or transmural fibrotic scar;

   Aneurysms (predominantly posterior-basal and apical);

   Destruction of the autonomous nervous system.

7.2. Laboratory investigation for diagnostic and therapeutic definition of arrhythmias in CCC

The initial assessment of patients with CD should consider the presence or absence of symptoms and of ventricular dysfunction. Rest ECG, ambulatory ECG (Holter monitoring), exercise testing and ECHO are extremely important and have precise indications.

Patients with the indeterminate form of CD have normal ECG findings, even in the presence of myocardial lesion. With progression to the cardiac form, the most frequently found changes include right bundle-branch block, often associated with left anterior hemiblock, presence of electrically inactive zones, ST-T abnormalities, ventricular extrasystoles and AVB. The ECG also allows risk stratification. According to the Rassi score[79,85], low QRS voltage is assigned 2 points, probably associated with diffuse myocardium fibrosis.

The exercise test can induce or worsen complex ventricular arrhythmias and guide the treatment and clinical follow-up[108,208], in addition to objectively establishing the patients' FC and tolerance to exercise.

7.2.1. Ambulatory electrocardiography (Holter monitoring)

Patients with CCC, mainly those with electrocardiographic changes, regional or global ventricular dysfunction and HF, usually have a high density of ventricular arrhythmias[209,210]. In those patients, Holter monitoring should be performed independently of symptoms, because it can identify complex arrhythmias, impacting on the treatment and prognosis[79,85]. According to the Rassi score, the presence of NSVT on Holter is a marker of worse prognosis, being assigned 3 points[79]. Periodical Holter monitoring is not required for asymptomatic patients in the indeterminate form[209].

In CCC, autonomous nervous system impairment is evidenced on several physiological and pharmacological tests[30-32,211]. However, RR variability, the most clinically available autonomic function index is inconsistent for prognostic assessment or therapeutic guidance in CCC.

Ventricular function assessment on ECHO allows therapeutic and prognostic guidance[198,201]. Chagasic patients with ventricular arrhythmias can have ventricular aneurysms as follows: in the left ventricle, 80%; in the right ventricle, 10%; and in both ventricles, 10%. The presence of aneurysm is associated with the occurrence of ventricular tachycardia and ischemic CVA[212]. Transesophageal ECHO is indicated for patients with CVA, and lack of visible thrombi in the left cavities on transthoracic ECHO.

7.2.2. Electrophysiological study

The ideal anatomical substrate for reentry is present in CCC, justifying the programmed ventricular stimulation protocol to assess the possibility of inducing reentrant arrhythmias[209,210]. Being an invasive exam, the EPS can cause more risks than benefits in patients with the indeterminate form of disease.

The EPS has proved to be useful for risk stratification of patients with CCC. Some authors have shown that patients with NSVT undergoing programmed ventricular stimulation and who had SVT induction had worse prognosis, with a higher event rate during clinical follow-up[209,213-215]. A study has shown that, in patients with previous SVT or NSVT treated with amiodarone, programmed ventricular stimulation was useful in identifying those with the worst prognosis[214]. In addition, the EPS has a significant role in the assessment of syncope in CCC, especially when non-invasive exams are inconclusive. In those cases, syncope can be caused by both bradyarrhythmia (sinus node dysfunction, atrioventricular blocks, asystole) and ventricular tachyarrhythmia (Table 7).

7.3. Pharmacological treatment of the arrhythmias of chagasic cardiopathy

The pharmacological treatment of arrhythmias in CCC is aimed at controlling symptoms, with no clear evident effectiveness in SD prevention. Although ventricular arrhythmias in CD are associated with a higher risk of SD and increased total mortality[70,205,206,208,216], there is no conclusive evidence that antiarrhythmic drugs have clinically relevant benefits. The most frequent ventricular arrhythmias in chagasic patients are isolated or repetitive ventricular ectopies. The presence of those arrhythmias in asymptomatic patients with preserved ventricular function requires no antiarrhythmic treatment. When symptomatic in patients with ventricular dysfunction, the antiarrhythmic treatment can be individualized[217]. Amiodarone, despite being the most efficient antiarrhythmic drug, has a high incidence of side effects. Beta-blockers, sotalol and group I drugs, such as propafenone, mexiletine, disopyramide and procainamide, have been considered for the treatment of those patients. However, currently those group I drugs should be avoided in patients with structural cardiopathy (LV dysfunction) because of their higher risk of proarrhythmias.

When ventricular ectopies and NSVT are present in patients with LV dysfunction, amiodarone is the only safe drug. Although there is no evidence that it changes the long-term prognosis of those patients, its power to reduce the density of arrhythmias and to control symptoms is well known[218-223]. At the usual doses of 200-400 mg/day, amiodarone can be associated with beta-blockers to reduce severe arrhythmic events[79]. Sustained ventricular tachycardia in CD should be carefully assessed, because it can result in SD as at its first manifestation, even in the absence of left ventricular dysfunction[199,224].

When approaching SVT at the emergency room, electrical cardioversion should be used for hemodynamically unstable patients. For stable patients, cardioversion reversal with injectable amiodarone, at the dose of 150 mg in 10 minutes, can be attempted, and can be repeated in case of no reversal. After reversal, amiodarone infusion should be continued at the dose of 1 mg/minute in the first 6 hours, and later, 0.5 mg/minute in the following 18 hours. Antiarrhythmic drugs should be used for patients with SVT and severe important LV dysfunction (LVEF < 35%) only as an auxiliary treatment to implantable cardioverter defibrillator (ICD) implantation. Amiodarone, at the dose of 200-400 mg/day, remains the drug of choice under such circumstances. For patients with well-tolerated SVT and preserved ventricular function, amiodarone use and catheter ablation can be considered, although ICD is the safest option (Table 8).

7.4. Surgical and catheter ablation of ventricular tachycardia in CCC

The occurrence of SVT in patients with CCC is an important risk factor for SD[199], mainly in the presence of severe LV dysfunction (LVEF < 30%)[216]. Ablation has improved the patients' quality of life, preventing the discomfort of shocks in those with ICD and reducing the number of hospitalizations for SVT reversion during the antiarrhythmic treatment[225].

7.4.1. Surgical ablation

The use of SVT ablation in CCC has been initiated and developed with cardiac surgery[225,226]. Pre- and intraoperative electrophysiological mapping has allowed the identification of the site of origin and its relationship to akinesia and dyskinesia areas usually located in the left ventricle[227]. The analysis of biopsy specimens obtained during surgical treatment guided by electrophysiological mapping has confirmed the presence of the scar substrate[228], showing that the inferior, lateral and basal LV walls were the most frequent sites of origin of SVT, independently of the presence of apical aneurysm[225]. With technological development, the surgical treatment of SVT in CCC has been gradually replaced by the treatment via catheter, being currently rarely recommended, except for highly selected patients (Table 9).

Table 7 – Recommendations and levels of evidence for the indication of intracardiac electrophysiological study in chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
I	Patients with cardiopathy and syncope, whose etiology has not been identified with noninvasive tests	B
	Patients with recurrent SVT despite drug treatment, and intention to perform arrhythmia ablation	B
IIb	For risk stratification of patients on amiodarone	B
	For patients with defined indication for ICD	B
IIb	For patients with NSVT and ventricular dysfunction, with no evidence of SVT, for risk stratification	C
III	For patients with the indeterminate form	C

Table 8 – Recommendations and levels of evidence for drug treatment of ventricular arrhythmias in chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
I	Amiodarone for patients with ventricular ectopies, symptomatic NSVT and LV dysfunction	B
	Amiodarone for patients with symptomatic or asymptomatic SVT, with or without LV dysfunction, not treated with ICD	C
I	Amiodarone to reduce adequate shocks in patients with ICD	C
IIa	Routine amiodarone for patients with symptomatic SVT treated with ICD	C
IIb	Propafenone or sotalol for patients with ventricular ectopies and NSVT with symptoms, but without LV dysfunction	C
	Amiodarone for asymptomatic patients with ventricular ectopies and NSVT, and LV dysfunction	C
	Propafenone or sotalol to reduce adequate shocks in patients with ICD	C
III	Class I antiarrhythmic drugs for chagasic patients with any type of arrhythmia and LV dysfunction	C

Table 9 – Recommendations and levels of evidence for surgical ablation of SVT in patients with chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
I	Recurrent monomorphic SVT, refractory to drug treatment, in a FC I-II patient receiving multiple ICD shocks, with left apical aneurysm as a highly probable site of origin, associated with adhered old mural thrombus, which hinders access to endocardial ablation, and unsuccessful epicardial ablation	C
IIa	Recurrent monomorphic SVT, refractory to drug treatment, in a FC I-II patient with electrophysiological mapping showing aneurysm as the site of origin, after unsuccessful catheter ablation and availability of intraoperative electrophysiological mapping	C
IIb	Polymorphic SVT, refractory to drug treatment and catheter ablation in FC I-II patients receiving multiple ICD shocks, and availability of intraoperative electrophysiological mapping	C
III	First SVT episode	C
	Recurrent polymorphic SVT due to metabolic disorders or iatrogenic proarrhythmic effect	C
	Recurrent SVT without previous antiarrhythmic treatment	C
	Recurrent SVT, refractory to drug treatment, without electrophysiological mapping to determine the site of origin of tachycardia	C

7.4.2. Catheter ablation of SVT in CCC

The origin of SVT in CCC is usually topographically related to the endocardial, epicardial or intramyocardial segmentary scar. In addition, SVT can have multiple sites of origin, making the task of eliminating all circuits a challenge[201,207,213,229,230]. In general, the site of origin of well-tolerated recurring SVT can be identified and the SVT interrupted in 60%-80% of the patients, but rapid and poorly tolerated SVT are frequently induced in the final assessment of the procedure[201,213,227-229]. During long-term follow-up, at least 50% of the patients undergoing conventional ablation have clinical relapse, justifying the maintenance of antiarrhythmic drugs or ICD implantation[230]. Clinical results have been more consistent in patients with incessant SVT or receiving ICD shocks, undergoing simultaneous endocardial and epicardial mapping, with the help of electroanatomical mapping[207]. The procedure can bear high risk in the presence of clinically unfavorable conditions and severe ventricular dysfunction. Although rare, the major complications are as follows: ventricular dysfunction worsening, cardiogenic shock, electromechanical dissociation, cardiac tamponade, complete AVB, CVA, coronary artery occlusion and death (Table 10).

7.5. Bradyarrhythmia and pacemaker indication in CCC

Bradyarrhythmia in CCC can result from sinus node dysfunction or AVB. The disease causes damage to the entire cardiac excito-conduction tissue, which is mainly evidenced at the sinus node and His-Purkinje system, with inflammatory infiltrate, replacement of the normal tissue with fibrosis, and possiblly autonomic denervation caused by substances released from the interaction with live or dead parasites[231]. Intraventricular blocks are also frequent in CCC, especially right bundle-branch block associated with left anterior hemiblock[232]. Several observational studies have suggested that cardiac pacemakers are beneficial in CCC[233-235], which, in some Latin American regions, where CD is endemic, is the most frequent indication for pacemaker implantation. The indications for cardiac pacemakers in CCC are approached in the Brazilian Guidelines for Implantable Electronic Cardiac Devices[236] (Table 11).

7.6. Indications for CDI

The scientific evidence regarding indications for ICD in CCC is limited to publications of case series, retrospective

Table 10 – Recommendations and levels of evidence for catheter ablation of SVT of patients with chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
I	Incessant monomorphic SVT, after eliminating proarrhythmic effect of antiarrhythmic drugs	B
	Recurrent monomorphic SVT in patients with ICD receiving multiple shocks despite the use of antiarrhythmic drugs	B
IIa	Recurrent paroxysmal monomorphic SVT despite the use of antiarrhythmic drugs	C
	Well-tolerated monomorphic SVT, induced on EPS to clarify recurrent syncope	C
IIb	First episode of monomorphic SVT, in the absence of potentially controllable triggering factors	C
	Well-tolerated recurrent SVT without previous antiarrhythmic treatment	C
	Poorly tolerated monomorphic SVT, induced on EPS to clarify recurrent syncope	C
III	Polymorphic SVT due to metabolic disorders or iatrogenic proarrhythmic effect	C

Table 11 – Recommendations and levels of evidence for artificial cardiac stimulation in patients with chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
I	Irreversible sinus node dysfunction, spontaneous or induced by necessary or irreplaceable drugs, with documented manifestations of syncope, presyncope or dizziness, or of HF, related to bradycardia	C
	Sinus node dysfunction with effort intolerance clearly related to chronotropic incompetence	C
	Permanent or intermittent second-degree AVB, irreversible or caused by necessary or irreplaceable drugs, independently of type and location, with defined symptoms of low cerebral flow or HF consequent to bradycardia	C
	Permanent or intermittent and irreversible, although asymptomatic, Mobitz type II second-degree AVB, with enlarged QRS or infra-His block	C
	Flutter or AF with periods of low ventricular response in patients with defined symptoms of low cerebral flow or HF consequent to bradycardia	C
	Permanent or intermittent, although asymptomatic, third-degree AVB	C
	Documented alternating bilateral bundle-branch block with recurring syncope, presyncope or dizziness	C
IIa	Spontaneous sinus node dysfunction, irreversible or induced by necessary or irreplaceable drugs, with syncope, presyncope or dizziness or HF aggravation probably related to bradycardia (undocumented)	C
	Irreversible, although asymptomatic, Mobitz type II second-degree AVB	C
	Flutter or AF with mean HR < 40 bpm during wakefulness, irreversible or due to the use of necessary or irreplaceable drugs, although asymptomatic	C
	Spontaneous intraventricular block with HV interval > 70 ms or intra- or infra-His AVB induced by atrial stimulation or drug test in patients with syncope, presyncope or dizziness of undetermined cause	C
	Spontaneous intraventricular block with HV interval > 100 ms	C
	Bifascicular/alternating bundle-branch block, associated or not with first-degree AVB, with syncope episodes and no documentation of paroxysmal TAVB, in which other causes were ruled out	C
IIb	Sinus node dysfunction in oligosymptomatic patients with chronic HR < 40 bpm during wakefulness	C
	Permanent or intermittent and irreversible advanced AVB, although asymptomatic	C
	Permanent or intermittent and irreversible asymptomatic type 2:1 second-degree AVB, associated with ventricular arrhythmias that require treatment with irreplaceable depressants of AV conduction	C
	Asymptomatic bilateral bundle-branch block	C
III	Sinus node dysfunction, either asymptomatic or with symptoms unrelated to bradycardia	C
	Bifascicular bundle-branch block in asymptomatic patients, with or without first-degree AVB	C

cohorts or registries, involving only secondary prevention of cardiac SD[237-249]. So far, no large-scale randomized clinical trial, comparing the efficacy of ICD with active drug or placebo in CCC, has been published (Table 12).

There is no scientific evidence supporting the indication for ICD in primary prevention of cardiac SD, and, thus, there is currently no recommendation about it.

7.7. Cardiac resynchronization therapy (CRT)

Cardiac resynchronization therapy is the defined therapeutic alternative for advanced HF in patients with dilated cardiomyopathy and dyssynchrony of ventricular activation[244]. Cardiac resynchronization therapy is based on the concept that QRS prolongation can cause intra-and interventricular dyssynchrony, impairing ventricular systolic function[245,246]. The global results of clinical trials have shown that CRT causes a significant reduction in FC, improves the quality of life, and increases the distance covered in 6 minutes and peak VO_2; in addition, they have suggested a reduction in total mortality[247,248]. Those trials have mainly included patients with ischemic cardiopathy and idiopathic dilated cardiomyopathy. Although those results may be reproduced in CCC, there is no report of cohort, registry or randomized study including exclusively chagasic patients. It is worth noting that complete left bundle-branch block, the major electrocardiographic indication for that procedure, is rare in CCC[249].

Conversely, it is worth noting that the conventional pacemaker, frequently indicated in CCC, causes a morphology pattern of left bundle-branch block (delayed LV activation), mainly for leads positioned at the RV apical site[250] leading to There is evidence of significant hemodynamic impairment, mainly in the presence of preexisting ventricular dysfunction.

In clinical practice, despite the lack of consistent scientific evidence, the criteria for CRT indication in CCC are extrapolated from those used for ischemia and idiopathic dilated cardiomyopathy, whose results, despite restrictions, are well known[236,251,252] (Table 13).

8. Cardiac and cellular transplantation and other surgical therapies in CCC

Brazilian researchers have pioneered the performance and development of orthotopic CT to treat CCC[253-256]. Heterotopic CT is not usually indicated because chagasic patients have neither pulmonary hypertension nor hyper-resistance; in addition, it is associated with a higher number of complications[257]. Orthotopic CT can be used with bicaval

Table 12 – Recommendations and levels of evidence for the use of ICD in patients with chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
I	Patients resuscitated from sudden death, other causes for the event being ruled out	C
	Patients with documented syncopal ventricular tachycardia and LVEF < 35%	C
IIa	Patients resuscitated from sudden death with LVEF > 35%	C
	Patients with syncopal ventricular tachycardia and LVEF > 35%	C
	Patients with unexplained syncope due to other causes and unstable EPS-induced SVT	C
III	Incessant ventricular tachycardia	C

Table 13 – Recommendations and levels of evidence for the use of resynchronization therapy in patients with chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
IIb	Patients with EF ≤ 35%, sinus rhythm, FC III-IV HF, refractory to optimal drug treatment, and QRS > 150ms	C
	Patients dependent on ventricular pacemaker, with QRS > 150ms and EF ≤ 35%, FC III-IV HF, refractory to optimal drug treatment	C
	Patients with EF ≤ 35%, permanent AF, FC III HF, refractory to optimal drug treatment, and QRS > 150ms	C
	Patients with indication for pacemaker implantation (indispensable ventricular stimulation), EF ≤ 35% and FC III HF	C
III	Patients on non-optimal drug treatment for HF or with good response to that therapy	C

anastomosis and prophylactic tricuspid annuloplasty[258,259]. In Brazil, CCC chagasic cardiomyopathy is the third most common indication for CT[260,261].

8.1. Etiopathogenic and pathophysiological peculiarities to consider for CT in patients with CCC

Regular tests have shown that parasitemia can be persistent in chronic chagasic patients[262]. Several techniques have shown parasite DNA or antigens in myocardial inflammation foci[263-265]. *T. cruzi* can induce changes in the host's immune system, such as no interleukin receptor (IL)-2 expression and lower expression of CD3+, CD4+ and CD8+ surface molecules of lymphocytes[265]. Local production of IL-7 and IL-15 can be associated with CD8+ cells[264]. *T. cruzi* coinfections, by such as archaea, have been recently suggested, and they have potential repercussion after transplantation, because of the immunosuppression induced[266].

8.1.1. Indication and contraindication (Tables 14 and 15)

Although the criteria defined for other etiologies apply, the indications for CT in CCC have peculiarities[81]. Patients with CCC usually tend to have lower pulmonary vascular resistance, pulmonary artery pressures and transpulmonary gradient, minimizing the chance of RV dysfunction, frequent after CT[267]. Thus, some centers of CT have not even performed invasive tests in patients with pulmonary artery systolic pressure indirectly estimated by use of Doppler ECHO below 50 mm Hg. When invasive tests are indicated, the pulmonary reactivity test should be performed with vasodilators, such as sodium nitroprusside, nitric oxide, prostaglandins, phosphodiesterase-5 inhibitors, if pulmonary artery systolic pressure ≥ 50 mm Hg, if transpulmonary gradient ≥ 15 mm Hg or if pulmonary vascular resistance > 3 Wood units[268]. Nitric oxide bears the risk of acute pulmonary edema[269,270]. Determining BNP level may be useful in that population[66].

Table 14 – Recommendations and levels of evidence for the indications of cardiac transplantation in chronic chagasic cardiopathy

Recommendation	Indications	Level of evidence
I	Refractory HF, depending on inotropic drugs and/or circulatory support and/or mechanical ventilation	C
	VO_2 peak ≤ 10 mL/kg/min	C
	Ventricular fibrillation or refractory sustained ventricular tachycardia	C
	Persistent FC III/IV HF with optimal therapy	C
IIa	Use of BB with VO_2 peak ≤ 12 mL/kg/min	C
	No BB use with VO_2 peak ≤ 14 mL/kg/min	C
	Cardiopulmonary test with LV/VCO_2 > 35 and VO_2 peak ≤ 14 mL/kg/min	C
IIb	FC IV HF without optimal therapy	C
III	FC III HF without optimal therapy	C

Table 15 – Contraindications to isolated cardiac transplantation in chronic chagasic cardiopathy

Absolute	Fixed pulmonary vascular resistance > 5 Wood units, even after pharmacological tests
	Megacolon or megaesophagus of a severity that jeopardizes the result of transplantation
	Advanced liver failure, severe pulmonary disease
	ABO incompatibility in prospective cross-match tests between recipient and donor
	Severe psychiatric disease, chemical dependence and non-adherence to medical recommendations
Relative	Unfavorable psychological conditions on follow-up
	Comorbidities impairing long-term life expectancy
	Morbid obesity
	Active systemic infection
	Active peptic ulcer
	Pulmonary embolism for less than 3 weeks
	Neoplasm with approval of the oncologist
	Diabetes mellitus of difficult control
	Renal failure with creatinine clearance below 30 mL/min/1.73 m^2
	Unfavorable social conditions
	Lymphocyte panel > 10%

Usually patients with CD have a less favorable social and cultural status, the indication for CT constituting an additional challenge for them. However, no relationship between socioeconomic level and outcome after CT has been reported[271]. Nevertheless, special attention should be given to the identification and improvement of social conditions, acceptability, access to the transplantation center, adherence to recommendations, educational level and family dynamics.

Considering the worse prognosis of CCC as compared to other HF etiologies, the use of inotropes/vasopressors and mechanical assistance devices (intraaortic balloon, ventricular assistance, mechanical ventilation) should be valued in that etiology. In addition, ascitis and RV dysfunction can be associated with liver dysfunction and higher risk of bleeding (Table 14).

In CCC, the contraindications to CT should be assessed individually, because the patients are usually younger and have a low rate of co-morbidities[272] (Table 15). It is worth noting the possibility of megaesophagus and megacolon, which, according to their severity, can contraindicate CT.

8.1.2. Organ acceptance criteria

The diagnosis of CD is important for organ donation because of its high prevalence in Latin America and developed countries due to immigration[16,21]. As a rule, *T. cruzi*-infected individuals should not donate organs, because disease transmission and death have been reported in cases of chagasic donors to non-chagasic recipients[273,274]. In selected situations and emphasizing the marginal recipient in countries with no regulation, donors with positive serology for CD and no heart impairment could be considered for recipients with CCC. In a case report, a recipient of a donor with positive serology for CD underwent prophylaxis with benznidazole and there was no manifestation of CD[275]. However, chagasic myocarditis has been reported in recipients of organs from donors with negative serology for CD[276].

8.1.3. Immunosuppression

Several regimens combining immunosuppressive drugs, with or without graft tolerance induction, have been used for CT in CCC, with a good outcome[277-279]. Of the drugs that can be used to prevent rejection, the following stand out: corticosteroids, cyclosporine, tacrolimus, azathioprine, mycophenolate, rapamycin and everolimus. In maintenance immunosuppression, the most used regimen is the association of cyclosporine and azathioprine, and corticosteroid withdrawal as soon as possible. There are studies comparing the various immunosuppression regimens; however, more reactivations have been diagnosed with the use of mycophenolate mofetil[280]. Experience with the use of tacrolimus, rapamycin, methotrexate and everolimus has not been published, despite their potential benefit[281]. The following can be used to induce tolerance or to treat a rejection episode: corticosteroids; cyclophosphamide; methotrexate[282,283]; interleukin-2 receptor antagonists; polyclonal antibodies; monoclonal antibodies; and apheresis. The use of drugs for induction is controversial and reserved for selected cases and centers[284].

The preponderant concept is that, having the *T. cruzi* infection, a chagasic patient should receive the lowest intensity of immunosuppression possible, provided there is no rejection (Figure 5).

8.1.4. *T. cruzi*-infection monitoring before and after CT (Table 16)

Monitoring *T. cruzi*-infection reactivation, before and after CT, by use of clinical, laboratory or histological findings, is fundamental, because of its inherent risk, including infection transmission[285-287].

8.1.5. Follow-up chronology of seropositive recipients after CT

Monitoring of *T. cruzi*-infection reactivation after CT should be performed routinely and during suspected reactivation episodes. However, there is no scientific data defining exactly when that should be routinely done. Some centers perform it during the same period of biopsies, but others recommend it weekly up to two months after CT, then, fortnightly up to the sixth month, and, finally, monthly until the end of the first year of CT.

8.1.6. Methods to assess *T. cruzi*-infection reactivation (Tables 16 and 17)

Serological tests are useful only for seronegative patients receiving organs from seropositive donors. Hematoxylin-eosin and giemsa staining, in addition to specific agent screening, should be used in the histological analysis of endomyocardial and other tissue biopsies. Patients suspected of clinical reactivation based on symptoms should undergo the following exams: skin biopsy, in the presence of skin lesions; endomyocardial biopsy, if myocarditis is suspected; cerebrospinal fluid analysis, in the presence of neurological manifestations; and myelogram or bone marrow biopsy, if bone marrow involvement is suspected. Polymerase chain reaction has been tested to assess *T. cruzi* infection with promising preliminary results[288-290].

8.1.7. Methods to detect *T. cruzi* in tissues (Table 17)

The histological diagnosis is made in the presence of *T. cruzi* amastigote nests or antigens. The major differential diagnosis is with toxoplasmosis; therefore, immunohistochemistry is fundamental, and can reveal parasite antigens even in the absence of the characteristic nests. Nodules of disease reactivation usually present as panniculitis foci in the subcutaneous tissue, with accumulation of lymphocytes and histiocytes, and intense proliferation of *T. cruzi* amastigotes inside macrophages and endothelial cells[291,292].

8.1.8. Differential diagnosis between rejection and *T. cruzi* myocarditis after CT (Table 18)

Differentiating between acute cellular rejection and chagasic myocarditis is particularly difficult, because those processes have histopathological similarities represented by

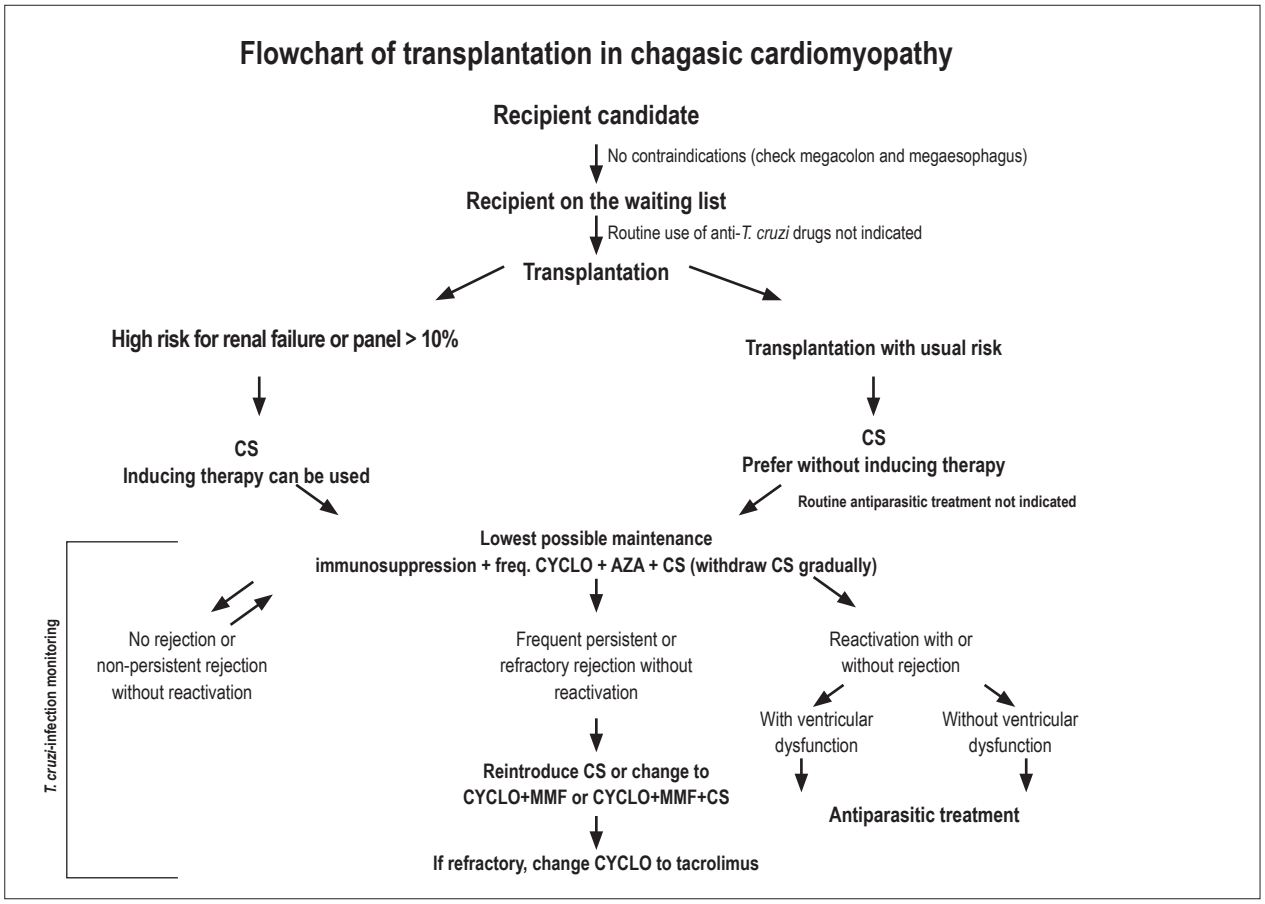

Figure 5 – *Flowchart for immunosuppression in patients with chronic chagasic cardiopathy undergoing cardiac transplantation. CYCLO - cyclosporine; AZA - azathioprine; CS - corticosteroids; MMF - mycophenolate mofetil or mycophenolate sodium.*

Table 16 – Recommendations and levels of evidence for monitoring indication for cardiac transplantation in chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
I	Serological tests for Chagas disease in donors	C
	Serological tests in the potential recipient with a possibility of chagasic cardiomyopathy	C
	Routine *T. cruzi* screening via endomyocardial biopsy after transplantation	C
	Routine *T. cruzi* screening (blood smear, xenodiagnosis, blood culture) after cardiac transplantation for the diagnosis of infection reactivation	C
	T. cruzi screening on tissues (myocardium, skin, bone marrow) in situations compatible with *T. cruzi* infection reactivation	C
	T. cruzi screening (blood smear, xenodiagnosis, blood culture) after cardiac transplantation following treatment for *T. cruzi* infection reactivation	C
IIb	Routine serological tests for the diagnosis of *T. cruzi* infection reactivation	C
	Serological tests after treatment for *T. cruzi* infection reactivation	C
	T. cruzi screening on tissues after treatment for *T. cruzi* infection reactivation	C

Table 17 – Recommendations and levels of evidence for the indication of procedures for parasitological diagnosis of *T. cruzi*-infection reactivation after cardiac transplantation

Recommendation class	Indications	Level of evidence
I	*T. cruzi* screening on circulating blood or bone marrow	C
	T. cruzi screening via endomyocardial biopsy	C
	T. cruzi screening via skin or other organ lesion biopsy	C
IIb	*T. cruzi* screening via PCR	C

Table 18 – Recommendations and levels of evidence for the differential diagnosis between rejection and *T. cruzi* myocarditis

Recommendation class	Indications	Level of evidence
I	Immunohistochemical analysis for *T. cruzi* on endomyocardial biopsy	C
IIa	Analysis by use of PCR	C
III	Analysis by use of *in-situ* hybridization	C
	Analysis by use of conventional histopathology	C

foci of lymphocytes attacking non-parasitized cardiac fibers, although they differ regarding some characteristics of the infiltrate[292-294]. Parasitic nests should be routinely sought in histological sequential sections, and immunohistochemistry against *T. cruzi* antigens should be performed. Polymerase chain reaction has been used for that purpose, but the sensitivity and relationship with reactivation are yet to be confirmed[288,295].

8.2. Results of CT in CCC treatment

A registry of patients undergoing CT has suggested that the prognosis of chagasic recipients is better than that of non-chagasic recipients. The survival probability of those patients is 76%, 62% and 46% in one year, two years and six years after the cardiac procedure, respectively[296]. Other centers have reported survival similar to that of non-chagasic individuals. That might be due to the following factors: younger patients with less co-morbidities; less severe rejections; low incidence of graft vascular disease; lower prevalence of pulmonary hyper-resistance; and no previous surgery[296]. Reactivation of CD and neoplasms have already been important problems, but that has been overcome with higher experience and with the use of low doses of immunosuppressive drugs or of alternative immunosuppressive regimens[119].

Currently, infection is the major cause of death (21%) of chagasic recipients of CT in the mid- and long-term[297]. Rejection is the second cause of death, affecting 10%-14% of chagasic recipients[260,297]. Surprisingly, in a limited experience[38], chronic pericarditis was the cause of death of 14% of the patients. Currently, graft coronary artery disease and neoplasms are not frequent causes of death.

8.3. Complications

8.3.1. Immediate postoperative period

In the perioperative period, the clinical outcome, as well as morbidity and mortality, of chagasic patients receiving CT is similar to that of non-chagasic patients. This might be related to the fact that, in the perioperative period, the complications are related to the conditions of the donor, the cardiac procedure and general conditions of the recipient, rather than to the etiology of the recipient terminal chronic HF.

The major complications observed in those patients during that period are as follows: graft dysfunction (20%); grade 3A rejection or more intense (10%-20%); acute renal failure; bleeding (10%), mainly in patients using an artificial ventricle; and bacterial infection (20%-30%)[269]. Infection and rejection are the most frequent complications, affecting up to 30% and 20% of the patients, respectively[270]. It is worth noting that clinical reactivation of CD, frequently found in chagasic patients receiving CT, is exceptional in the immediate postoperative period. The major causes of early death are acute graft failure (right or left HF) and infection, mainly those located in the respiratory tree[293]. The RV dysfunction usually normalizes afterwards[298].

8.3.2. *T. cruzi*-infection reactivation

8.3.2.1. Clinical presentation

The frequency of *T. cruzi*-infection reactivation in cardiac transplanted patients ranges from 0% to 50%, being a rare cause of death[260,279,289,294,296, 297,299-301]. It manifests as fever,

skin lesion, bone marrow impairment, myocarditis, and neurological symptoms and signs. The parasite is frequently detected on direct smear inspection, xenodiagnosis or blood culture, in addition to serological tests[302,303]. The most frequent presentation form is myocarditis, which can be asymptomatic, but can manifest as HF or even cardiogenic shock[293]. Patients can have several reactivation episodes during follow-up, with different manifestations, even if the initial episode was treated or the patient received preventive treatment. So far, CCC in the recipient has not been reported[277].

8.3.2.2. Reactivation diagnosis

Infection reactivation is confirmed when, in addition to symptoms and signs of infection, the parasite is detected in the blood, cerebrospinal fluid, or tissue samples. However, infection reactivation is also considered in asymptomatic individuals, in whose tissues or blood the parasite is persistently detected. The following factors are associated with *T. cruzi*-infection reactivation: number of rejection episodes; neoplasms; and immunosuppression grade (use of mycophenolate)[304,305]. The decrease in immunosuppression reduces the chance of reactivation. It is still controversial whether the *T. cruzi* characteristics would have a preponderant role in infection reactivation[306].

8.3.2.3. Routine etiological treatment before (waiting list) or after transplantation (Table 19)

During the treatment of a rejection episode, the dose of immunosuppressive drugs increases, consequently increasing the risk of *T. cruzi*-infection reactivation. Although the prophylactic use of anti-*T. cruzi* drugs might be simple, no study has shown their efficacy in this context. Thus, follow-up and strict monitoring of the reactivation possibility is the ideal management (Table 12). Treatment with benznidazole has been indicated as carcinogenic in an experimental model, but that has not been confirmed in human beings[307].

8.3.2.4. Drugs used in the treatment (Table 19)

The therapeutic regimen was reported in the chapter about etiological treatment. Benznidazole is the preferred drug, nifurtimox being the second option, including for parasite strains resistant to the former[308,309]. Although experience with a small number of patients has reported the effectiveness of allopurinol, that treatment is not recommended[310-312].

8.3.3. Infection

Infections are the most important mid- and long-term morbidities of chagasic patients undergoing CT, affecting approximately 30% of the patients in the first year, and 50% of them after two years[293,298,303]. Infections can occur in the surgical site or other organs[313-315]. However, the current incidence of infection in chagasic recipients seems to be lower than that observed in the past[294], and also lower as compared with that of non-chagasic individuals[303]. Infection is the cause of death in 10%-21% of chagasic recipients of CT[297].

8.3.4. Rejection

Humoral rejection, although theoretically possible, has not been reported in chagasic patients undergoing CT[315]. However, cellular rejection is frequently found in those patients – approximately 70% of them have that complication in the first year after CT[305]. The great problem of finding an inflammatory mononuclear infiltrate in the myocardial biopsy is that it can actually be due to CD reactivation, because the parasite is not always seen with the routine staining techniques, and the inflammatory infiltrate of CD reactivation is similar to that observed in grade 3A or 3B rejection. Actually, up to 43% of the patients can have myocardial inflammation consistent with the diagnosis of 3A rejection or more severe, which does not respond to pulse corticosteroid therapy, but subsides with the specific treatment for CD[316]. Cellular rejection usually responds

Table 19 – Recommendations and levels of evidence for infection or reactivation prevention, and treatment of *T. cruzi*-infection reactivation

Recommendation class	Indications	Level of evidence
	Prevention before and during cardiac transplantation	
I	Prophylactic treatment of a non-chagasic recipient, when an accidental donor has positive serology for Chagas disease	C
IIb	Prophylactic treatment of a chagasic recipient in the waiting list for CT to prevent post-transplant reactivation	C
	Prevention after cardiac transplantation without rejection	
IIb	Prophylactic use in a chagasic recipient of anti-*T. cruzi* medication post-transplantation to prevent *T. cruzi*-infection reactivation	C
	Prevention after cardiac transplantation with rejection	
IIa	Prophylactic use of anti-*T. cruzi* medication during treatment of a rejection episode, when doubt about the likelihood of *T. cruzi*-infection reactivation still persists	C
III	Prophylactic use of anti-*T. cruzi* medication during treatment of a rejection episode	C
	Prophylactic use of anti-*T. cruzi* medication during long-term treatment of patients with persistent rejection or frequent rejection episodes	
	Treatment	
I	Treatment of the episode of *T. cruzi*-infection reactivation with benznidazole or nifurtimox	B

properly to pulse corticosteroid therapy. Exceptionally, rescue therapy can be required to overcome rejection. Invasive and noninvasive methods are used to detect rejection[317,318].

8.3.5. Neoplasms

At the beginning, chagasic recipients of CT had shown an apparent increase in the incidence of neoplasms[275,319]. A recent re-analysis has shown that such higher incidence of neoplasms was more likely related to the use of a more elevated dose of cyclosporine[296]. Currently, with the use of lower doses of immunosuppressive agents, the incidence of neoplasms in chagasic recipients of CT is extremely low, accounting for the death of 2% of those patients[296].

8.3.6. Graft coronary artery disease

The incidence of graft coronary artery disease in chagasic recipients of CT is little known. However, it seems to be low, less than 10% of the patients undergoing CT[280,297,320]. For the purpose of diagnosis and prevention, the same methods used for other etiologies are recommended[321-324].

8.4. Cellular transplantation and other special therapies

8.4.1. Experimental results of cellular transplantation

Bone marrow cells have been obtained from healthy mice and intravenously injected in mice in the chronic phase of chagasic infection. A significant reduction in myocarditis has been observed two months after transplantation as compared with controls[325]. A study with nuclear magnetic resonance imaging has shown, in mice treated with bone marrow mononuclear cells, a regression in RV dilation[326]. The potential mechanisms of those beneficial effects include: a reduction in apoptosis, in fibrosis, and in the inflammatory process; stimulation of local resident cells and transplanted cells that acquired the morphology of cardiomyocytes and myosin expression, indicating possible differentiation of transplanted cells into that cell type or fusion with cardiomyocytes of the recipient animal[327,328].

8.4.2. Clinical results

Phase I-II studies have reported favorable initial results of the treatment with stem cells in CCC[69,329-332]. However, the results of an unpublished phase II-III randomized study have shown no benefit, even when assessing only surrogate endpoints and not clinically relevant events[333]. Nevertheless, the research with stem cells is still considered to be promising. It is worth noting that the following remain to should be determined: the best cell type; doses to be used; time and form of application; and the adequate patient. In addition, it is worth noting the potential of mesenchymal cells, and the use of cellular hormones capable of recruiting, inducing proliferation and differentiation of stem cells, such as G-CSF[328,329], which seems to significantly reduce both inflammation and fibrosis in the heart of chronic chagasic mice[334].

8.4.3. Others and new novel surgical therapies in the treatment of HF due to CD

Because of the limitations in the number of donors[335] and contraindications to CT, several other procedures have already been or are currently tested for the treatment of CCC[336]. Of those procedures, the following stand out: cardiomyoplasty[337-342]; isolated mitral valve surgery to repair mitral regurgitation with reconstruction or prosthesis[343-345], or associated with other procedures[345,346]; and reduction ventriculectomy (Randas procedure)[347-354]. **In addition to** Despite the small number of patients included, from the clinical viewpoint, none of those procedures proved to be effective in the long run, although some hemodynamic or functional class benefits have been observed[274,275]. Those surgical procedures were aimed at repairing the remodeling or its consequences, such as mitral regurgitation and excessive ventricular diameter enlargement[355-360]. Thus, no surgical procedure other than CT is indicated for the treatment of CCC, except for the use of temporary mechanical support.

Mechanical circulatory support, such as bridge to transplant, bridge to bridge, or bridge to recovery, has a high potential for future use in CCC, as in other etiologies and observing the same criteria of indication[361]. The first mechanical circulatory support as bridge to transplant for CCC was performed in 1994, and the patient remains well up to the present time[361]. However, the major limitation to its applicability is its high cost.

9. Special subgroups in Chagas disease: coinfection (HIV); immunosuppressive therapy and non-cardiac transplantation; pregnant women; newborns; children and adolescents; seropositive individuals and blood banks

9.1. HIV coinfection

T. cruzi/HIV coinfection is important because of the risk of trypanosomiasis reactivation in patients with chronic CD in the presence of immunosuppression caused by HIV, particularly in patients with CD4+ T lymphocyte count < 200 cells/mm^3 [362-367]. In addition, high frequency of congenital *T. cruzi* transmission with severe meningoencephalitis and/or myocarditis was observed, as was high mortality in offsprings of coinfected mothers[364,368].

Conversely, CD can negatively interfere with HIV outcome, because it activates the immune system[5], which favors HIV replication, and can lead to faster disease progression. Transient increase in HIV viral load concomitantly with CD reactivation has been reported[369].

The prevalence of CD/HIV coinfection is not well known. In an outpatient clinic specialized in the treatment of HIV/AIDS infection in São Paulo, an investigation on trypanosomiasis has been conducted in 52.8% of the patients assessed, coinfection being diagnosed in 2.3% of them[370]. In a health care service in Buenos Aires, serological tests for CD have been performed in 51.3% of the HIV+ patients, coinfection being identified in 4.2% of them[371].

The diagnosis of *T. cruzi*/HIV coinfection is based on serological tests. Serological tests for CD should be indicated for all HIV+ patients coming from an endemic area or exposed to the risk of *T. cruzi* infection (blood transfusions, mother with CD)[363,369].

The follow-up of coinfected patients should be performed preferentially at reference centers[363]. In addition to the diagnosis and treatment of the various manifestations associated with HIV infection and chronic CD, the initial assessment and follow-up of those patients are aimed at the early detection of reactivation.

The frequency of trypanosomiasis reactivation in HIV coinfected patients is not well known. In a prospective study with long-term follow-up, approximately 20% of coinfected patients had reactivation[364]. In addition to reduced levels of CD4+ T lymphocytes (< 200 cells/mm^3), high parasitemia (observed with quantitative methods) has been identified as a predictive factor of reactivation (50% of the cases).

The most common clinical manifestation of reactivation is meningoencephalitis[363-365,367,369]. Myocarditis has been reported in 30%-40% of the cases[363-365,372]. Other manifestations, such as pericarditis, peritonitis, erythema nodosum and colpitis, have been occasionally described. Oligosymptomatic and asymptomatic forms can also occur[364].

Chagas disease reactivation in HIV+ patients has high lethality[363,364,367], which can reach 100% in untreated patients or those treated late. Early treatment is associated with better prognosis and a 20% reduction in lethality for patients completing 30 days of specific treatment.

Preemptive etiological treatment of *T. cruzi* infection can be considered for HIV+ patients with high parasitemia detected on semiquantitative xenodiagnosis or quantitative PCR[363,364].

Secondary prophylaxis with benznidazole (5 mg/kg/day, 3x/week) has been used, mainly for patients with CD4+ T lymphocytes < 200 cells/mm^3, similarly to other opportunistic diseases[363,369,373], but it still requires validation in prospective studies.

In parallel with the treatment of trypanosomiasis, antiretroviral treatment should be maintained or initiated as early as possible.

Specific treatment should be monitored with clinical and laboratory assessment, which includes hemogram, liver enzymes, urea, creatinine, electrolytes and parasitemia control (direct parasitological tests twice a week to control the therapeutic response, until they become negative). In addition, after treatment suspension, periodical parasitological tests should be performed because therapeutic effectiveness has not been well established in those patients[363] (Table 20).

9.2. Noncardiac transplantation and immunosuppressive therapy

The following three mechanisms can account for CD in recipients of solid organs and bone marrow[374,375]:

- Transmission via contaminated blood derivatives given to a recipient negative for CD. This pathway is easily controlled in endemic countries, where serology for CD in blood derivatives is mandatory;
- Acquisition of *de novo* infection via infected grafts, which would also be easily controlled in endemic regions, where serology for CD is mandatory in the donation process;
- Reactivation of latent disease in a previously infected recipient, with acute invasion of the disease-free graft via dissemination of the parasitemia associated with immunosuppression.

The CD reactivation rate has been reported to range from 9% to 16% with renal transplantation[58] and from 17% to 40% with bone marrow transplantation[376], being more common in the first year, when immunosuppression is more intense. In general, the response to treatment is good, but there are reports of graft dysfunction and loss or even death, regardless of the appropriate use of benznidazole[377].

When infected renal grafts are given to used for negative recipients, the estimated transmission rate is 35%[378]; however, cases originating from infected renal or liver grafts are usually reported as mild, some with undetected parasitemia and excellent response to trypanocidal therapy[378,379]. It is worth noting that CD in a potential recipient is no contraindication to any type of transplantation, because, as already mentioned, the specific treatment can rapidly suppress the clinical manifestations of reactivation.

Cases of CD reactivation clinically manifested as meningoencephalitis and/or myocarditis and skin lesions have also been reported in immunosuppressed patients with hematological malignancy (leukemia and lymphoma). In such cases, the parasite is easily found in peripheral blood, and mortality can be high, mainly when the diagnosis is established late. Treatment with nifurtimox or benznidazole can lead to remission and significantly reduce mortality[380].

Corticotherapy, frequently used chronically in patients with autoimmune diseases, is associated with an increase in parasitemia, but its role in the clinical reactivation of the disease has not been entirely proved. The cases reported involve cell immunity impairment by the underlying disease or by the concomitant use of other immunosuppressive drugs. Thus, the prophylaxis with trypanocidal drugs in chagasic patients on chronic corticosteroids is still controversial,

Table 20 – Recommendations and levels of evidence for the diagnosis and trypanocidal treatment of *T. cruzi*/HIV coinfection

Recommendation class	Indications	Level of evidence
I	The HIV+ patient with Chagas disease reactivation should be hospitalized and treated specifically with benznidazole or nifurtimox	C
	Preemptive treatment for HIV+ patients with high parasitemia detected on semiquantitative xenodiagnosis or quantitative PCR	C
IIa	Secondary prophylaxis with benznidazole or nifurtimox for patients with CD4+T lymphocytes < 200 cells/mm^3	C

with some authors reporting possible benefits of primary prophylaxis[380], while others point to the lack of controlled clinical trials and the risk for side effects of that medication[381].

9.3. Pregnant women

CCC is the second most common cardiopathy of the pregnancy/puerperium period, rheumatic cardiopathy being the first. A study carried out in the state of Minas Gerais in 2009 identified a 0.5% prevalence of CD in puerperal women, the most elevated rates being observed in the Northern region of the state, ranging from 2.3% to 23%[382].

The risk of vertical transmission is substantially higher in the acute phase (62%) than in the chronic phase (1.6%)[383]. The vertical transmission mechanisms are not entirely known. The production of immunoregulatory cytokines and parasite load seem to play a relevant role in the context[384]. Chagasic mothers not transmitting their infection to the fetus have no higher frequency of abortion, prematurity or perinatal mortality; however, those transmitting their infection have higher natimortality. Successive pregnancies seem to increase the risk for transmission[385].

The impact of CD on the course of a pregnancy is controversial. Some studies have pointed to the benignity of the association[386], while others have reported higher incidence of gestational complications, perinatal mortality, and neonatal hypotrophy, considering chagasic pregnant women at high obstetric risk[387].

The prognosis of pregnant women with chagasic cardiopathy is closely related to the severity of ventricular dysfunction and FC at the beginning of gestation. Those beginning pregnancy in FC I and II usually have an uneventful pregnancy. Conversely, those beginning pregnancy in FC III or IV have a 25% to 50% likelihood of maternal death[388].

The presence of cardiopathy, when as long as followed up and not severe, does not contraindicate pregnancy, but patients should be closely followed. In such situation, CCC does not limit the number of gestations, does not predispose to prematurity, does not accelerate the birth date and does not significantly affect the newborn weight. Patients with high FC and/or severe arrhythmias should be discouraged from becoming pregnant. Because of the likelihood of aggravation during gestation, pregnant women under those conditions require special follow-up and care.

The etiological treatment with trypanocidal drugs should not be instituted in pregnant women or those at childbearing age who are not on contraceptives. Cardioactive drugs should only be used in chagasic pregnant women in accordance with absolute medical indication, because of their potential effects on the fetus (Table 21).

Table 21 – Recommendations and levels of evidence for the management of pregnant women with chronic chagasic cardiopathy

Recommendation class	Indications	Level of evidence
I	Serology for Chagas disease should be included in the prenatal care program of pregnant women living in or originating from endemic areas	C
IIa	Patients with severe arrhythmias and/or FC III-IV HF should be discouraged from getting pregnant due to the high risk of maternal death	C
III	Etiological treatment with trypanocidal drugs should not be instituted in pregnant women or those at childbearing age not on contraceptive drugs	C

9.4. Newborns

In the current stage of vectorial and transfusional control, vertical transmission has become an important mode of CD transmission in Brazil and other Southern Cone countries[81,389]. The *T. cruzi* vertical transmission rate has regional differences, ranging from 1% in Brazil to 4%-12% in other Southern Cone countries, and seems to depend on parasite- and host-related factors. The high likelihood of cure of congenital CD makes its early diagnosis imperative.

Studies carried out in Brazil, Argentina, Chile and Paraguay have shown that 60%-90% of the newborns with congenital infection are asymptomatic. In symptomatic newborns, the most frequent clinical findings are prematurity, low weight, fever and hepatosplenomegaly[390].

In the first weeks of life, the diagnosis of congenital infection is based on finding *T. cruzi* by using the direct parasitological test, which should be performed in children with clinical manifestations suggestive of congenital infection. The micro-hematocrit technique is easy to perform and has good sensitivity, especially in the first month of life. If the result is positive, etiological treatment should be initiated immediately. Congenital CD is considered acute, its notification being, thus, mandatory.

If the result is negative, diagnostic investigation should be completed with serological tests (with two distinct techniques) after the seventh month of life. Serological study before the sixth month is not useful because of the passive passage of maternal antibodies. Between the sixth and ninth months, such antibodies disappear, and the diagnosis of congenital CD can be made. Seropositivity implies initiating specific treatment. Negative serology after that period permits allows excluding the diagnosis of chagasic infection.

The use of PCR for the diagnosis of chagasic infection is a recent advance[391], but, some centers have had problems with specificity, thus it should not be used in clinical practice.

Chagasic infection treatment in newborns can be performed with benznidazole or nifurtimox for 30 to 60 days, with similar results and high cure rates[392].

After the end of treatment, serological control should be performed every six months, until two consecutive negative results are obtained. If the treatment of the newborn is initiated with positive micro-hematocrit, this parasitological test should be repeated 15 days after initiating the medication[389].

The current criterion for cure is a persistent negative serology after the treatment. The time required for that depends on the age the treatment is initiated. Infants diagnosed in the first months of life will have a negative serology between the second and twelfth months, after initiating treatment. Polymerase chain reaction, which has been proposed as a marker of therapeutic response, still awaits higher standardization to be used in clinical practice (Table 22).

9.5. Seropositive individuals and blood banks

Routine CD screening in blood banks is part of a preventive strategy for *T. cruzi* transmission established by Southern Cone countries in the 1990s, and should be performed in all candidates for donation in endemic countries[283].

In non-endemic countries, two strategies have been used to prevent transmission via blood transfusion: routine exclusion of donors with a positive epidemiological history or acceptance of donation after a negative serological test. The second strategy has been introduced in countries with a huge population of Latin American emigrants, such as the United States of America, Spain and France.

Several tests using the ELISA technique are considered sensitive enough to be recommended as a single tool to screen CD in blood donors[393]. The practical technique to screen CD in blood banks will have to abide by local legislations. Reacting or positive results of the tests performed in blood banks should be considered as only preliminary screening, that is, a non-definitive result, and further confirmatory diagnostic investigation being thus performed indicated at reference centers.

10. Recommendations for constituting structured follow-up services for patients with CCC

Considering the importance of the impact of social, economic and cultural factors involved in the CCC genesis and progression, its approach requires the adoption of a health care model that transcends the purely biological aspect, offering integral care to the patient, and considering a set of biological, psychological and social determinants. That initiative requires the creation of a multiprofessional team, technically well prepared and in tune with the caring ideology.

Considering those peculiarities, the experience has shown that the health system has been challenged, because there are innumerous gaps in patients' management, regarding follow-up at clinics with no appropriate structure. An appropriate structure implies an outpatient clinic linked to a hospital, preferentially a teaching hospital, with availability of invasive and non-invasive diagnostic methods, clinical and surgical treatment, and high complexity beds. Such service is aimed at improving adherence to treatment, reducing morbidity and mortality, and at having a positive impact on the patients' quality of life[394].

10.1. Attributions of a structured service

1 To make the etiological diagnosis by use of clinical and epidemiological data and serological tests (two tests of different methodologies);

2. To stage the cardiac impairment, that will determine the periodicity of follow-up;

3 To establish the therapeutic plan (based on etiology and symptoms) and prognosis according to the stage of cardiac impairment;

4 To monitor the patient systematically;

5 To identify associated digestive impairment, when present, and to instruct the patient or refer him/her the patient to a reference center in gastroenterology;

6 To treat the comorbidities identified or refer the patient for interconsultation at a specialized service;

7. To stimulate adherence to pharmacological and non-pharmacological treatment optimizing the cost/effectiveness ratio;

8. To educate the patient, family members and caregivers about the disease and self-control, aiming at the early identification of signs and symptoms of cardiac decompensation;

9. To explain the impossibility of donating blood, organs and tissues;

10. To provide nutritional guidance;

11. To provide psychological support to the patient and family, aiming at reducing the stigma, the self-bias, taboo and improper beliefs related to the disease;

12. To instruct about medical, labor and insurance aspects, gestation, family planning, physical exercise and sexual activity;

13. To inform the patient and family when pacemaker or ICD implantation or CT is required;

14. To instruct about the prevention of aggravating factors (alcohol, smoking, legal and illegal drugs);

15. To provide care to patients under special conditions (e.g. those with pacemakers or ICD);

16. To enable and recycle health professionals focusing on the peculiarities of CCC patients, stimulating learning and research;

17. To identify other family members contaminated with *T. cruzi*, and to include them in the program for therapeutic management;

18. To stimulate and support the creation of associations of patients with CD, aiming at the best integration of participants (patients and families), establishing a communication channel with the scientific community and a policy of respect to their claims[394].

Table 22 – Recommendations and levels of evidence for the diagnosis and treatment of newborns suspected of having Chagas disease

Recommendation class	Indications	Level of evidence
I	In the first weeks of life, the diagnosis of congenital infection is based on *T. cruzi* screening via direct parasitological test	C
	After the seventh month of life, the diagnosis of Chagas disease can be established via serological test (2 different techniques)	C
	In the presence of positivity (parasitological test or serology), use specific treatment with benznidazole or nifurtimox	C
	After treatment, perform serological control every 6 months up to 2 consecutive negative results. If the newborn treatment is initiated with positive micro-hematocrit, that parasitological test should be repeated after 15 days of medication	C

10.2. Multiprofessional team

A multidisciplinary team is currently recognized as the best way system to care for patients with chronic diseases[81,395-397]. When creating a service destined and devoted to patients with CD, it is important to consider their peculiarities, and to understand them within a biopsychosocial context[398-400]. In that approach, all each members of the team play a defined role, and should know their limits, possibilities and responsibilities, understanding that it is fundamental that all interact with each other. Each member observes one aspect of the same individual. The team needs to have basic knowledge on CCC, and the routine of its management, so that all speak the same language, avoiding distorted or even iatrogenic information. Considering that multiple knowledge areas need to interact, the great challenge is to maintain a cooperative environment, avoiding predatory competition.

The structured service should ideally count on the following professionals: general physician, cardiologist, nurse, psychologist, nutritionist and social worker. It can be extended according to the adoption of new therapies, with the participation of a physical educator, physical therapist, pharmacist and occupational therapist. The size of the team should be adjusted to the reality and possibilities of each service, patients' demand, and mainly to its purpose[394,401].

10.3. Identification of comorbidities and creation of reference and counter-reference mechanisms

As the population with CCC ages and the management of the cardiopathy becomes more demanding appropriate, the prevalence of comorbidities increases and their identification is required, mainly of those that increase the cardiovascular risk and contribute to worsen the cardiopathy, aggravating the prognosis[402].

10.4. Education and health

The education of the patient and family starts with the assessment of their knowledge on the disease and its treatment. Individual or collective educational activities should be periodically performed, focusing on information about the disease, its contagion mechanisms, course, need for periodical assessment even in asymptomatic individuals, importance of regular treatment and, usually, impossibility of donating blood, organs or tissues. Nowadays, chagasic individuals can donate blood, organs and tissues under the "expanded donation" circumstance, that is, patients with CD can be donors as long as recipients consent to it and have the same pathology[403].

10.5. Management model for a structured service

Health care and promotion to patients with CCC should be based on a health care structure allowing integral actions, permeated with humanization practices and quality management[404-406]. The health care model to that patient in the public health network integrated with the Brazilian Unified Health Care System (SUS) presupposes the existence of the conditions necessary to its development, via the technical and managerial strengthening of the institutions involved in planning, coordination, execution and assessment of services at all levels, aiming at providing better care and observing the cost/effectiveness of the actions[407-409].

10.6. Benefits expected of a structured service for the follow-up of patients with CCC

The structured service for the follow-up of patients with CCC should emulate might confirm that used which has been described for other chronic diseases[81,395,397]. Although the implantation of a structured service is known to require a higher investment in the number of professionals involved, limited financial resources and managerial aspects, its creation is believed to become cost/effective in the middle and long term[21-410]. That proposition should not be considered a closed mathematical model, but as based on general guidance principles to aid in the composition of structured services. Briefly, structured services have the major mission to promote care that favors the patient's clinical, psychological and social stability.

11. Preventing transmission and *addendum* on serological criteria

11.1. Introduction

In 2005[81], the endemic area at risk for vectorial transmission of CD in Latin America comprised 19 countries, and involved 108,595,000 people. In 1950, actions against the insect vector were initiated in Brazil, Chile, Argentina and Venezuela, concomitantly with the intensification of urbanization, rural exodus and agricultural modernization. Since 1980, the Brazilian program of CD control has been prioritized, and blood banks began to screen donors for CD, which resulted in the current 100% coverage of serological assessment of donors in Brazil. The transmission has been drastically reduced, and the certification of elimination of *T. infestans* and of transfusional transmission has been achieved in Uruguay, Chile and Brazil[81]. Thus, there has been a decrease in disease prevalence in childbearing-age women, and in the congenital transmission of the disease. Of the estimated 100,000 new cases per year in Brazil in 1979, currently around 200 cases are detected, most of which in the Amazon region, due to outbreaks of oral transmission[81,410]. Currently available actions and strategies are sufficient to control the major modes of CD transmission in the most common situations. No safe and effective vaccine against CD exists[411]. The basic challenges are to maintain blood banks under control and to support and maintain the necessary epidemiological surveillance of the vector[88]. The present chapter is based on field results, longterm investigation and documents of official consensus[81] (Table 23).

11.2. Modes of transmission and factors involved

The following modes of CD transmission are admitted or possible[412,413]:

A. Usual:
- Vectorial
- Transfusional
- Congenital

B. Alternative (or secondary):
- Accidental in the laboratory
- Oral (including maternal milk)
- Organ transplantations

C. Hypothetical:

- Insect bite (triatomines and others)
- Contact with feces of infected triatomines
- Sexual contact
- Bizarre (sadomasochist practices, blood oaths for love, criminal).

11.2.2. Briefly description of the major mechanisms

11.2.2.1. Vectorial transmission

Occurs via the contact of a susceptible individual with feces of *T. cruzi*-infected triatomines. The parasite enters the host through a skin lesion or intact mucous membrane. Out of more than 140 vector species described, the most competent transmitters are those with the greatest power of household colonization, more anthropophilic habits and metacyclogenesis, and shortest feeding-defecation time. Currently there are virtually controlled areas with occasional risk of transmission through secondary or wild vectors (Uruguay, great part of Brazil), and areas with still active transmission and poor or nonexistent control. Because of the presence of wild foci throughout Latin America, transmission will always be possible. However, domiciliary transmission can be virtually eliminated through continuous control and surveillance actions[21,283].

11.2.2.2. Transfusional transmission

Occurs between an infected donor (usually chronic) and a susceptible recipient. The parasite maintains its infecting ability for more than two weeks in stored blood. The transmission risk for 500 mL of chronically infected total blood ranges from 12% to 25%, increasing for donors in the acute phase and immunosuppressive situations (donor or recipient). Infected frozen fresh plasma and concentrates (platelets, red blood cells and leukocytes) can also transmit CD[414].

11.2.2.3. Congenital transmission

Occurs mainly after the third gestational month. It consists in the colonization of the placenta by with the parasite, but can also occur through the ingestion of contaminated amniotic fluid or fetal contact with maternal blood. Its risk ranges from 1% to 5% in pregnant women with chronic disease (less frequent in Brazil than in Bolivia), being higher among pregnant women with acute disease or immunosuppressed. An infected woman can transmit the parasite in one or several pregnancies. Most commonly, the newborns are full term and asymptomatic, but fetal death and prematurity can occur. Symptomatic newborns have fever, low weight, tachycardia and hepatosplenomegaly[414,415].

11.2.2.4. Accidents in the laboratory

Are due to contamination with different infected materials, management of triatomine bugs and manipulation of infected mammals, cultures, and blood of acute cases. Sporadic contamination during surgeries of chagasic patients and aerosol aspiration has been reported[416].

11.2.2.5. Oral transmission

In the past, oral transmission events have been described in Argentina, Mexico, and in the Brazilian states of Pará, Rio Grande do Sul, and Paraíba, and, more recently, in other the Amazon regions (especially states of Pará and Amapá), Venezuela, Colombia, and in the Brazilian states of Santa Catarina, Ceará, and Bahia. Several types of contaminated food, especially juices (sugar cane, açaí fruit, bacabá fruit, guava), milk, soups, and raw game meat, could be implicated. Except for the breast milk of an infected mother (extremely rare and unlikely event) and poorly cooked meat of infected mammals (armadillo, for example), the events described seem to correspond to contamination of foods with infected triatomine bugs or their feces, in environments with peridomiciliary infestation or near a wild area. An outbreak of probable contamination with urine or gland secretion of a marsupial has been reported[81].

Table 23 – Recommendations for prevention of Chagas disease transmission

Recommendation class	Indications	Level of evidence
I	Use of available actions and strategies to control the major mechanisms of CD transmission in the most common situations (blood bank control and epidemiological surveillance of the vector)	B and C
	Control of transfusional transmission by selecting donors with previous serology and chemoprophylaxis	B
	Better use and indication of hemotherapy and elimination of paid donors	C
	Control of congenital transmission via conventional serology on the seventh month of life, and immediate start of specific treatment	C
	Prevention of laboratory accident, and immediate start of specific treatment with the usual doses of benznidazole for 10 days. After 30 days, repeat serology, and perform integral treatment (60 days) in the presence of seroconversion.	B and C
	Chemical control of vectorial transmission for domiciliary vectors and actions of housing improvement	
	Insecticides – synthetic pyrethroids	A
	Carbamates	B
	Environmental planning and removal of natural ecotopes and wild reservoirs from the household	C
	Housing improvement	C

11.2.2.6. Transmission via organ transplantations

It presupposes an infected donor and susceptible recipient, and has been described in transplantations of kidneys (the most frequent), heart, pancreas, liver and bone marrow. The risks increase in donors with more intense parasitemia (acute phase) and immunosuppressed recipients (due to the underlying disease or the medication received after transplantation)[416].

11.3. Major programs and strategies to control CD

Chagas disease is not eradicable because of the persistence of *T. cruzi* wild cycle and oral transmission cases. However, proper control (of domiciliary vectors and blood banks) is highly effective, resulting in the virtual elimination of transmission, which reduces the risks of congenital and transfusional transmission[81,283]. In general, CD control is the responsibility of public health systems, and, to a lesser extent, of private health systems, particularly private blood banks. In Uruguay and Brazil[417], once controlled the major vector and blood banks, the disease transmission has decreased to minimal levels in the past decades; occasional cases of congenital transmission are currently reported, along with unpredictable outbreaks of oral transmission[21]. The consolidation of control in those countries will depend on the continuity of sustained surveillance programs[81,413].

11.3.1. Control of vectorial transmission

It is based on the chemical fight against domiciliary vectors and housing improvement actions.

11.3.1.1. Use of insecticides

It is the most common isolated measure, with faster results, performed with the systematic and continuous application of insecticides in contiguous areas. In Brazil, until 1999, it depended on centralized teams (SUCAM, FNS, SUCEN); after that, the actions were decentralized to the municipalities, becoming under state coordination. The program presupposes steps of investigation, planning, massive attack and surveillance[414,415]. Until 1980, the major insecticides were organochlorine (BHC, Dieldrin®) and organophosphate (Malathion®, Fenitrothion®) insecticides. They have been currently replaced by synthetic pyrethroids, with greater residual action and lower human and environmental risks. They have long residual action through contact, affecting mainly the nervous system of the insect.

The major products used and their recommended doses are as follows[416]:

- Deltamethrin: 25 mg/m² (K-Othrine®, Bayer Brasil);
- Lambda cyhalotrin: 30 mg/m² (Icon®, Aventis Brasil);
- Cyfluthrin: 50 mg/m² (Solfac®, Bayer Brasil);
- Cypermethrin: 125 mg/m²
- Beta cyfluthrin: 25 mg/m²
- Alpha cypermethrin: 50 mg/m²

} Several laboratories

They are mainly applied inside the houses (residual action longer than six months) and peridomiciliary annexes (shorter action). The best formulations are the wettable powder, microcapsules and suspension concentrate[416]. They have low toxicity on people, usually limited to skin and mucosa irritations. The current great challenge is the peridomiciliary environment, which concentrates most of the residual foci in the country. Chemical fight is not justified in the wild environment, but environmental planning and removal of natural ecotopes and wild reservoirs from the household are recommended. In surveillance, domiciliary foci are notified by the population and eliminated by municipal teams when indicated. Triatomine resistance to pyrethroids has appeared in focal areas of Bolivia and Argentina[416]. In such cases, the use of carbamates, another family of insecticides, is indicated.

11.3.1.2 Household improvement

Implies the improvement of house sectors (walls, roofs) or new constructions. In general, that is a longer lasting measure, but does not replace the use of insecticides in endemic areas. In addition to life promotion, it is a protection measure against CD, because it makes the vector entrance and colonization difficult. A growing body of evidence accumulated over many years has shown that sustained control levels depend mainly on the population's participation in the entomological surveillance of CD[81].

11.3.2. Control of transfusional transmission

The basic strategies comprise the selection of donors through previous serology and chemoprophylaxis[417]. The former is more used and foreseen in the legislation of several Latin American countries. In Brazil, until 2004, serological screening was required through two different techniques. Since 2004, considering the low prevalence of CD infection in donors, only one technique has been required, as long as it has an immunoenzymatic basis, with high sensitivity rates[417]. Seropositive donors are considered permanently unsuitable and should be referred to a medical service for assessment and treatment. Chemoprophylaxis is performed by adding gentian violet (1:4,000) to suspected blood for 24 hours, time necessary for *T. cruzi* eradication. In the past, that was useful in highly endemic regions for CD, being currently used in some areas of Bolivia. Another control possibility would be the use of cellular filters for leukocytes, capable of retaining the parasite, but extremely expensive. It is worth noting that better use and indication of hemotherapy (avoiding arm-to-arm and total blood transfusions) and the elimination of paid donors are fundamental measures to the definitive control of transfusional CD[417].

11.3.3. Control of congenital transmission

Primary prevention is not possible, because the specific treatment of pregnant women with currently available drugs is not indicated. In addition, prognostic markers of transmission do not exist. Therapeutic abortion in chagasic pregnant women is not prescribed, except for extremely severe cases of cardiopathy. Detection and specific treatment are indicated as early as possible for infected children, who usually heal and tolerate the medication well[81,382]. Because

newborns maintain the antibodies (IgG class) passively transferred from their mothers up to the fifth or sixth month of life, an early positive serology will not indicate infection until that age. For the children of chagasic individuals, conventional serology should be performed at the age of seven months, and specific treatment immediately initiated for the seropositive ones[81]. For newborns strongly suspected of having congenital disease, the parasitological test should be performed for some days, at least three times a day, to increase sensitivity[382].

11.3.4. Prevention of laboratory accidents

All professionals manipulating *T. cruzi* should undergo conventional serology at the beginning of their activities. If negative, they should repeat it annually while their activity lasts, which will allow the detection of inapparent infection and enable specific treatment. It is important to promote awareness and technical training, to keep an environment suitable for handling the parasite and mandatory use of equipment for individual protection (goggles, masks, gloves, closed shoes). In case of accident, one should proceed to immediate local disinfection with iodine alcohol or silver nitrate eye drops, if eye contamination occurs. Blood for conventional serology should be immediately collected. Specific treatment should be initiated immediately at the usual doses of the medications available (nifurtimox or benznidazole) for ten days. After 30 days, repeat serology, and, if it is positive, integral treatment (60 days) should be performed[81].

11.3.5. Prevention of oral transmission

Because of the unpredictability and sparsity of oral transmission, there is little to be done regarding primary prevention. Removal of houses and annex from the wild environment, good hygiene in food handling and preparation, and no ingestion of raw or poorly cooked game meat are valuable general measures. Similarly to congenital transmission, the most practical measure is early detection and specific treatment, and the immediate epidemiological study of the occurrence to find out other cases. Transmission through maternal breast milk is extremely rare, thus, maternal breastfeeding should not be contraindicated, except for acute maternal CD and nipple bleedings[21]. Acute CD is of mandatory notification, the local/regional health system being responsible for its confirmation and epidemiological study. That allows the adoption of pertinent measures, such as the disease active screening in individuals exposed to common factors and triatomine control. In the Brazilian Amazon region, malaria microscopists are being trained to detect *T. cruzi* on blood smears of individuals with fever[21].

11.4. Appendix

11.4.1. Serological diagnosis of chronic *T. cruzi* infection

This completes the previous topics and has been well established in recent documents[81,88,382,392,414,415,417].

Basically, two serological techniques among those available and recommended by the WHO, such as IIF, enzyme-linked immunosorbent assay (ELISA) and IHA, are used. When concordant, the serological results will be positive or negative. When discordant, the tests should be repeated. If the discrepancy persists, a new test should be performed using PCR or Western blot techniques (Figure 6)[81].

11.4.2. Practical notes

a. For *postmortem* diagnosis, serology of the pericardial fluid is viable;

b. For extensive field survey, blood collection by use of digital puncture on 2-cm filter-paper discs (Whatmann Nº 4) is very practical. Seropositive results should be confirmed by use of venous blood collection as follows;

c. Negative initial serology followed by a positive one after 30 days indicates acute CD;

d. Unconventional tests[14,18] are modern techniques that use recombinant antigens, synthetic peptides and mixtures capable of identifying multi epitopes of high specificity. Examples: "PaGIA" (particle agglutination of sensitized polymers), "INNO-LIA" (nitrocellulose strips loaded with recombinant antigens), "Chembio" (immunochromatography rapid test);

e. A PCR test can be negative in infected individuals, mainly in the chronic phase, and should be repeated in doubtful cases of doubt or high clinical suspicion;

f. Extremely rare cases of persistently negative serological and parasitological tests in certainly infected individuals not submitted to specific treatment mean spontaneous healing of the infection, according to some reports[5].

12. Brief retrospective and perspectives

Regarding CD, much has been accomplished since Carlos Chagas' discovery one century ago. But there is still much to be done in coming decades. Popular wisdom has established the notion that 'every cloud has a silver lining'. This can be applied to CD globalization and the recent substantial diversification of its epidemiology in traditionally endemic countries. This context has aroused the interest in the social and medical problems related to CD of public health agencies and related national and international entities, research institutions and even industrial groups. There is currently a notable activation of several efforts to control CD epidemiology, to better know *T. cruzi* biology, its interaction with man, and the pathogenesis and pathophysiology of chronic phase complications, in addition to more properly and effectively treat the late cardiac and digestive manifestations. From that promising scenario, the following several aspects that deserve special attention emerge.

Although most vectorial and transfusional CD transmissions have been controlled in several countries, the need for sustained surveillance of the measures leading to that accomplishment persists. In addition, the changing ecological

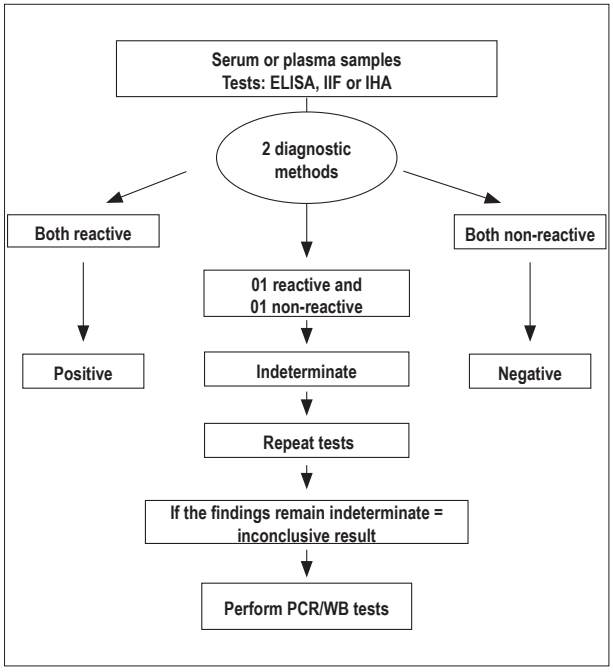

Figure 6 - *Flowchart for the performance of laboratory tests for Chagas disease in its chronic phase.*
PCR - polymerase chain reaction; WB - Western blot.

situation of extensive regions, such as the Amazon region, where new epidemiological aspects of the disease have the potential to develop and constitute more complex and difficult challenges, is matter of concern.

Furthermore, it is necessary to adopt initiatives that enable the proper management of the social and medical conditions resulting from the migration of infected individuals to countries where the disease never existed. The standardization of more reliable methods to detect *T. cruzi* infection is awaited, not only for diagnosis, but, more importantly, for healing criteria.

The etiological treatment of millions of patients in the chronic phase of the disease is a mystery to be unveiled. There is currently a renewed interest in the area, including the perspective of studies focusing on the association of drugs, such as benznidazole and posaconazole, because of their potential to act synergically against circulating (benznidazole, more active) and tissue (posaconazole, maybe more efficient) parasites. Confirmation of the real efficacy of the etiological treatment to favorably impact on the natural history of chronic disease is awaited, as is the development of new more effective trypanocidal agents with fewer side effects. Innumerous preferential targets for the pharmacological attack to *T. cruzi* have been identified based on the deeper knowledge of its interaction with the host cells and of its recently decoded genome.

Finally, cardiologists have to perfect the clinical management of their chagasic patients, properly administering drugs and interventions, respecting the peculiar pathophysiology of the disease, without using measures of no confirmed benefit, and not missing reasonable therapeutic opportunities.

13. Abbreviations used in the text and tables

Abbreviations	
ACEI	angiotensin-converting enzyme inhibitors
AF	atrial fibrillation
ARB	angiotensin receptor blocker
AVB	atrioventricular block
AZA	azathioprine
BB	beta-blocker
BNP	brain natriuretic peptide
CCC	chronic chagasic cardiopathy
CD	Chagas disease
CDC	Centers for Disease Control and Prevention
CHF	congestive heart failure
CRT	cardiac resynchronization therapy
CS	corticosteroids
CT	cardiac transplantation
CVA	cerebrovascular accident
CYCLO	cyclosporine
ECG	electrocardiogram
ECHO	echocardiography
EF	ejection fraction
ELISA	enzyme-linked immunosorbent assay
EPS	electrophysiological study
HF	heart failure
HIV	human immunodeficiency virus
ICD	implantable cardioverter defibrillator
IHA	indirect hemagglutination
IIF	indirect immunofluorescence
IL	interleukin
LV	left ventricular
LVEF	left ventricular ejection fraction
MMF	mycophenolate mofetil
NSVT	non-sustained ventricular tachycardia
NYHA	New York Heart Association
PAHO	Pan-American Health Organization
PCR	polymerase chain reaction
RV	right ventricular
SBP	systolic blood pressure
SD	sudden death
SVT	sustained ventricular tachycardia
T. cruzi	*Tripanosoma cruzi*
TAVB	total atrioventricular block
VO_2	oxygen consumption
WB	Western blot
WHO	World Health Organization
XR	radiography

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