I Latin American Guidelines for the Diagnosis and Treatment of Chagas' Heart Disease. Executive Summary

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Abstract

Much has been achieved in one century after Carlos Chagas' discovery. However, there is surely much to be done in the next decades. At present, we are witnessing many remarkable efforts to monitor the epidemiology of the disease, to better understand the biology of the *T. cruzi* and its interaction with human beings as well as the pathogenesis and pathophysiology of the complications in the chronic phase, and deal more appropriately and effectively with late cardiac and digestive manifestations.

Although the vector and transfusion-derived transmission of the disease has been controlled in many countries, there remains a pressing need for sustained surveillance of the measures that led to this achievement. It is also necessary to adopt initiatives that enable appropriate management of social and medical conditions resulting from the migration of infected individuals to countries where the disease formerly did not exist. It´s also necessary to standardize the most reliable methods of detection of infection with T. *cruzi*, not only for diagnosis purposes, but more crucially, as a cure criterion.

The etiological treatment of millions of patients in the chronic stage of the disease is also to be unraveled. A renewed interest in this area is observed, including prospects of studies focusing on the association of drugs with benznidazole. We also wait for full evidence of the actual effectiveness of the etiological treatment to impact favorably on the natural history of the disease in its chronic phase.

Eventually, cardiologists are primarily responsible for improving the clinical management of their patients with Chagas' disease, judiciously prescribing drugs and interventions that respect, as much as possible, the peculiar pathophysiology of the disease, wasting no plausible therapeutic opportunities.

Keywords

Chagas' cardiomyopathy/history/trend/epidemiology/pathophysiology/diagnosis/complications/therapy/mortality, guidelines, Latin America.

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Introduction

Soon after the celebration of 100th anniversary of the discovery of Chagas' Disease (CD), this is an opportunity to celebrate this event with the first issue of the Latin American Guidelines on Chagas' Heart Disease (CHD) and pay tribute to the man who has ingeniously described the new disease, from its etiology and clinical features, including the main mode of transmission, the vector.

Epidemiological aspects

Organized and coordinated campaigns to control vectorial and transfusional borne transmission have significantly reduced new cases. In June 2006, Brazil received from the World Health Organization (WHO) the certificate of eradication of CD transmission by the wild vector *Triatoma infestans*. The cost-effectiveness of CD control program was verified, since for every US$ 1.00 spent, savings were US$ 17.00. That does not represent the eradication of the CD, as isolated outbreaks and sporadic records of acute cases continue to occur in several Brazilian states.

With the globalization of the CD, a new epidemiological, economic, social and political problem has emerged from the legal and illegal migration of individuals infected with the *T. cruzi* from endemic countries to non-endemic countries, mainly the United States, Canada, Spain, France, Switzerland, Italy, Japan, emerging countries from the Asia and Australia, which contributed to increasing the visibility of the CD. In the US, it is estimated that 300,000 individuals are infected with the T. cruzi. Of these, 30,000 to 45,000 have clinical manifestations. In 2007, screening on blood and organ donors became mandatory. In the Americas, the epidemiological features of the CD can be divided into the following groups of countries, according to the cycle of transmission and control programs.

Group I - Argentina, Bolivia, Brazil, Chile, Ecuador, Honduras, Paraguay, Peru, Uruguay and Venezuela have the domestic, peridomicile and sylvatic cycles, with high prevalence of human infection and prevalence of chronic Chagas' cardiomyopathy (CCC).

Group II - Colombia, Costa Rica and Mexico, characterized by domestic and peridomicile cycles with presence of CCC.

Group III - El Salvador, Guatemala, Nicaragua and Panama have domestic, peridomicile and sylvatic cycles with poor clinical information.

Group IV - Caribbean, Bahamas, Belize, Cuba, United States, French Guiana, Guyana, Haiti, Jamaica and Suriname, with sylvatic cycles and little clinical information.

Pathogenesis and pathophysiology

The chronic Chagas' cardiomyopathy (CCC) is essentially a dilated cardiomyopathy in which a chronic inflammation, usually of low intensity but constant, leads to progressive tissue destruction and extensive fibrosis in the heart. Several mechanisms may contribute to the pathogenesis of cardiac lesions and the subsequent installation of various pathophysiological disorders, according to recent reviews.

Although the morphological and functional changes of the autonomic heart system are detectable in patients with chronic Chagas' disease, they occur in varying degrees and do not directly correlate to the degree of ventricular depression. Hence, the so-called "neurogenic theory", as understood on the basis of pioneering studies, does not convincingly explains the myocardial damage caused by the CCC.

Many patients with CCC have anginal symptoms, electrocardiographic abnormalities suggesting ischemia and various myocardial perfusion defects detected by scintigraphy. In general, the epicardial coronary arteries are angiographically normal in these patients, but may have abnormal reactivity to stimulation of vasodilators or vasoconstrictors. It is assumed that microcirculatory disturbances detected in experimental models of infection with *T. cruzi* and humans with Chagas' disease, contribute as amplifiers of the inflammatory effects and produce myocardial ischemia[24]. Similarly to the "neurogenic theory", the "microvascular hypothesis", as an independent and fundamental pathogenic mechanism, needs further definitive clinical support.

There is unequivocal evidence that pathogenic reactions of autoimmunity occur in the CCC, by molecular mimicry, polyclonal activation or other mechanisms. However, it is less clear whether aggression to the cardiac structures depending on autoimmunity is decisive for the installation of those lesions that characterize the chronic cardiomyopathy of the Chagas' disease. In contrast, it is assumed that a proper mechanism of immunoregulation is crucial to distinguish those individuals who would control their infection without developing any relevant tissue damage (through limited inflammatory response) from those who would develop a severe disease, with intense inflammation, necrosis and reactive fibrosis.

Based on recent experimental and clinical evidence, there is consensus that the essence of the pathogenesis of CCC lies in inflammation directly dependent on parasite persistence and consequent adverse immunological reaction, elicited by such persistence, thus redeeming the notion that even in its chronic phase, the heart disease is primarily an infectious inflammatory process.

The pathophysiology of chronic heart disease is expressed by inflammatory, degenerative and fibrotic abnormalities that cause sinus node dysfunction, various atrioventricular and intraventricular blocks, re-entry ventricular arrhythmias, and dyssynergia or ventricular aneurysms that lead to thromboembolic complications. With the progressive myocardial injury, heart failure or a dilated cardiomyopathy pattern characteristically biventricular then emerges.

Clinical presentation and classification

The CD can be classified into two evolutionary stages: acute and chronic. The acute phase may be due to primary infection or reactivation of a chronic phase. After the initial infection, the acute phase lasts 06-08 weeks. In many patients infected by vector transmission, the acute phase is not diagnosed. The clinical picture resembles that of other cases of myocarditis, with systemic symptoms of fever, disproportionate tachycardia, splenomegaly and edema. Inflammation can be observed where the parasites penetrate the skin, such as the Romaña's sign - unilateral palpebral edema and preauricular lymphadenopathy, sometimes accompanied by conjunctivitis. Electrocardiogram (ECG) may reveal sinus tachycardia, low QRS voltage, prolonged PR and/or QT interval and ventricular repolarization. Ventricular arrhythmias and atrial fibrillation may also be observed. These situations that indicate a worse prognosis. When the disease is transmitted congenitally, it may be associated with hepatosplenomegaly, jaundice, cutaneous hemorrhage and neurological signs, especially in premature neonates.

In the chronic phase, 04 clinical situations may evolve: indeterminate form, heart form, gastrointestinal form, and mixed form (cardiac and digestive involvement in the same patient).

The indeterminate form (IF) may last 30 to 40 years. Approximately 30 to 40% of the patients develop the cardiac, digestive, or mixed form, and the others remain with the IF throughout life. Patients with this form have serology and/or parasitological tests positive for *Trypanosoma cruzi*, but no symptoms, physical signs or evidence of organ damage (cardiac and extracardiac) on ECG and chest X-rays or other radiological studies (esophagus and colon). However, if the patient is subjected to more rigorous and sophisticated testing (echocardiogram, autonomic evaluation, exercise testing, Holter monitoring, myocardial scintigraphy, magnetic resonance imaging, cardiac catheterization, endomyocardial biopsy), some changes may be observed, generally mild with no established prognostic value in any study.

The cardiac form can occur with or without global ventricular dysfunction (usually known as arrhythmogenic form). Although the most common form is the coexistence of arrhythmic events with congestion, some patients may have a form of CCC only characterized by arrhythmias and intraventricular and atrioventricular conduction disorders, with normal ventricular function. This malignant ventricular arrhythmia is an important prognostic marker due to MS, which has multiple mechanisms (tachycardia and ventricular fibrillation or asystole), associated with multiple myocardial scarred areas.

The chronic heart failure usually settles 20 years or more after infection. The most frequent clinical presentation is the biventricular HF, sometimes with right ventricular (RV) predominance. Patients complain of weakness, rather than dyspnea, and chest pain (usually atypical angina). Dilated ventricles with aneurysms and, in addition to the high prevalence of atrial fibrillation in advanced stages, are important sources of mural thrombi, causing systemic, pulmonary and

cerebral thromboembolic events. The prognosis worsens as the HF picture progresses and arrhythmias become uncontrollable.

As for left ventricular (LV) dysfunction and HF manifestations, the chronic phase can be further classified into stages (A, B, C and D), according to international recommendations adapted to the Chagas' disease.

The stage A includes IF patients with no present or previous symptoms of HF, without structural heart disease (normal ECG and chest X-ray). As long as the patient remains in this form of the disease, prognosis is not compromised.

The stage B includes those patients with structural heart disease, who have never had signs or symptoms of HF. This stage is divided into:

B1 - patients with ECG changes (arrhythmias or conduction disorders) may present mild echocardiographic abnormalities (abnormalities of regional contractility), but global ventricular function is normal.

B2 - patients with global ventricular dysfunction (decreased LV ejection fraction).

Stage C includes patients with LV dysfunction and prior or current symptoms of HF (NYHA I, II, III and IV).

Stage D includes patients with symptoms of HF at rest, refractory to maximized medical therapy (NYHA IV) requiring specialized and intensive interventions.

Clinical diagnosis and prognosis in chronic phase - Table 1

Given the low parasitemia in the chronic phase of the disease, parasitological examinations are not routinely used and serological tests based on detection of antibodies against the *T. cruzi* should be employed. The diagnosis of infection with *T. cruzi* is confirmed (or excluded) with at least two serological tests of different principles and the most commonly used are: enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence (IIF) and indirect haemagglutination (IHA). When the three tests are conducted, it is possible to obtain a consistency level exceeding 98%. The sensitivity and specificity of these tests vary: ELISA and IFA with sensitivity > 99.5% and specificity from 97 to 98%. IHA tests have a sensitivity of 97 to 98% and specificity of 99%.

Electrocardiographic abnormalities are often the first indicator of CCC. Right bundle branch block is more frequently associated with left anterior hemiblock. Involvement of left branch and left posterior fascicle is rare. Atrioventricular block (AVB) of varying degree is common. Sinus node dysfunction may cause episodes of sino-atrial block with bradycardia or ectopic atrial tachycardia. Flutter and atrial fibrillation are delayed and associated with significant ventricular dysfunction, as well as polymorphic ventricular extrassystoles. Complex ventricular arrhythmias such as nonsustained ventricular tachycardia (NSVT) or sustained ventricular tachycardia (SVT) occur even in patients without HF, but tend to be associated with more advanced stages and worse prognosis.

In advanced stages, acute global cardiomegaly generally contrasts with discrete degrees or absence of pulmonary congestion and increased right cavities may prevail in the chest radiography. Systemic venous congestion, and pleural and pericardial effusion also occur.

Table 1 - Recommendations and levels of evidence for complementary methods for the diagnosis and prognosis of patients with Chagas' disease and/or chronic Chagas' cardiomyopathy

Degree of recommendation	Indications	Level of evidence
I	12-lead ECG for periodic diagnosis of patients with Chagas' disease	C
	Chest radiography for periodic diagnostic assessment of patients with Chagas' disease	C
	Doppler echocardiography for additional diagnostic and prognostic assessment of patients with CCC	C
	Dynamic electrocardiography (Holter) for evaluation of arrhythmias and prognostic stratification of patients with CCC	C
	Cardiopulmonary stress test for functional assessment, risk stratification and support in the indication of cardiac transplantation in patients with advanced HF	C
	Cardiac catheterization for evaluation of coronary anatomy in patients with typical angina and important risk factors for coronary disease or high predictive value test for ischemia	C
IIa	Doppler echocardiography to evaluate patients with the indeterminate form	C
	Right cardiac catheterization for evaluation of pulmonary vascular resistance in candidates for heart transplantation with noninvasive evidence of pulmonary hypertension	C
	Cardiac catheterization for evaluation of apical or inferobasal aneurysm, in events of proposed aneurysmectomy or percutaneous ablation of arrhythmogenic circuits.	C
III	Cardiac catheterization as a routine indication in Chagas' disease patients with atypical pain.	C

Echocardiography (ECG) allows evaluating left ventricular (LV) regional and global contractile performance, right ventricular (RV) impairment, the presence of aneurysms and cavity thrombus and changes in diastolic function. Even in the indeterminate phase of the disease, the echocardiogram may show, in 10 to 15% of the cases, changes in segmental contractility in the inferior or apical LV wall. In advanced stages, there is great cardiac chamber dilatation with diffuse hypokinesia and mitral and tricuspid insufficiency secondary to dilation of the annulus, as well as ventricular aneurysms, 47 to 67% of cases associated with increased thromboembolic risk (in apical position) and malignant ventricular arrhythmias (inferobasal or posterolateral).

Continuous electrocardiographic monitoring (Holter) is indicated in patients with LV dysfunction, especially in the investigation of syncope due to bradyarrhythmias or ventricular tachyarrhythmias, which may coexist in the same patient, and the SVT and advanced AVB are the most serious ones.

A stress test is useful for detection and prognosis of arrhythmias induced by stress. Cardiopulmonary exercise

testing with direct measurement of oxygen consumption (VO_2) demonstrates that patients with VO_2 smaller than 12 ml/kg/min present high mortality in one year, and is also used as an auxiliary method of indication of cardiac transplantation.

Myocardial perfusion scintigraphy shows segmental perfusion deficits in up to 30% of patients with anginal pain and normal coronary angiography - an examination performed unnecessarily in many patients - indicating changes in the coronary microcirculation. The assessment of the biventricular function by nuclear angiocardiography with ^{99m}Tc is an alternative to the ECO, mainly in quantifying the RV ejection fraction.

The electrophysiological study (EPS) allows investigating the sinus function and the AV conduction, and is indicated for clarifying syncope of undetermined origin after noninvasive evaluation, and reversed sudden death, as well as mapping ventricular refractory tachycardia for potential ablation.

In CCC patients evaluated with noninvasive methods, Rassi's death risk score has been recently described. It used 06 independent prognostic factors: functional class III or IV (5 points), cardiomegaly on x-ray (5 points), ventricular dysfunction on ECG (3 points), NSVT on Holter monitoring (3 points), low QRS voltage (2 points) and male sex (2 points). Patients were classified as low risk (score 0-6 points), intermediate (score 7-11 points) and high (score 12-20 points), with a mortality of 10%, 44% and 84% in 10 years of follow-up study, respectively.

In a systematic review of follow-up studies covering 3928 patients, the following were identified as independent prognostic variables: LV systolic dysfunction, functional class III/IV and cardiomegaly on chest X-ray. The combination of ventricular dysfunction in the presence of NSVT on Holter monitoring identifies a group with a 2.14 times greater risk of death. The presence of ventricular arrhythmia with heart failure identifies patients at higher risk for sudden death. These algorithms are able to stratify the prognosis in a simplified way (Figure 1).

Etiological treatment

Two drugs have proved to be trypanocidal agents: nifurtimox and benznidazole. The former is not available for widespread use in Brazil. Its tablet contains 150 mg of active ingredient. The recommended dose is 15 mg/kg/day in children or acute cases, and 80 to 10 mg/kg/day in adults for 60 days of treatment, and the daily oral dose is divided into three times. Its side effects are: anorexia (the most intense and frequent), abdominal pain, nausea, vomiting and weight loss.

Benznidazole tablets have 100 mg of active ingredient. The recommended dose is 10 mg/kg/day in children or acute cases, and 05 mg/kg/day in chronic cases for 60 days, divided into two doses. The maximum recommended daily dose is 300 mg. For adults weighing over 60 kg, the total dose expected should be calculated, extending the treatment time beyond 60 days. Thus, patients weighing 65 kg receive 300 mg daily for 65 days, and patients weighing 70 kg receive this daily dose for 70 days to a maximum of 300 mg. The most common side effect is urticarial dermatitis, which occurs in up to 30% in the first week of treatment, with a good therapeutic response to antihistamines or corticosteroids. When there is fever and adenopathy, the medication should be discontinued, as well as leukopenia and agranulocytosis (rare). Other adverse effects include polyneuropathy (usually at the end of the 60-day treatment) with pain and/or tingling in the legs, anorexia. Lymphoma was described in rabbits and

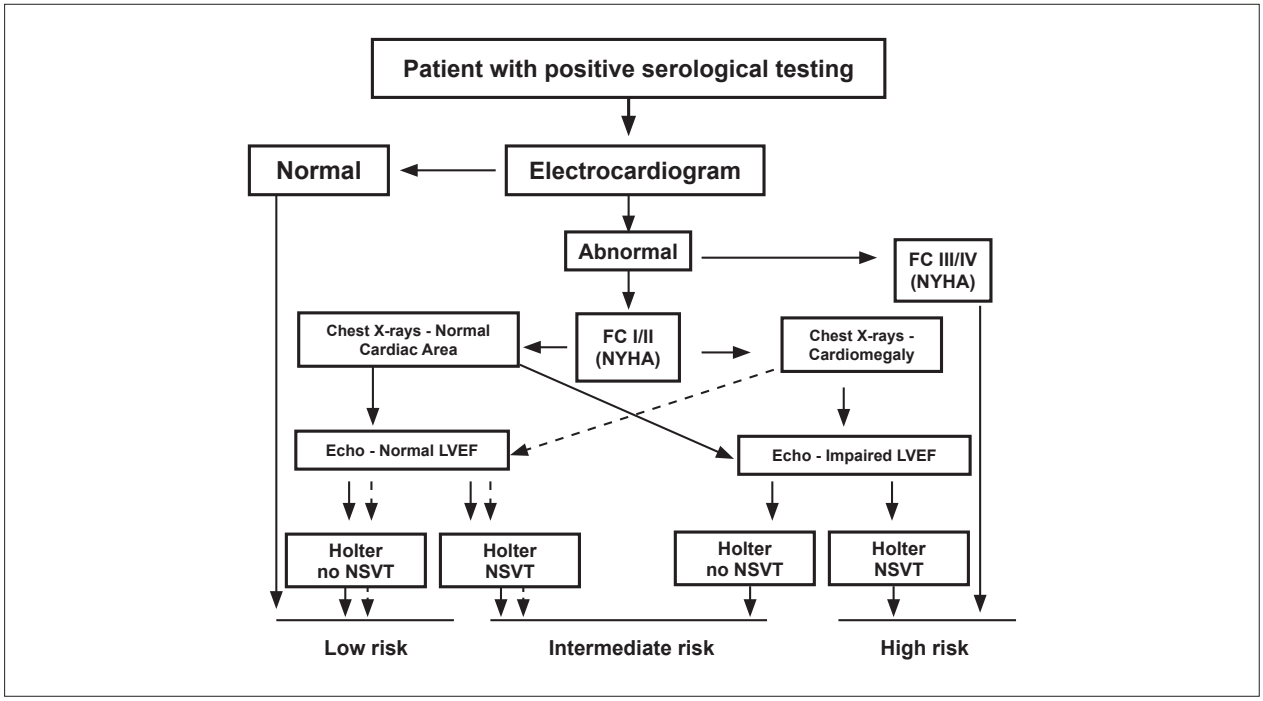

Figure 1 - Algorithm for risk stratification in the chronic phase of the Chagas' disease (*). (*) Adapted from Rassi A Jr, Rassi A, Rassi SG. Predictors of mortality in chronic Chagas' disease. Circulation. 2007;115:1101-8.

rats, unrelated to humans. It is contraindicated in pregnant women, renal and liver failure.

Although in most acutely infected patients the disease is not diagnosed due to nonspecific symptoms and signs at this stage, treatment should be performed in all cases and as soon as possible (CR = I, LE = B), regardless of the type of transmission, exception made to pregnancy, which contraindicates etiological treatment (CR = III, LE = C). Chagasic children in chronic phase should also receive trypanocidal treatment (CR = I, B = LE) for 60 days.

In accidental contaminations of high risk, with cutting/piercing instruments or mucous contact with material containing living parasites, samples for culture, infected vectors and laboratory animals, samples from patients suspected of high parasitemia and necropsy material, the use of benznidazole (7-10 mg/kg) is maintained for at least 10 days. With evidence of a high parasite load, treatment should continue for at least 30 days (CR = I, LE = C).

Reactivation of Chagas' disease may occur in pharmacologically immunosuppressed patients, or in those co-infected with the human immunodeficiency virus. Specific conventional treatment is indicated in these situations for a period of 60-80 days, depending on the patient's clinical condition (CR = I, LE = C).

In adult patients with the indeterminate form or with established CCC, indication for parasiticide treatment remains controversial. Many researchers believe that a defensible practice is to treat based on: a) experimental evidence that the etiological treatment attenuates the progression of heart disease, reported by different groups of researchers; b) observational studies in humans, though not definitive, with clinically relevant outcomes point to the possibility of concrete a positive impact on the natural history of the disease, even at a (not advanced) stage of CCC; c) the relative paucity and low severity of side effects in comparison with the potential benefit on the treatment of short duration (two months in general). To try to resolve conclusively the dilemma, given the opposing risks of committing alpha or beta errors, international multicentre, randomized, double-masked and placebo-controlled research is ongoing to evaluate the clinical course of 6 years in patients with CCC treated with Benznidazole (the BENEFIT study).

The results of the BENEFIT study may be strategic in the context of Chagas' disease patients who clearly have heart disease. In these situations, there was no consensus among the Guideline Editors to the class of recommendation and level of evidence for the indication of treatment for these groups of patients. While a percentage of Editors suggest that the treatment of the advanced cardiac form should receive class IIa recommendation with evidence level B, and that the indeterminate form in young adults should receive class IIa recommendation with evidence level C, another percentage of the Editors suggests IIb recommendation percentage of the Editors suggests IIb recommendation and awaiting awaiting for the results of investigations for a possible final recommendation.

The laboratory follow-up of patients treated aims to examine whether there are parasites in the body and whether the antitripanosoma antibodies are still present. The parasitological tests (xenodiagnosis, blood culture, polymerase chain reaction - PCR) are valuable only when *T. cruzi* is found, meaning treatment failure. Parasitologically negative results are insufficient to secure that healing has occurred (CR = IIa, LE = B). Serologic tests for detection of antibodies, when positive, not necessarily attest trypanocidal therapy failure, while persistent negative results (over many years) mean cure (CR = IIb, LE = B). In cases treated during the acute phase, the decline is observed in the first year and reaches a negative result in less than 05 years. In children (12-14 years) or adults treated during the first years after infection, the decline is observed in the first 05 years and a negative result in general, is found even after 10 years. In adults treated later, the curve has inflections only after 10-20 years and negativity may occur after 30 years.

Treatment of ventricular dysfunction and heart failure

The management of Chagas' Heart Disease is the treatment of different clinical manifestations of the disease (including the control of parasitic infection) and the approach of ventricular dysfunction and heart failure, as well as thromboembolic events and rhythm disorders. As in other heart diseases, HF caused by CCC is based on the routine use of a combination of three types of drugs: diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and adrenergic beta-blockers. However, although the CD is a major cause of HI in Latin America, patients with CD and HI were not included in large studies that validated these drugs. The real effectiveness and tolerability of these drugs in patients with CCC have not been established and its use is extrapolated due to the benefit obtained in HF from other causes (Table 2).

Prevention of thromboembolic events

Annual incidence of thromboembolic events is between 1 to 2% in patients with Chagas' disease cardiomyopathy, the highest one (60%) in the subgroup of patients with chronic heart failure. In this series, apical aneurysm and LV mural thrombosis were observed in 23% and 37% of patients, respectively. Pulmonary thromboembolism is rarely seen in patients without HF, but it can occur in 37% of patients with HF. In 85% of the cases, it is associated with mural thrombosis of the right heart chambers.

A score derived from prospective cohort of 1,043 patients was recently described to assess risk and implement the prevention of cardioembolic cerebrovascular accident (CVA) in CCC (incidence of 0.56% per year). LV systolic dysfunction contributed with two points. As for the apical aneurysm, the primary change in ventricular repolarization on electrocardiography and age > 48 years participated with one point for each of these changes. Through the risk-benefit analysis, warfarin is indicated for patients with 4-5 points (in this subgroup, there is an incidence of 4.4% CVA *versus* 2% of severe bleeding per year). In the subgroup with a score of 3 points, event rates and bleeding with oral anticoagulation are equivalent. In this case, aspirin or warfarin can be indicated. In patients with two points, with low incidence of ischemic CVA (1.22% per year), aspirin or no therapy was recommended. Patients with 0-1 point, with incidence close to zero, would not need prophylaxis.

Arrhythmias and conduction disorders

CCC patients usually have high density of ventricular arrhythmia, particularly those with electrocardiographic abnormalities, regional or global ventricular dysfunction

Table 2 - Recommendations and levels of evidence for the treatment of heart failure in chronic Chagas' cardiomyopathy

Degree of recommendation	Indications	Level of evidence
Renin-angiotensin-aldosterone blockers		
I	ACEI or ARB (for those intolerant to the former) in patients with LV systolic dysfunction, LVEF < 45% and IH FC I/II/III/IV	C
	Spironolactone in patients with LV systolic dysfunction, LVEF < 35% and IH FC III/IV	B
IIb	Spironolactone in patients with LV systolic dysfunction, LVEF < 35% and IH FC II	C
Beta-blockers		
IIa	Carvedilol, bisoprolol and metoprolol succinate in patients with LV systolic dysfunction, LVEF < 45% and IH FC I/II/III/IV	B
Hydralazine and Nitrate		
I	Patients of any ethnicity, with LV systolic dysfunction, LVEF < 45% and FC II-III with contraindications or intolerance to ACEI and ARB (e.g. progressive renal failure or hyperkalemia)	C
IIa	Patients with LV systolic dysfunction, LVEF < 45% and FC III-IV as an addition to the use of optimized therapy	C
Diuretics		
I	Patients with signs and symptoms of congestion (FC II to IV)	C
III	Patients with asymptomatic LV systolic dysfunction (FC I) or hypovolemic patients	C
Digitalis		
IIa	Patients with LV systolic dysfunction, LVEF <45% and sinus rhythm or atrial fibrillation, symptomatic despite optimized therapy	C
IIb	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 inotropes		
I	Dobutamine in cardiogenic shock	C
IIb	Levosimendan in patients with BP > 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	Score IPEC/FIOCRUZ ≥ 4 [51]	B
IIb	LV apical aneurysm (without thrombosis)	C

and HF. In these patients, Holter monitoring should be performed regardless of the symptoms, in order to identify complex arrhythmias (CR = IIa, LE = B). The EPS is also used to investigate syncope, especially when noninvasive tests are inconclusive.

The goal of pharmacological treatment of arrhythmias in CCC is the control of symptoms without concrete evidence of effectiveness in preventing sudden death and overall mortality. In general, the presence of these arrhythmias in asymptomatic patients with preserved ventricular function eliminates the need for antiarrhythmic treatment. For symptomatic patients without ventricular dysfunction, antiarrhythmic treatment can be individualized and in those with left ventricular dysfunction, amiodarone is the only safe drug. In usual doses of 200 to 400 mg/day, it may be associated with beta blockers to reduce serious arrhythmic events.

In the approach of SVT in the emergency room, electrical cardioversion should be used for hemodynamic instability. If stable, injectable amiodarone can be used in a dose of 150 mg in every 10 minutes (it may be repeated if there is no reversal). After reversal, infusion of 01 mg/minute is applied in the first 6 hours and then 0.5 mg/minute in the following 18 hours. Pharmacological therapy in patients with SVT and relevant left ventricular dysfunction (LV ejection fraction < 35%) should be instituted as an adjunct to implantable cardioverter defibrillator (ICD). In patients with well tolerated SVT and preserved ventricular function, the use of amiodarone and ablation can be considered, although ICD implantation is the safest option. The role of ablation has been to improve patients' quality of life, avoiding the discomfort of shocks in patients with ICD

Table 3 - Recommendations and levels of evidence for the drug treatment of ventricular arrhythmias in chronic Chagas' cardiomyopathy

Degree of recommendation	Indications	Level of evidence
I	Amiodarone for patients with ventricular ectopy, asymptomatic NSVT and left ventricular dysfunction	B
	Amiodarone for patients with symptomatic SVT or not, with or without left ventricular dysfunction not treated with ICD	C
I	Amiodarone to reduce shocks in patients with ICD	C
IIa	Routine amiodarone for patients with symptomatic SVT treated with CDI	C
IIb	Propafenone or Sotalol for patients with ventricular ectopy and NSVT with symptoms but without left ventricular dysfunction	C
	Amiodarone for patients with ventricular ectopy and NSVT, asymptomatic, with left ventricular dysfunction	C
	Sotalol or propafenone to reduce shocks in patients with ICD	C
III	Class I antiarrhythmic drugs for Chagas' disease patients with any form of arrhythmia and left ventricular dysfunction	C

and reducing the number of hospital admissions for reversal of SVT (Table 3).

CCC bradyarrhythmias may result from sinus node dysfunction or atrioventricular blocks. Intraventricular blocks are also common in the CCC, in particular the right bundle branch block associated with anterosuperior divisional left bundle-branch block. Indications for cardiac pacemakers in the CCC are shown in Table 4.

Scientific evidence regarding ICD indications in CCC is restricted to publications of case series, retrospective cohorts or registries, involving only the secondary prevention of sudden cardiac death. To date, no randomized clinical study on a large scale has compared the ICD effectiveness with active drug or placebo in CCC. There is no scientific evidence that supports the indication of ICD in the primary prevention of sudden death. Therefore there is no recommendation to be suggested at this moment.

Despite the lack of solid scientific evidence, the indication of resynchronization in CCC follows criteria extrapolated from those used for patients with ischemic and idiopathic dilated cardiomyopathy, in which the results, albeit with restrictions, are well known.

Cardiac transplantation

In Brazil, Chagas' cardiomyopathy is the 3rd most common cause of indication for cardiac transplantation (CT). Indications for CT are summarized in Table 5. Registry of patients undergoing CT suggests that the prognosis of recipients with Chagas' disease can be even better than that observed in non-chagasic recipients. The overall survival rate was 76%, 62% and 46% in one year, two years and 06 years after CT, respectively.

The diagnosis of CD is relevant in the context of organ donation and, as a rule, patients infected with *T. cruzi* should not be organ donors. Various schemes that combine immunosuppressive drugs, with or without induction of tolerance to graft, have been used in CT for CCC, with a good outcome. In maintenance immunosuppression, the most commonly used scheme is the combination of cyclosporine with azathioprine and withdrawal of corticosteroid as soon as possible. The prevailing concept is that, for being infected with *T. cruzi,* patients with Chagas' disease should receive the lowest possible intensity of immunosuppression, as long as rejection is avoided.

Monitoring of the reactivation of infection with *T. cruzi* after heart transplantation should be performed routinely and during suspected episodes of such occurrence. There is

Table 4 - Recommendations and levels of evidence for artificial heart stimulation in patients with chronic Chagas' cardiomyopathy

Degree of recommendation	Indications	Level of evidence
I	Spontaneous or irreversible sinus node dysfunction induced by indispensable and irreplaceable drugs, with documented events of syncope, near syncope or dizziness, or HF related to bradycardia.	C
	Sinus node dysfunction with intolerance to exertion, clearly related to chronotropic incompetence.	C
	Intermittent or permanent 2nd degree AVB, irreversible or caused by necessary and irreplaceable drugs, regardless of the type and location, with defined symptoms of HF or low cerebral blood flow consequent to bradycardia.	C
	Mobitz type II AVB with wide or infra-His bundle QRS, even asymptomatic, permanent or intermittent and irreversible	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
	3rd degree AVB, permanent or intermittent, even asymptomatic.	C
	documented alternating bilateral bundle branch block with syncope, near syncope or recurrent dizziness	C
IIa	Spontaneous sinus node dysfunction, irreversible or induced by indispensable and irreplaceable drugs, with documented events of syncope, near syncope dizziness or worsened HF probably related to bradycardia (non documented).	C
	Mobitz type II AVB, irreversible even if asymptomatic	C
	Flutter or AF with average HR below 40 bpm while awake, irreversible or through use of necessary or irreplaceable drugs, even if asymptomatic	C
	Intraventricular block with spontaneous HV interval > 70 ms or intra or infra-His bundle AVB induced by atrial stimulation or pharmacological testing in patients with syncope, near syncope or dizziness without determined cause	C
	Intraventricular block with spontaneous HV > 100 ms	C
	Bifascicular/alternate branch block associated or not to 1st degree AVB with syncope events without paroxysmal CAVB documentation, where other causes were ruled out.	C
IIb	Sinus node dysfunction in mildly symptomatic patients with chronic HR < 40 bpm while awake.	C
	Advanced AVB, intermittent or permanent and irreversible, even if asymptomatic	C
	Type 2:1 2nd degree AVB, asymptomatic, permanent or intermittent and irreversible, associated with ventricular arrhythmias that require medical treatment with irreplaceable AV conduction depressor drugs	C
	Asymptomatic bilateral branch block	C
III	Sinus node dysfunction asymptomatic or with symptoms demonstrably unrelated to bradycardia.	C
	Branch block or bifascicular block in asymptomatic patients with or without 1st degree AVB.	C

Table 5 - Recommendations and levels of evidence of indications for heart transplantation in chronic Chagas' disease

Recommendation	Indications	Level of evidence
I	Refractory HF, dependent on inotropic drugs and/or circulatory support and/or mechanical ventilation	C
	VO_2 peak ≤ 10 ml.kg/min	C
	Fibrillation or sustained refractory ventricular tachycardia	C
	Functional class III/IV with persistent therapeutic optimization	C
IIa	Use of BB with VO_2 peak = 12 ml/kg/min	C
	Without use of BB with VO_2 peak = 14 ml/kg/min	C
	Cardiopulmonary exercise test with VE/VCO_2 > 35 and VO_2 peak = 14 ml/kg/min	C
IIb	Functional class IV without optimized therapy	C
III	Functional class III without optimized therapy	C

a particularly difficult diagnosis to distinguish acute cellular rejection from reactivated chagasic myocarditis, because these processes may have histopathologic similarities, basically represented by foci of lymphocytes attacking not infected cardiac fibers, although with some differences as to the characteristics of the infiltrate. Parasite nests should be often looked for in sequence histological sections obtained by biopsy and immunohistochemistry reaction should be performed against *T. cruzi* antigens. The PCR technique has been used for this purpose, but the sensitivity and relationship with reactivation remain to be proven.

Special subgroups in Chagas' disease

The importance of coinfection with *T. cruzi*/HIV is due to the risk of reactivation of chronic CD in the presence of immunosuppression caused by HIV, particularly in those with lymphocytes T-CD4+ < 200 cells/mm. We also observed a high frequency of congenital transmission of *T. cruzi* with severe meningoencephalitis and/or highly lethal myocarditis in children of coinfected mothers. The diagnosis of coinfection *T. cruzi*/HIV is based on serological tests and these are indicated in all HIV+ patients coming from endemic areas or exposed to the risk of acquiring *T. cruzi* (blood transfusions, mother with CD). The most common clinical manifestation of reactivation is meningoencephalitis. Myocarditis is described in 30 to 40% of the cases. The reactivation of CD in HIV+ patients has a high fatality rate, affecting 100% in those untreated or treated late. Early treatment is associated with better prognosis and mortality reduced to 20% in those completing 30 days of specific treatment.

The rate of CD reactivation has been described as between 9 and 16% with renal transplantation, and 17 to 40% with bone marrow, most frequently in the first year, when immunosuppression is more intense. In general, there is good response to treatment, but there are reports of dysfunction and graft loss or even death, regardless of the proper use of benznidazole. Importantly, the CD is a potential receptor is not contraindicated for any type of transplant, since the specific treatment, as mentioned, usually suppresses the clinical manifestations of reactivation.

The CCC is ranked second among the heart diseases present in pregnancy and childbirth, only behind rheumatic heart disease. The risk of vertical transmission is substantially greater in the acute phase (62%) than in the chronic phase (1.6%). The impact of CD in the course of pregnancy is controversial. Some studies point to the benignity of this association, while others report high incidence of complications during pregnancy and perinatal mortality and neonatal hypotrophy, considering chagasic pregnant women as a group at high obstetrical risk. Chagasic pregnant women with heart disease have prognostic closely related to the severity of ventricular dysfunction and functional class in early pregnancy. The presence of heart disease, as long as assisted and without severity, provides no contraindication to pregnancy. Patients with heart failure and severe arrhythmias should be discouraged from becoming pregnant.

The rate of vertical transmission with *T. cruzi* presents regional differences, ranging around 1% in Brazil and from 4 to 12% in other Southern Cone countries, and appears to depend on factors related to the parasite and to the host. The high chance of cure for congenital CD makes early diagnosis imperative. In general, newborns are asymptomatic and the more frequent clinical changes are prematurity, low birth weight, fever and hepatosplenomegaly. In the first weeks of life, the diagnosis of congenital infection is based on direct parasitological methods and should be performed in children with clinical manifestations suggesting congenital infection. The microhematocrit technique is easy to perform and has a good sensitivity, especially in the first month of life. If the result is positive, etiological treatment should be immediately started. Congenital CD is considered acute, and therefore notifiable. In case of negative test, diagnostic investigation should be completed with serological tests (with two different techniques) after the 7th month of life. The treatment of Chagas' disease infection in newborns can be done with benznidazole or nifurtimox for 30 to 60 days, with similar results and high curing rates. The criterion for cure is negative serology in tests after treatment.

Chagas' Heart Disease and comorbidities

With an increased life expectancy of patients infected with *T. cruzi,* in many cases we see the presence of comorbidities, including hypertension, coronary heart disease, diabetes mellitus and thyroid disorders.

The control of hypertension and diabetes mellitus in patients with positive serology should as careful and effective as in serologically negative patients, for whom the combination and choice of drugs is similar.

Mainly from 1980, with the increased urbanization of the chagasic population, they began to incur the same risks as those individuals not infected with *T. cruzi*. It is therefore natural that the prevalence of atherosclerotic disease as a cause of acute myocardial infarction be similar in chagasic and non

chagasic patients. It is important to recognize the inherent difficulty in delivering differential diagnosis for Chagas' disease patients with chest pain, which sometimes is severe and disabling. ECG may reveal abnormalities consistent with coronary artery disease (e.g. abnormalities of repolarization, Q waves of fibrosis) or preventing the correct interpretation (such as intraventricular blocks), in addition, these patients often present perfusion disorders. Thus, many patients with Chagas' disease are referred to coronary angiography which, in most cases, reveals angiographically normal coronary arteries.

As a general rule, it is reasonable to prescribe, for Chagas' disease patients with coronary artery disease, the same treatment prescribed for patients not infected with *T. cruzi*.

Constitution of structured monitoring services

Health care and health promotion for patients with CCC should be based on a service structure that allows full action, humanization practices, and quality management.

A multidisciplinary approach is now recognized as the best way to assist patients with chronic diseases. By setting up services designed and geared towards patients with CD, it is important to contemplate their peculiarities, trying to understand them within a biopsychosocial context. Ideally, such structured service should include the following professionals: cardiologist, nurse, psychologist, nutritionist and social worker, and may also include, according to the adoption of new therapies, a physical educator, physical therapist, pharmacist, and occupational therapist. In short, the structured services are primarily responsible for promoting a type of assistance able to provide patients with clinical, psychological and social stability.

Prevention of transmission

The CD is ineradicable due to the persistence of the sylvatic cycle of the *T. cruzi* and cases of oral transmission. However, adequate control (domiciled vector and blood) is highly effective, resulting in the virtual elimination of transmission, which reduces the risk of congenital and transfusion transmission. In general, the control of CD is a duty of the state health systems. Some of this control should be performed by the private systems, particularly private blood banks.

Every professional that will handle the *T. cruzi* should undergo conventional sorology before starting activities. If negative, it should be repeated annually for the duration of the activity. It is important to provide awareness raising and technical training programs, a proper environment to handle the parasite and compulsory use of personal protective equipment (goggles, mask, gloves, closed shoes etc...) Once an accident occurs, local disinfection should be immediately performed (with iodine alcohol or silver nitrate eye drops for eye contamination), immediate conventional serology and specific treatment at usual doses for ten days. After 30 days, serology should be repeated, performing full treatment (60 days) in the event of a seroconversion to positivity.

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