Consensus Statement on Chagas-Mazza Disease

ARGENTINE SOCIETY OF CARDIOLOGY
COUNCIL ON CHAGAS DISEASE "DR. SALVADOR MAZZA"

CHAPTER I. Preface

The challenge to carry out a review and update of a consensus as outstanding as the one conducted in 2002 by leading experts with the aim of introducing new diagnostic and therapeutic tools, as well as paradigm shifts, has not been an easy task. However, we have relied on an outstanding and large team of physicians from the Argentine Society of Cardiology (Sociedad Argentina de Cardiología, SAC) and members of Councils and Districts, who have actively and enthusiastically participated in this project.

Over the past decades, the great development and subsequent impact of new technologies on medical knowledge changed the approach toward certain conditions such as the Chagas-Mazza disease in Cardiology, its most affected area.

The SAC Area of Standardizations and Consensus suggests the review and update of Consensus and Guidelines in the light of the new diagnostic possibilities and knowledge, at least every five years.

PURPOSE

The purpose of this update is not to replace medical criteria regarding each individual patient and his/her socio-economic circumstance, but to be a guide in the description of its evolutionary stages, the early and accurate diagnosis of its cardiac expression, and the search of new treatments that –for different reasons– is not related to major clinical trials and evidence-based medicine.

We would like to thank the SAC Area of Standardizations and Consensus for the opportunity of this update in order to give relevance and significance to Chagas-Mazza disease, not only in Latin America, where it is originated, but also to that acquired in Europe, United States of America, Japan, and Australia due to the constant migrations that have forced the World Health Organization (WHO) to take action for the definitive management of this disease.

Today, this poverty-related disease still causes all types of disabilities, sudden death, and high costs to public health. Chagasic patients have their voice, but they are not heard; it is our duty as healthcare professionals to be their spokespersons to the authorities. Consensus like this one would help to establish state policies and find solutions for the weakest sectors of our society. The poverty rate of 23.3% at the national level and the homelessness in rural areas, with no sewers, running water or poor education and health care services, call for the need of several responses; therefore, it is essential to articulate plans to reverse these realities.

METHODOLOGY

The usual classification of the ACC/AHA and ESC –Classification of Indicators for Diagnostic and Therapeutical Procedures and the types of evidences used in prior SAC Consensus– were used.

CLASSES OF RECOMMENDATIONS

Class I: Evidence and/or general agreement that a given procedure or treatment is useful, and effective.
Class II: conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb: usefulness/efficacy is less well estabished by evidence/opinion.
Class III: evidence or general agreement that treatment method/procedure is not useful/effective and, in some cases, it may be harmful.

LEVELS OF EVIDENCE

Level of Evidence A: consistent evidence from randomized clinical trials or cohort studies with appropriate design to draw statistically accurate and biologically significant conclusions.
Level of Evidence B: Data derived from a unique randomized clinical trial or from major non-randomized studies.
Level of Evidence C: consensus of opinions from experts.

In order to summarize this document, those topics whose scientific information from recent years justifies updates have been dealt with in greater depth. For all the other aspects regarding general, pharmacologic, and exception treatments, please refer to the Consensus Statement on Chagas Disease. Council on Chagas Disease "Dr. Salvador Mazza", Rev Argent Cardiol 2002; 70 (Supl 1):1- -87.

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CHAPTER III. Background

CURRENT SITUATION WITH CHAGAS DISEASE VECTOR IN ARGENTINA

Chagas disease is a trypanosomiasis that, in its chronic form, involves large sectors of the community; its diagnosis and treatment require easy access to health care systems. Due to its morbitidy and mortality, and socio-economic impact, it is one of the diseases with most global burden in the region.

According to recent estimates, the Latin American population exposed to the risk for Trypanosoma cruzi infection is above 108 million, the number of infected patients is higher than 7 million, and the new vector-borne acute cases per year were estimated in 41,200 individuals.

In July, 1991, during the Third Meeting of the Ministers of Health of the Southern Cone, within the framework of the Southern Cone Initiative on Health carried out in Brasilia (Brazil), the six Member States –Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay– elaborated and approved the Resolution 04-3-CS on Zoonotic Diseases, which created an intergovernmental commission for Chagas disease, supported by the Pan American Health Organization (PAHO). Its purpose was the elaboration of a Subregional Action Plan for the elimination of Triatoma infestants in homes, the most common vector in the Southern Cone countries, and the interruption of T. cruzi transmission through blood transfusion. This intergovernmental initiative, with the PAHO/WHO support, had wide health impact in five of the six Member States of the Southern Cone, in which sustained action drastically reduced the T. infestants popualtion and improved the safety of blood for transfusions. As part of this initiative, National Programs were developed to meet the goals of the Southern Cone Initiative (Iniciativa del Cono Sur, INCOSUR); the political support of the governments was essential to provide financial resources for prevention and control of Chagas disease in the different countries. Thus, in 1997, Uruguay was the first country to halt the transfusion and vector transmission in all its endemic area. In 1999, Chile was the second member country to certify the interruption of vector transmission.

In 2000, Brazil certified the interruption in 6 of the 13 states of this country, and gradually in other states, until in 2006, the state of Bahía was the last to certify the interruption. Since then, Brazil was declared free of vector transmission. It was a relevant fact for the neighboring country, which achieved it before the 100th anniversary of the description of the disease by Carlos Chagas.

In 2001, Argentina interrupts vector transmission in five endemic provinces: Jujuy, Río Negro, La Pampa, Neuquén, and Entre Ríos.

INCOSUR produced a reduction in household infestation of the vector in all the member countries of the Southern Cone.

In the Southern Cone countries, the main vector of Chagas disease is Triatoma infestans, which has almost exclusively domestic or paradomestic habits, since it colonizes inside households or in their surrounding areas. Transmission control programs have traditionally been based on spraying houses with residual insecticide and on continuous surveillance for reinfestation with triatomine bugs. Implementing sustained surveillance leads to a reduction of natural infection and also of other forms of transmission, such as blood transfusion or congenital transmission.

CURRENT SITUATION IN ARGENTINA

Up to 1997, vector control actions carried out in our country showed a 92% reduction of the household infestation rate in all the endemic provinces. This reduction correlated with human infestation reduction, which was evident in the T. cruzi infection decrease in young individuals aged 18 from 5.8% in 1983 to 1% in 1996.

Despite these achievements, the poor political priority of health policies at the national and provincial levels, and its consequences –a low economic budget for vector control actions (attack phase) and sustained surveillance– increased Argentinian endemicity with its most accurate indicator: the increased number of acute vector cases.

The enormous challenge for the great objective of the vector elimination is the control of vector transmission in the Great Chaco, an ecosystem that involves Paraguay and Bolivia, but whose greatest area belongs to Argentina. In this hyperendemic area for Chagas disease, resistance of Triatoma infestants to pyrethroids has been recently demonstrated.

CHAPTER IV. Acute chagas disease

MODES OF TRANSMISSION

1. Vector-borne Chagas infection

Infection is transmitted by blood-sucking insects of the order hemiptera, subfamily Triatominae, usually called “kissing bugs”.

There are about 130 species in the triatomine family, and the infectivity of T. cruzi has been demonstrated in more than half of them. In Argentina, there are 17

species distributed in three genres: Psammolestes, Panstrongylus and Triatominae.

Psammolestes: coreodes.

Panstrongylus: megistus, guentheri, geniculatus, and rufotuberculatus.

Triatominae: breyeri, delpontei, garciabesi, infestans, limai, melanosome, platensis, eratyrusiformis, rubrovaria, patagonica, guasayana and sordida.

These species differ in epidemiological significance depending on their habitat, population density, and geographical distribution. In Argentina, T. infestans is the only domiciled triatomine and, therefore, the only one with epidemiological significance. Other species, such as T. guasayana, T. sordida, T. eratyrusiformis y T. patagonica, although they are wild and peridomiciliary species, they often invade and, in some cases, colonize homes; these species have been found to be infected by T. cruzi.

The other species are wild and/or peridomiciliary and do not colonize in homes, so they are not significant for the public health sector.

The infection is caused by the contaminating faeces of these insects, which penetrate through the skin abrasions caused by scratching after the stinging of the kissing bug bite (Figure 1).

After penetrating the body through the skin or mucosal portals of entry, trypanosomas spread vía blood or lymphatic vessels and reach different organs. The protozoa reproduces by binary division in the tissues, multiplying and turning into a nonflagellated stage, called amastigote. In each localization, complex phenomena of destruction, and inflammatory and immunopathological reactions occur, which prolong the disease.

However, this traditional form of vectorial transmission in rural areas has been changing due to internal migrations, and it has been replaced by the cross-contamination between humans in urban areas, in which it occurs through the blood of infected to healthy individuals, with no intervention of the kissing bug. This has given rise to the so-called 4th cycle or urbanization of Chagas disease, characterized by the spread through connatal, transfusional infections, and organ transplant.

Trypanosomiasis cruzi has different stages: it starts with an acute phase characterized by an infection and fever syndrome, and then it is followed by a chronic phase, which may present no evident pathology or may progress with manifested and irreversible lesions, particularly cardiac complications.

Another peculiarity of this disease is the long time that usually goes by after the acute stage, and the disorders of the chronic stage, which appear 20, 40 years –or even more– after the beginning of the disease.

The health and demographic importance of Chagas disease is that it develops forms of fatal disease both in childhood and adulthood.

If a patient is suspected of an acute vectorial form of the disease, it is advisable to evaluate the following information, according to national regulations:

– Epidemiological and ecological history (vector type, household characteristics, place of residence, place of birth/origin, trips to endemic areas, etc.).

– Presence of persistent fever syndrome and tachycardia, which cannot be controlled with conventional medication.

Clinically, this disease may be symptomatic, oligosymptomatic or asymptomatic (Table 1), and acute infection may occur in different forms (Table 2).

Severe clinical expressions in the acute stage include myocarditis and meningoencephalitis. Typical signs of presentation represent less than 5% of the acute cases of Chagas disease. With children under 1 year of age with manifestations of myocarditis, clear-

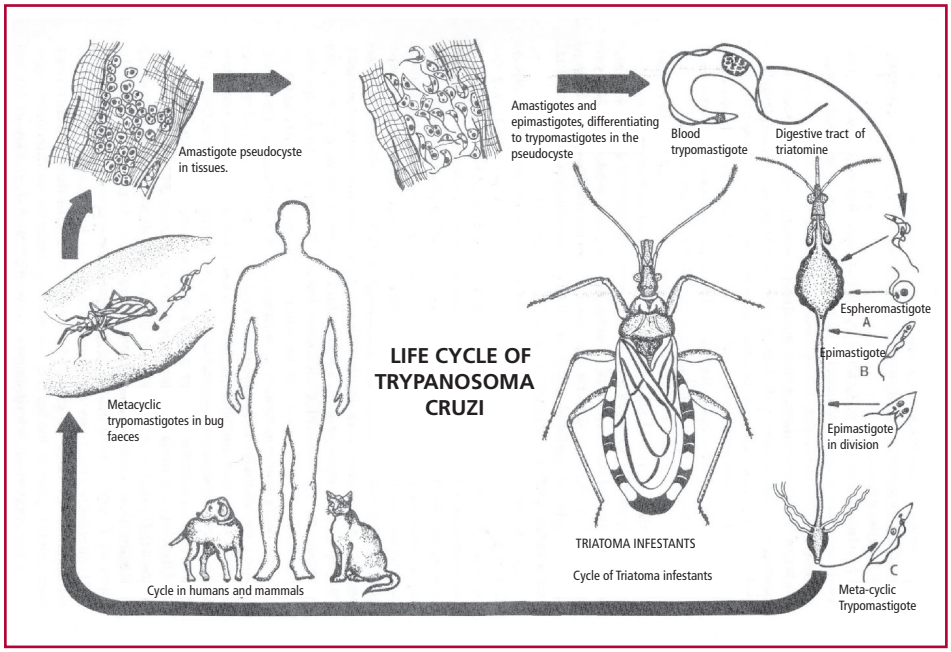


Fig. 1. Life cycle of Trypanosoma cruzi.

fluid meningoencephalitis or febrile or non-febrile seizures, and especially in an endemic area, there is the obligation to confirm or discard the chagasic etiology by studying the parasite in blood and in cerebral spinal fluid.

2. Transplacental (congenital) infection

Class I. Level of Evidence A

A transplacentarian infection may occur only if there is parasitaemia. T. cruzi causes a persistent infection to its host, so the parasite may be found in the peripheral blood both in the acute and chronic stages. This biological fact determines that a pregnant woman can transmit the infection in any of those two stages. Therefore, a serologically positive woman can give birth to babies with congenital infection in a single pregnancy or in subsequent pregnancies.

T. cruzi reaches the fetus through the blood, after its passage through the placenta by active mechanism. In the Hofbauer cells, trypomastigote becomes amastigote, which multiplies until it is liberated again as trypomastigote. These forms penetrate through the trophoblast and infect the embryo or fetus. Infection may occur even before the 4th month of pregnancy, when the trophoblast epithelium shows further development.

The prevalence of this type of transmission remains high, because a large number of pregnant women who go to hospitals and clinics when they are about to give birth are unaware of their chagasic chronic condition, and they are found out about their seropositive status at that moment.

The medical condition in children with congenital Chagas disease can be classified in asymptomatic and symptomatic; in turn, the latter is divided into early and late, whether the symptoms appear before or after 30 days of life. Clinical manifestations vary widely; they include from premature newborns with significant symptoms and high mortality to asymptomatic full-term newborns.

Babies may have nonspecified involvement of their general condition, loss of muscular tone, fever, and usually hepatosplenomegaly. Heart failure is observed in individual cases, and meningoencephalitis with seizures is very rare.

To diagnose congenital chagasic infection, the parasite must be searched for by direct parasitological methods in any newborn from a chagasic woman. In babies older than 6 months, the serologic study will be added, using at least two methods:

after 6 months of age, a seropositive status as a method of diagnosing for congenital Chagas disease has a value outside the endemic area, since within this area, it is impossible to discard vectorial transmission even when there is no apparent portal of entry.

Table 3 shows the clinical manifestations to be considered in any newborn suspected of congenital Chagas disease (Class I).

The sequence to follow for diagnosis and treatment of congenital Chagas disease once the mother has a reactive serology is outlined in Table 3 and Figure 1.

Table 1. Clinical manifestations in the acute phase

Nonspecified symptoms (most common)	Specific symptoms (less common, 5% of the cases)
Persistent fever syndrome	Ophtalmic ganglionar complex
Adenomegaly	Inoculation chagoma
Hepatosplenomegaly*	Inoculation chagoma
Anemia*	Hematogenous chagoma
Anorexia*	Lipochagoma
Irritability or drowsiness	
Seizures	
Edema*	

* Of common occurrence in infants and children under 4 years of age.

Table 2. Classification of the early forms of acute infection

With apparent portal of entry:
Ophtalmic ganglionar complex
Inoculation chagoma
With no apparent portal of entry:
Typical forms:
Hematogenous chagoma
Lipochagoma
Atypical forms:
This subgroup includes general symptoms that constitute an expression of real complications and that, in endemic areas, may lead to suspicion of chagasic etiology:
– Fever
– Anemia
– Edema
– Hepatosplenomegaly
– Tachycardia
– Arrhythmias
– Cardiomegaly
– Heart failure
– Manifestations of meningoencephalitis

3. Transfusional Chagas disease.

Class I. Level of Evidence A

In Latin America, transfusional Chagas disease is the third most common form of T. cruzi transmission. This portal of entry of trypanosomas derives from blood transfusions from asymptomatic infected donors, who are unaware of their condition.

Given the great migration of people from rural areas to urban centers, the latter now includes serologically positive population. This increases the risk of transmission of the infection through transfusions from the potential donors and is the main cause of spread in large cities.

The incubation period in transfusional Chagas disease varies between 28 and 116 days (Table 4).

Chagas disease and immunosuppression:

Immunodeficiency for different infectious conditions such as AIDS causes severe clinical manifestations in different organs, which should be detected and treated early (Class I. Level of Evidence A).

Reactivity for Trypanosoma cruzy should be known in transplant recipients, since reactivations, as well as infections, have a favorable response to early treatment (Class I. Level of Evidence A).

Lately, severe acute cases of infection (including deaths) acquired by oral intake of juices in Brazil (Santa Catarina, year 2005), and in Venezuela (Caracas, year 2010) have become relevant.

LABORATORY DIAGNOSIS

Class I. Level of Evidence A

Acute stage

Diagnosis is confirmed by finding the Trypanosoma cruzi, but performing a serology test to discard or confirm the early contact with the parasite should also be considered (Figure 2).

Determinate and indeterminate chronic stage

In the chronic stage, either determinate or indeterminate, laboratory diagnosis is very important. At this point, the little or no concentration of circulating parasites and antibodies against Trypanosoma cruzi contained in the serum should be considered.

CHAPTER V. Pathophysiology

CHRONIC CHAGAS DISEASE

Clinical classification of Chagas-Mazza disease

See classification in Table 5.

CONSIDERATIONS OF PATHOGENESIS IN THE CHRONIC STAGE

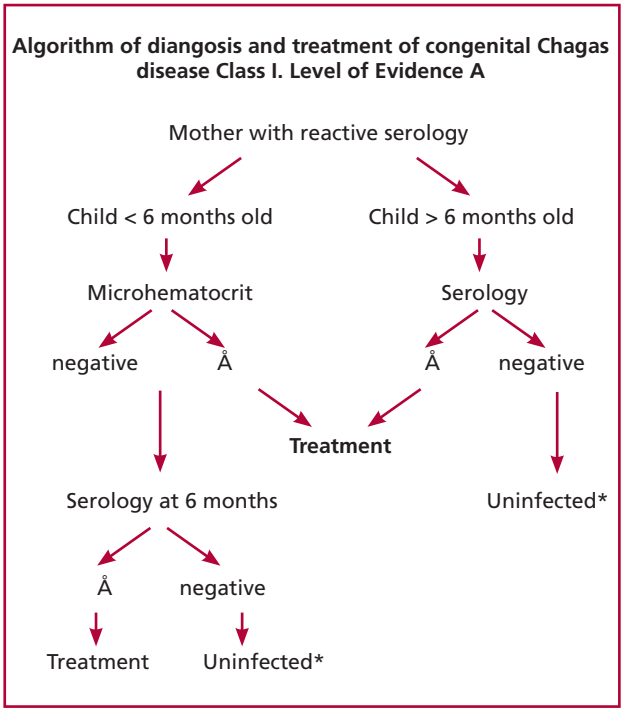
Postulated mechanisms:

- Direct aggression by the parasite or through a neurominidase.
- Microvascular theory.
- Immunological theory.
- Neurogenic theory.

Table 3. Congenital Chagas disease

In newborns, the following clinical manifestations should be evaluated:
– Hepatomegaly
– Splenomegaly
– Jaundice
– Prematurity
– Persistent tachycardia
Less common signs:
– Severe forms: sepsis, myocarditis, edema, adenopathy, fever, rash, chagoma
– Rare forms: megaesophagus, megabladder, cerebral calcifications, etc.

Fig. 2. Algorithm of diangosis and treatment of congenital Chagas disease. *National diagnostic guidelines suggest performing a new study at the age of 12 years.



* Of common occurrence in infants and children under 4 years of age.

Table 1. Relationship between professional activities and competence areas

Major signs	Minor signs	Laboratory	Diagnosis	D. differential
Fever 37.5 to 38.5 ºC	Edemas	Anemia	Direct methods	Cytomegalovirus
Adenomegalies	Hepatomegaly	Limpho-monocytosis	Blood culture	Toxoplasmosis
Splenomegaly	Fleeting rash	Eosinophilia	Xenodiagnosis	Sepsis
		Normal or sightly	Serology	Infectious pathologies
		high ESR		False positive serology

* By the law 22,990 (year 1983), in Argentina it is mandatory to control donors' blood (HAI-ELISA). In case of positive result, blood is discarded and donor is advised to receive medical attention due to positive serology.

Results from myocardial damage would be: a) global and segmental motility disorders, b) arrhythmias and conduction disorders (due to injury of the excitoconduction system), c) valve incompetence (due to regurgitation), d) heart failure.

DISORDERS IN MICROCIRCULATION, ENDOTHELIAL DYSFUNCTION AND ISCHEMIA DURING THE CHRONIC STAGE WITHOUT DEMONSTRABLE PATHOLOGY (EX INDETERMINATE PERIOD)

Even since the first descriptions, changes in small coronary vessels found in autopsies on patients who had died of this disease were already mentioned. Miguel Jörg described a "universal capillaritis".

Contemporary authors include, in the first place, P. Cossio and his group, with their description of the antibody against the endothelium, the vascular structures, and muscle interstitium (EVI), both in acute and chronic cases, and also in experimental studies; in some cases, they were studied with biopsy and reactive EVI, which showed lesions consistent with cell hypoxia.

More than 30 years ago, Tanowitz et al highlighted the precocity of finding the disorders in microcirculation, both in experimental models and in endothelial cell cultures of parasited patients. They have also pointed out about spasms and thrombosis in microcirculation from the earliest acute stages.

Recently, Rossi remarked that microvascular disorders were the cause of chagasic cardiomyopathy development in a long evolutionary process, relating it to a deterioration in autonomic balance.

Marin-Neto and Simões analyzed the role of microcirculation in the progress of the chronic stage of Chagas disease, with special emphasis on pointing out microvascular condition as the main cause of the lesions that are typical of the most advanced stages of the cardiopathy, in combination with the autonomic nervous system disturbances. After 5 years of follow-up, patients with no organ involvement in which endothelial dysfunction was detected had a significant drop in the ejection fraction compared with those whose endothelial function was not evident.

The group of Acquatella and Palacios has also demonstrated that chagasic patients with angiographically normal coronary arteries progressed to precordial pain and even had signs of myocardial infarction in ECG or ventricular aneurisms; it was a

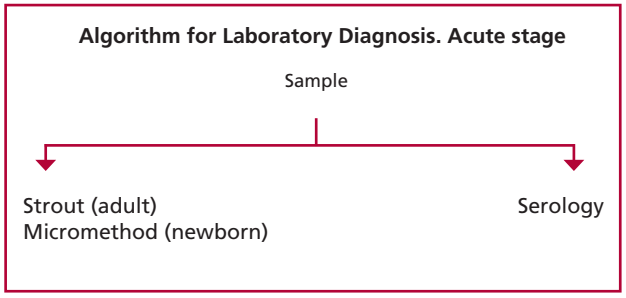


Fig. 3. Algorithm for laboratory diagonsis in the acute stage.

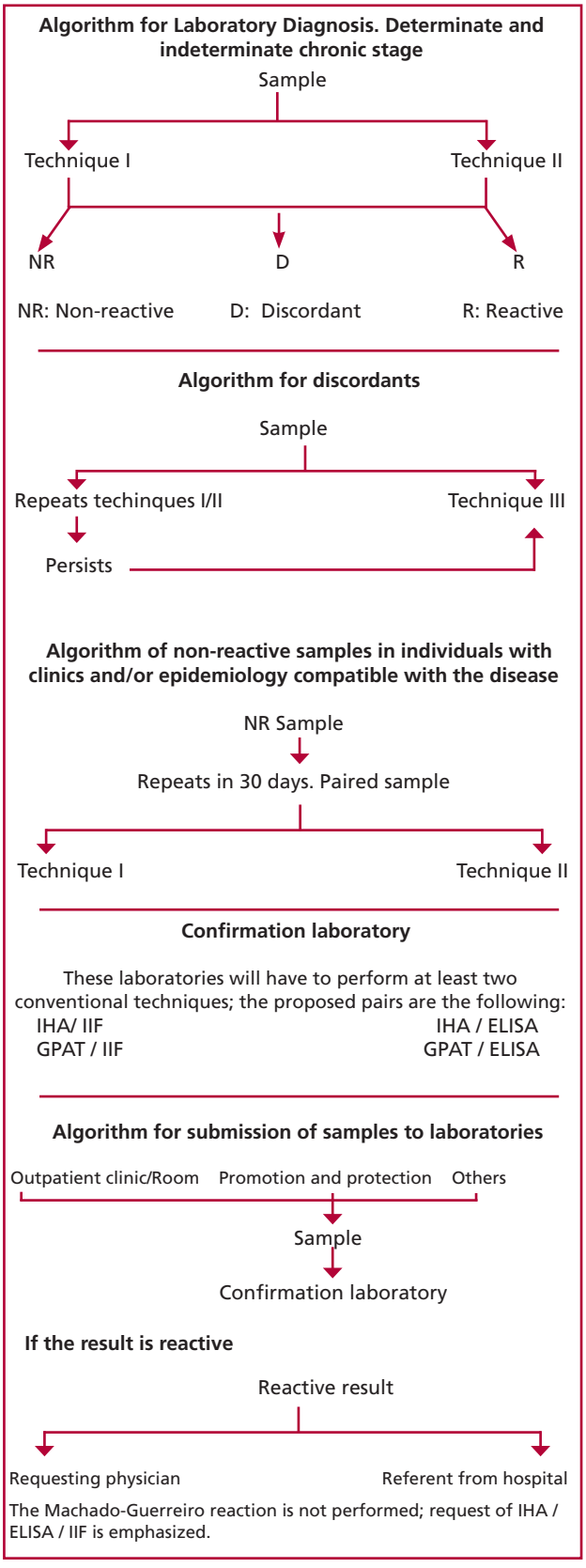


Fig. 4. Algorithms for Laboratory Diagnoses. Determinate and indeterminate chronic stage. GPAT: Gelatin particle agglutination test. IHA: Indirect hemagglutination. ELISA: Enzyme-linked immunosorbent assay. IIF: Indirect immunofluorescence.

Table 5. Clinical classification of Chagas-Mazza disease

ACUTE	VECTORIAL	CONGENITAL	TRANSFUSIONAL	TRANSPLANTS/ORAL/ LABORATORY ACCIDENTS
CHRONIC	WITHOUT DEMONSTRABLE PATHOLOGY (ex indetermined)			
	WITH DEMONSTRABLE PATHOLOGY		CARDIOLOGIC	A. ARRYTHMIAS
				B. HEART FAILURE
			DIGESTIVE	MEGA-ORGANS
				DYSAUTONOMIA
			NEUROLOGIC	STROKE
				PNS DISORDERS

paradoxical reaction to intracoronary acetylcholine, evidence of endothelial dysfunction in the microvascular territory.

Regarding the molecular territory, the Fatala Chaben Institute calls the attention about the role of interleukins 1 and 6 in the damage to endothelial cells, and points out that these cytokines intervene in the progression of the disease through this endothelial damage. The role of endothelin-1 in vasoconstriction that is present in these phenomena is also postulated. Alterations in the microvasculature show occlusive platelet thrombus in subepicardial and intramural coronary arteries.

DYSAUTONOMIA

Amorin et al, in early stages of the disease, used ergometry and tilt test to analyze the effects of the autonomic nervous system of these patients; they argue that their outcomes are consistent with those postulated about neuronal denervation and autonomic deterioration.

For the first time in the literature about Chagas disease, Junquera Jr. called the attention about the relationship between dysautonomia and sudden death.

Between 1994 and 1997, Sterin-Borda and Borda et al published several works in which they showed the role of antibodies against either beta-andrenergic or muscarinic receptors. They point out the relationship between this detection and the presence of bradycardia and other dysautonomic manifestations. Ribeiro et al concluded that parasympathetic dysautonomia is an early phenomenon that preceds ventricular dysfunction. Iosa et al studied the autonomic system disturbances, which they defined as cardioneuropathy.

Neuronal loss occurs mainly during the acute stage of the disease. Parasympathetic dysautonomia is an early process that may occur before systolic ventricular dysfunction becomes evident, and has been related with malignant arrhythmias and sudden death.

PATHOPHYSIOLOGY OF HEART FAILURE

Once the ventricles are hemodynamically overloaded, a series of adaptative –both hemodynamic and neurohormonal– mechanisms are set in motion trying to maintain pump function. This way, ventricular dilation, ventricular wall hypertrophy, and activation of the sympathetic system, renin-angiotensin-aldosterone system, antidiuretic hormone and atrial natriuretic peptide act as compensating factors.

Myocardial hypertrophy develops as a response to hemodynamic overload. Increased ventricular wall stress leads to the induction of specific proto-oncogenes that synthetize myofibrils. In turn, the increase of sarcomeres causes wall thickening, which reduces ventricular stress because tension excess is distributed among the larger number of sarcomeres. In addition, in the pathologic hypertrophy associated with heart failure, not only sarcomeres but also fibroblasts and interstitial collagen matrix increase, which contribute to the augmentation of wall thickening. This increase of total collagen and collagen type I/III ratio (type I provides greater stiffness to the heart) promotes diastolic heart failure.

Fibrosis, microvascular lesion, and myocardial reconstruction have a key role in chagasic dilated cardiomyopathy. The first one would be the main responsible for the progressive loss of heart contractility, and the second one would be an adjuvant factor for focal myocystolysis with subsequent fibrosis through disruption of the capillary system due to inflammatory infiltration and capillary damage.

The major histopathological finding in the dilated form of chronic chagasic cardiopathy is a difusse myocarditis with severe tissue damage and scarce presence of T. cruzi; this was found in all the autopsies and in 93% of endomyocardial biopsies. Thus, the autoimmune pathogenesis hypothesis would indicate that, even though T. cruzi would be able to produce certain degree of inflammation, it would not be enough to stimulate a dilated cardiomyopathy. The limited presence of parasites in chagasic dilated cardiomyopathy led the researchers to infer that lymphocytes were able to recognize a specific component of the myocardial tissue and generate a type of delayed immunity reaction against it as a result of the chronic infection due to T. cruzi.

PATHOPHYSIOLOGY OF ARRHYTHMIAS

In general, the pathophysiology of sudden death in chagasic dilated cardiomyopathy does not differ from dilated cardiomyopathies from other origins. At this stage of the disease, decreased left

ventricular contractility, poor ejection fraction and, in many cases, the presence of apical aneurysm –that causes malignant ventricular arrhythmias– have a significant role. Also, multiple foci of fibrosis are an important feature in the genesis of ventricular arrhythmias by reentry. Modulating factors include adrenergic hyperactivity and (drug-induced) ionic alterations, which may precipitate sudden death. Moreover, autonomic dysfunction is important in the genesis of sudden death, since non-uniform innervation of the heart in a chagasic patient results in a greater dispersion of ventricular refractoriness. Dysautonomia would cause extreme bradycardias and effects on cardiac conduction, which is responsible, in many cases, of syncopes and sudden death.

The increased activation of the coagulation system through the positive correlation between the levels of fibrinopeptide A and the thrombin-antithrombin III complex, together with increased left ventricular telediastolic volume encourage hypercoagulability, conditioning intramural thrombosis and embolism.

Myocyte apoptosis may contribute to accelerated cell loss in patients with advanced heart disease; thus, activation of angiotensin-aldosterone system, hypertrophy, and dilation may also be stimulated by specific genes that cause premature apoptosis.

CHAPTER VI. Indeterminate Chronic Chagas Disease

DEFINITION

The Chagas disease chronic period without demonstrable pathology (ex indeterminate period) is defined as the preclinical, subclinical, or inapparent stage in which patients have positive serology for Chagas, are clinically asymptomatic, their cardiovascular and digestive checkups do not show manifested signs of disease, and their complementary tests (ECG, chest teleradiography, stress test, Holter, echocardiography, etc.) are normal, as established for each practice.

CONCEPT OF INDETERMATE CHRONIC STAGE

1. Epidemiological history.
2. Positive serology (indirect hemagglutination; immunofluorescence; ELISA).
3. Cardiovascular clinical examination: normal.
4. Complementary tests: normal.
– 12-lead ECG.
– Chest teleradiography.
– Ergometry.
– Doppler bidimensional echocardiogram.
– 24-hour Holter.
5. Normal digestive system.
6. Complementary tests: digestive tests, based on medical criteria.

The simple presence of reactive serology should be considered as a risk factor for development of cardiomyopathy, and even of sudden death. Therefore, any patient with positive serology should be included in secondary prevention. Serology is an important diagnostic and epidemiological surveillance tool. Finding endothelial or dysautonomic alterations would allow to identify vulnerable patients, or at risk for cardiomyopathy in a variable period of years that should be included in secondary prevention, despite not having objectivable clinical manifestations with the current methodology. For that reason, this Consensus, with the purpose of delaying or preventing the disease, proposes flow charts to detect early alterations. Detecting these pathophysiologic alterations will allow to create not only diagnostic but also therapeutic algorithms in the future.

To the strategy of eliminating the vector, the education of the population about the need of periodical checkups should be added.

The new diagnostic technologies detect critical populations, who should generate different strategies in public health, with physicians trained in primary care attention, cardiology, and prevention, educating the community about the nature of this disease. At the same time, the State should set sustained policies of economic development and social inclusion.

STUDY METHODOLOGY

– Serology for Chagas disease (Class I. Level of Evidence A).
– Basic laboratory tests: blood count, glycemia, urea, creatinine, cholesterol, liver function test, and urine.
– 12-lead ECG (Class I. Level of Evidence A).
– Chest teleradiography (Class I. Level of Evidence A).
– Exercise stress test graduated according to incremental protocol (Class I. Level of Evidence C). T-wave alternans analysis.
– 24-hour Holter monitoring. Heart rate variability analysis (Class I. Level of Evidence C). QT interval dispersion analysis (Class IIb. Level of Evidence C). Heart rate turbulence analysis.
– Bidimensional echocardiogram (Class I. Level of Evidence C).
– Bidimensional-Doppler (Class I. Level of Evidence C).
– **Exploration of autonomic nervous system** (Class I. Level of Evidence C):
  – Active posture manoeuvre.
  – Hyperventilation test.
  – Valsalva manoeuvre.
  – Tilt test.
  – Antibodies against muscarinic receptors.
– **Exploration of endothelium** (Class I. Level of Evidence C):
  – Thrombomodulin.
  – Brachial echo-Doppler:
– **In tertiary care hospitals, based on medical criteria** (Class IIb. Level of Evidence C):
  – Studies with radiotracers: Rest/stress Tc 99m sestamibi gated myocardial perfusion SPECT,

to assess perfusion and ventricular function simultaneously.
– Cardiac MRI with gandolinum to evaluate if there is myocarditis.
– B-type natriuretic peptide (BNP).
– Assessment of anatomical-myocardial substrate
– Signal-averaged ECG (Class IIb. Level of Evidence B).
– Analysis of fibrosis (Class IIb. Level of Evidence C).

Appropriate tests in case of heart disease of other origin or comorbidities:
– Invasive tests (Class III. Level of Evidence B).
– Electrophysiological studies (Class III. Level of Evidence B).
– Cardiac catheterization and coronary angiography (Class III. Level of Evidence B).
– Endomyocardial biopsy (Class III. Level of Evidence B).
– Study of the digestive system: based on gastroenterological crieria.

ETIOLOGICAL TREATMENT WITH PARASTICIDE DRUGS

Its usefulness is demonstrated (serological negativization) until the age of 14 years (Class I. Level of Evidence B). In the absence of evidence at older ages, the physician should reach a consensus with the patient about its indication, explaining the therapeutic results not fully confirmed yet, and its adverse effects (Class IIb. Level of Evidence C).
a) Nifurtimox 8 to 10 mg/kg/day for 60 days.
b) Benznidazol 5 mg/kg/day for 30 to 60 days.

CONTROL AND FOLLOW-UP

Class I. Level of Evidence C.

No proven alteration:
Every 12 months: cardiovascular clinical examination, conventional ECG, chest teleradiography, ergometry, 24-hour Holter, and M-mode and bidimensional echocardiography.

It is important to point out that:
1. Any patient with positive serology must be included in a secondary prevention plan.
2. In Argentina, the law 26.281, in its article 5th, prohibits to perform serologic reactions to determine Chagas disease infection in applicants to any job or work activity.
3. Chronic patients without demonstrable pathology can work normally.
4. They can practise sports normally, according to their functional capacity.
5. They cannot donate blood.
6. Newborns whose mothers are within this period must be tested for parasites. Mothers must be included in secondary prevention.
7. The indeterminate chronic period is very long. The disease develops only in 20-30% of the patients.

While in rural areas cultural and socio-economic conditions are not ideal for treating a chronic long-term disease, it will be advisable that the rural physician refers the patient to tertiary care hospitals to have periodical checkups, and thus ensure the access to early diagnosis. Primary attention should not necessarily be primitive.

CHAPTER VII. Arrhythmias in chagas disease

This section includes the ECG disorders in Chagas disease outside of the acute stage.

STUDY METHODOLOGY

– Once a positive serology patient is detected, it should be determined what the degree of heart disease this patient has.
The value of echocardiography and Doppler in Chagas disease with arrhythmias (Class I. Level of Evidence A) is based on:
1. Early detection of ventricular diameter changes and their follow-up in subclinic stage of the disease.
2. Determination of systolic and diastolic functions.
3. Determination of wall motion changes with areas of hypokinesia, akinesia, and/or dyskinesia.
4. Detection of ventricular aneurysms and intracavitary thrombus.
5. Presence of pericardial effusion.
– Ergometry (Class I. Level of Evidence A).

To be analyzed:
1. Presence of intraeffort (atrioventricular and/or intraventricular) conduction disorders, or during the recovery period.
2. Detection of atrial and ventricular arrhythmias.
3. Determination of functional capacity.
4. Chronotropic assessment.
5. Blood pressure assessment.
– 24-hour Holter monitoring (Class I. Level of Evidence A).
– Signal-averaged ECG (delayed ventricular potentials) (Class IIb. Level of Evidence C).
– Electrophysiological study (Class IIa. Level of Evidence C).

It allows to investigate the following:
1. Sinus node function.
2. Intra-atrial conduction.
3. Atrioventricular and intraventricular conduction.
4. Arrhythmias, and their mechanism.
– Exploration of autonomic nervous system (Class I. Level of Evidence C):
– Active posture manoeuvre.
– Hyperventilation test.
– Valsalva manoeuvre.
– Tilt test.

CHRONIC PERIOD WITH ECG DISORDERS

Common to all examinations on heart rhythm disorders.

Class I. Level of Evidence A
1. Interview. With special attention in the symptoms, time of the day in which symptoms occurred, position (standing, supine, etc.), situation in which they occurred (rest, effort, sexual intercourse, etc.), psychological situations, etc. Assessment of drug action and possible adverse effects.
2. Complete semiotics test. Heart rate. Changes in inspiration and expiration. Lying and standing positions.
3. Routine lab tests, including thyroid hormones.
4. Conventional 12-lead ECG. Bradycardia and tachycardia maneuvers (carotid sinus compression, Valsalva maneuver, arrhythmogenic stress, isometric exercise).
5. Continuous ECG register, Holter system. Heart rate variability.
6. Chest teleradiography (front and lateral).
7. M-mode ECG, bidimensional, and Doppler.

Class II
1. Radioisotope tests (Level of Evidence B).
2. Signal-averaged ECG (Level of Evidence C).
3. Implantable monitoring systems. In case of recurrent syncope and/or traumas of undiagnosed cause in previous studies (Level of Evidence C).

Sinus node dysfunction (specific tests)

The following are added to the general tests:

Class I. Level of Evidence A
1. Pharmacological tests (atropine, isoproterenol).
2. Electrophysiological study. It is indicated when symptoms and results of previous studies mismatch.

Atrioventricular and intraventricular conduction disorders

Class I. Level of Evidence A
1. Electrophysiological study. It is indicated when symptoms and results of previous studies mismatch.

Ventricular tachycardia

The following are added to the general tests:

Class I. Level of Evidence A
1. Radioisotope tests.
2. Coronary angiography.
3. Electrophysiological study with arrhythmia induction if in doubt about the arrhythmia suffered or if transcatheter ablation is to be indicated.

Class IIb. Level of Evidence C
1. High-resolution, signal-averaged ECG, heart rate variability.
2. Endomyocardial biopsy.
3. Magnetic resonance imaging.

Treatment

Arrhythmias and heart failure are two aspects that rule the progression of Chagas disease in its chronic stage:
1. Indication of permanent pacemaker implantation in patients with severe conduction disorders and/or sinus node disease.
2. Pharmacologic or non-pharmacologic therapy of ventricular arrhythmias (SVT and/or NSVT).
3. Electrical treatment of heart failure (see Heart failure).

SINUS NODE DYSFUNCTION

Its main indication is the permanent pacemaker implantation.

Indication of pacemaker

Class I
1. Irreversible sinus node dysfunction, spontaneous or induced by necessary and irreplaceable drugs, with syncope, presyncope or dizziness and/or heart failure related to bradycardia (Level of Evidence A).
2. Symptomatic brady-tachy syndrome (Level of Evidence A).
3. Asymptomatic brady-tachyarrhythmia that requires additional antiarrhythmic treatment (Level of Evidence B).
4. Intolerance to efforts, clearly related to chronotropic incompetence (Level of Evidence B).
5. Brachy-tachy syndrome with paroxysmal atrial arrhythmias and high ventricular response, uncontrollable with drug therapy; AV node ablation is indicated prior to pacemaker implantation (Level of Evidence B).

Class II
1. Asymptomatic sinus node dysfunction, with chronotropic incompetence and heart rate lower than 40 beats per minute in waking hours (Level of Evidence B).
2. Sinus bradyarrhythmia that results in or worsens a heart failure, angina, or tachyarrhythmia (Level of Evidence B).

Class III
1. Sinus node dysfunction in asymptomatic patients (Level of Evidence B).
2. Sinus node dysfunction with symptoms independent from bradycardia (Level of Evidence B).

Recommendations to indicate the pacing mode

Class I
1. DDD/R if there is advanced AV block (Level of Evidence A).
2. AAI/R with automatic reversion to DDD/R if there is intermittent advanced AV block (Level of Evidence B).

Class IIb
1. VVI/R for the elderly, in the absence of

ventriculoatrial conduction (Level of Evidence B).
2. AAI/R in the presence of normal atrioventricular and intraventricular conduction. (Level of Evidence A).

Class III
1. VVI/R, VDD/R in the presence of retrograde ventriculoatrial conduction (Level of Evidence C).
2. AAI/R in the presence of advanced AV block (Level of Evidence C).

Recommendations to activate the response in heart rate.

Depending on the heart disease, associated diseases and lifestyle.

ATRIOVENTRICULAR BLOCKS

The presence of associated arrhythmias, left ventricular ejection fraction, life quality, patient's physical condition, and need to maintain the AV syncrony are factors to be considered when a pacemaker is indicated and the pacing mode is applied.

First-degree AV block

Class I
1. Irreversible first-degree AV block with dizziness, presyncope, or syncope, whose electrophysiological study shows an intra-Hisian or infra-Hisian block, worsening by atrial stimuli or pharmacological test (Level of Evidence B).

Second-degree AV block

Class I
1. Symptomatic permanent or intermittent second AV block, irreversible or caused by necessary or irreplaceable drugs, independent of the type of localization, with defined symptoms of low cerebral blood flow or heart failure resulting from bradycardia (Level of Evidence B).
2. Symptomatic second degree AV block Mobitz type II with narrow QRS (Level of Evidence B).
3. Irreversible asymptomatic second degree AV block, associated with ventricular arrhythmias requiring treatment with conduction depressants.

Class II
1. Asymptomatic second degree AV block, permanent or intermittent (Level of Evidence B).
2. Second degree AV block Mobitz type II with narrow QRS, asymptomatic, permanent or intermitent (Level of Evidence B).

Class III
1. Asymptomatic second degree AV block type I, with increased heart rate and improvement in AV conduction with physical exercise and/or intravenous atropine (Level of Evidence B).

Third-degree AV block

Class I
1. Full AV block, symptomatic, permanent or intermittent and irreversible (Level of Evidence A).
2. Full AV block, asymptomatic, irreversible, intra-Hisian or infra-Hisian localization, and with a critically low intraventricular escape rhythm (Level of Evidence A).
3. Full AV block, asymptomatic, irreversible, with narrow QRS, with ventricular arrhythmias that require automaticity depressing antiarrhythmic agents (Level of Evidene B).
4. Acquired full AV block, irreversible, asymptomatic, with heart rate lower than 40 beats per minute in waking hours, with no increase during daily activity (Level of Evidence A).
5. Full AV block, irreversible, asymptomatic, with documented periods of asystole longer than 3 seconds in waking hours (Level of Evidence A).
6. Full AV block, irreversible, asymptomatic, with progressive cardiomegaly (Level of Evidence B).
7. Full AV block, irreversible, permanent or intermittent, as a result of AV node ablation (Level of Evidence A).

Class III
1. Transient complete AV block by drug or chemical action, or any other reversible cause.

Recommendations to indicate the pacing mode

Class I
1. DDD/R with sinus node dysfunction and stable atrium (Level of Evidence A).
2. DDD/R with retrograde ventriculoatrial conduction (Level of Evidence B).
3. VVI/R with permanent atrial fibrillation (Level of Evidence B).

Class II
1. VDD with normal sinus function (Level of Evidence B).

Class III
1. AAI/R or VVI/R with retrograde ventriculoatrial conduction (Level of Evidence B).
2. VDD with sinus node dysfunction (Level of Evidence B).

INTRAVENTRICULAR BLOCK

Complete right bundle branch block (CRBBB) alone or associated with left anterior hemiblock (LAHB) are the most common conduction disorders of chagasic cardiopathy, but of poor prognostic value. Complete left bundle branch block (CLBBB) and left posterior hemiblock are uncommon, but their presence is related to unfavorable prognosis.

Permanent pacemaker implantation

Class I
1. Alternating bilateral bundle branch block, documented, asymptomatic or with syncope, presyncope or recurrent dizziness (Level of Evidence C).

Class IIa
1. HV interval longer than 70 msec., spontaneous or with intra-Hisian or infra-Hisian block, induced by atrial stimulation or pharmacological test, in patients with syncope, presyncope, or recurrent dizziness with no predetermined cause (Level of Evidence C).
2. Asymptomatic patient with spontaneous HV interval longer than 100 msec (Level of Evidence C).

Class IIb
1. Bundle branch or bifascicular block associated or not with first-degree AV block without documentation of paroxysmal complete AV block (Level of Evidence C).

Recommendations to indicate the pacing mode

Class I
1. VVI/R with permanent atrial fibrillation (Level of Evidence B).
2. DDD/R with sinus dysfunction (Level of Evidence B).
3. DDD/R with retrograde VA conduction (Level of Evidence B).

Class II
1. DDD/R with normal sinus function but no ventriculoatrial conduction (Level of Evidence C).
2. VVI/R without retrograde ventriculoatrial conduction (Level of Evidence C).
3. VDD with stable atrium and normal sinus function (Level of Evidence C).

Class III
1. AAI/R (Level of Evidence B).
2. VVI/R with retrograde ventriculoatrial conduction (Level of Evidence B).
3. VDD with unstable atrium or sinus node dysfunction (Level of Evidence B).

VENTRICULAR ARRHYTHMIAS

Primary prevention

Recommendations for a cardiodefibrillator implantation in primary prevention of sudden death for patients with chagasic cardiomyopathy

Class I
– A CDI is indicated in patients with ventricular dysfunction or parietal dyskinesias associated with syncopes of unknown origin with inducible VT/VF in the electrophisiological study, regardless of hemodynamic tolerance (Level of Evidence B).

Class IIa
– The CDI is reasonable in patients with syncope of unkown origin and with significant ventricular dyskinesia or dysfunction (Level of Evidence C).

Secondary prevention

Survivors of a heart attack due to ventricular tachycardia or ventricular fibrillation have a high degree of recurrence within the year after the event. For many years, different types of antiarrhythmic drugs were used in order to prevent a new episode. The amiodarone proved to be likely the only drug particularly effective in patients with ejection fraction higher than 35-40%. However, today, the introduction of CDI is considered the most important advance for treating the recurrence of these episodes.

Recommendations for a cardiodefibrillator implantation in secondary prevention of sudden death in patients with chagasic cardiomyopathy

Class I
1. Heart attack due to VT/VF of irreversible cause, regardless of the ejection fraction and life expectancy of at least 1 year (Level of Evidence A).
2. A CDI is indicated in patients with spontaneous VT and ventricular dysfunction (or associated parietal dyskinesias), regardless of hemodynamic tolerance (Level of Evidence B).
3. Survivors of a heart attack due to VT/VF of irreversible cause, with ejection fraction > 35% and life expectancy of at least 1 year (Level of Evidence B).

Class IIa
1. Patients with spontaneous, sustained VT, irreversible, with no hemodynamic involvement, and normal ventricular function (ejection fraction > 35%) refractory to other therapies, and life expectancy of at least 1 year.
2. Patients with syncope of unknown origin, with induction of hemodynamically unstable and sustained VT, and life expectancy of at least one year.

Class III
1. Constant VT.

Non-sustained ventricular tachycardia (NSVT) (Level of Evidence C).

Four variables are involved: ventricular function, syncope of unknown origin, NSVT, and induction in electrophysiological study (EPS) with induction:
– Syncope of unknown origin + NSVT + VT/VF induction = CDI (Class IIb).
– Syncope of unknown origin + NSVT + poor ventricular function < 35% = CDI (Class IIb).
– NSVT + poor ventricular function = EPS positive CDI (Class IIb).

– Negative antiarrhythmic drugs (Class IIb).

Rapid supraventricular arrhythmias are not a special circumstance in Chagas disease. Either when they occur as a braditachycardiac sydrome or as atrial fibrillation, atrial tachycardia, supraventricular tachycardia in the context of myocardiopathy, they are not different or special due to Chagas disease. Their treatment, either invasive or with drugs, is the same as that indicated in the Consensus on Arrhythmias by the Electrophysiology Council.

CHAPTER VIII. Chagasic dilated cardiomyopathy – heart failure

EPIDEMIOLOGY

Of the total of infected patients with T. cruzi, 20 to 30% progress to cardiomyopathy, and 10% to the dilated form of this condition.

CHAGASIC DILATED CARDIOMYOPATHY

According to the Remida study, its prevalence is 5.9%. Characteristics: 1) dilated cardiopathy, 2) predominantly in men between 40 and 60 years of age, 3) death between 30 and 50 years of age, 4) complications: arrhythmias (tachyarrhythmias and bradiarrhythmias), biventricular heart failure (prevalence according to the Hospital Study: 5.47%) and thromboembolism.

CLINICAL MANIFESTATIONS OF HEART FAILURE IN CHAGAS DISEASE

See Table 6.

STUDY METHODOLOGY

Diagnostic procedures in patients with chronic chagasic cardiomyopathy are directed to: 1) confirmed diagnosis of heart failure, 2) triggering or worsening causes, 3) analysis of the disturbed ventricular function, 4) assessment of functional disturbances, 5) assessment of the therapeutic response, 6) progressive and prognostic criteria. In this topic in particular, the study methodology will be evaluated on chagasic patients, dilated in the presence of: a) decompensated heart failure, and b) chronic heart failure.

A. Decompensated heart failure

Class I

1. Complete semiotics test.
2. Conventional 12-lead ECG.
3. Complete routine lab tests.
4. Continuous monitoring: ECG, pulse oximetry, invasive or non-invasive blood pressure, and body temperature.
5. Chest X-ray.
6. Doppler and bidimensional echocardiogram.

Class II

1. Evaluation of invasive ventricular function (Swan-Ganz) when there is no response from the conventional treatment.
2. Continuous register of 24-hour Holter monitoring.

Class III

1. Ergometry.
2. Myocardial perfusion at rest/stress.
3. Cardiac catheterization: in patients with life-limiting illness (cancer, HIV, etc.) that prevents from a major cardiovascular surgery.

B. Chronic heart failure

Class I

1. Clinical examination.
2. Conventional 12-lead ECG.
3. Chest teleradiography (front and lateral).
4. Complete routine lab tests.
5. Doppler and bidimensional echocardiogram.
6. Continuous register of 24-hour Holter monitoring.
7. Invasive tests: Catetherism or electrophysiological study (they will only be Class I in case of history of sudden death and/or severe ventricular arrhythmias).

Class II

1. Ergometry: in patients on functional class I to III, to assess therapeutic response.
2. Six-minute walking test.
3. Myocardial perfusion at rest/stress.
4. Transesophageal echocardiogram.
5. Oxygen consumption.
6. Endomyocardial biopsy: in patients on the waiting list for a heart transplant.

Class III

1. Ergometry: in patients on functional class IV or severe ventricular arrhythmias at rest.
2. Cardiac catheterization: in patients with life-limiting illness (cancer, HIV) that prevents from a major cardiovascular surgery.
3. Endomyocardial biopsy: in patients who are not referred for transplant.

C. Ventricular aneurysm of chagasic origin in the presence of dilated cardiomyopathy

Class I

1. Same tests as in A or B.
2. Electrophysiological study: prior to aneurysmectomy for mapping ventricular arrhythmia.

Class II

1. Same tests as in A or B.

Class III

1. Ergometry: in the presence of complex ventricular arrhythmia or functional class IV.
2. Angiography: if aneurysmectomy is not being performed.

TREATMENT OF CHRONIC DILATED CHAGASIC CARDIOMYOPATHY

Treatment of heart failure in chagasic cardiomyopathy is targeted on the neurohormone mechanisms that perpetuate or worsen the disease. Therapies should be oriented to improve lifestyle, to have a healthy diet, and to administer medications that change the natural evolution of the disease, such as angiotensin-converting enzyme inhibitors, aldosterone receptor antagonists, and beta-blockers. In appropriate cases, electrophysiological devices are effective (pacemakers, resynchronization devices, cardiodefibrillators), and other invasive treatments (Figure 4).

The new **ACC/AHA classification** for HF allows to differentiate risk stages for the development of the disease and HF stages in itself, and to establish their corresponding treatment. Stages A and B of this classification correspond to asymptomatic patients, in functional class (FC) I from the New York Heart Association (NYHA), while stages C and D correspond to patients with HF syndrome, in FC II to IV from the NYHA.This classification can also be applied to Chagas disease (See Figure 4).

Stage A: patients at high risk for the development of the disease, but without structural myocardial damage, who should be indicated primary prevention. This stage may include seropositive patients with no evidence of cardiomyopathy, and those with arrhythmias and conduction disorders, but without evident myocardial condition in the echocardiogram.

Stage B: patients with structural myocardial damage, who should be applied secondary prevention measures. The echocardiogram is of vital importance for evaluation at this stage. Ventricular remodeling, regional contraction disorders, dilation, and asymptomatic ventricular dysfunction are components of chagasic cardiomyopathy in stage B.

Stage C: patients with structural heart damage that have already developed signs and symptoms of HF. At this stage, general measures for HF, drug therapies, and ocassionally electrophysiological devices are recommended, so as to improve life quality and reduce mortality.

Stage D: patients with advanced HF, severe deterioration of ventricular function and functional capacity, refractory to optimal treatment available, and recurrently hospitalized; these patients require specialized interventions: intravenous inotropes, mechanical circulatory support, cardiac resynchronization therapy, heart transplant, experimental surgeries, cell therapy, etc.

With the purpose of summarizing this Consensus, only the special points for chagasic cardiomyopathy are mentioned.

GENERAL MEASURES

General –non pharmacological– measures are as important as drug therapy, and prognosis of the disease and life quality of the patient will largely depend on their compliance. Achieve an appropriate adherence to treatment is one of the most important objectives, especially considering the low socio-economic status of patients with Chagas disease, which makes it difficult for them to access to checkups and therapeutic measures.

Patient education, body weight control, low-sodium diet, fluid restriction in patients with severe symptoms or with hyponatremia, abstinence from smoking or alcohol, and regular physical activity in stable patients should be promoted. Programs of HF management may result highly useful, when they are available.

DRUG THERAPY

Chagasic cardiomyopathy has poor Level A evidences for its treatment. For that reason, recommendations will be based on evidences from Level B studies or on the experts' opinions (Level C).

Angiotensin-converting enzyme (ACE) inhibitors:

– Asymptomatic patients with EF < 40% or mild to severe HF (FC I-IV, stages B, C, and D) should be administered ACE inhibitors, unless there are contraindications or they are not tolerated (Class I. Level of Evidence B).

Angiotensin II receptor antagonists (ARA-II)

Its use in HF is more controversial. The SAC Consensus on HF suggests to indicate ARA-II in the following situations:

– Asymptomatic patients with EF < 40%, or mild to severe HF (FC I-IV, stages B, C, and D) with intolerance to ACE inhibitors (Class I. Level of Evidence B).
– Patients with EF < 40% and symptomatic HF (stages C and D) under treatment with optimal doses of ACE inhibitors and BB, unless they are treated with AA (Class IIb. Level of Evidence B).

Devices and systems	Signs and symptoms
Cardiovascular	Palpitations, atypical angina, syncope, bimalleolar edemas, hepatojugular reflux, hypotension.
Respiratory	Palpitations, atypical angina, syncope, bimalleolar edemas, hepatojugular reflux, hypotension.
Gastrointestinal	Anorexia, nauseas, congestive hepatomegaly with pain in the right hypochondrium and the epigastrium, postprandial heaviness, constipation.
Urinary	Oliguria with nocturia.
Brain	Confusion, headaches, impaired concentration, memory loss.

Table 6. Clinical manifestations of chagasic chronic cardiomyopathy

Beta-blockers

In chagasic cardiomyopathy, the presence of bradycardia and autonomic nervous system disturbances entails taking precautions with the use of beta-blockers (BB).

– Asymptomatic patients with EF < 40% or mild to severe HF (FC I-IV, stages B, C, and D) should be administered BB, unless there are contraindications or they are not tolerated (Class IIa. Level of Evidence B).
– They are contraindicated in patients with bronchospasm, second or third degree of atrioventricular block, sinus node disease, and symptomatic sinus bradycardia (HR < 50 bp/min) (Class III. Level of Evidence B).

Aldosterone antagonists (AA)

Spirolactone might attenuate the fibrotic process, predominant in chagasic cardiomyopathy.

– Patients with EF < 35% and advanced HF (FC III-IV, stage D), unless there are contraindications or they are not tolerated (Class I. Level of Evidence B).
– Patients with moderate HF might benefit from AA (FC II, stage C) (Class IIa. Level of Evidence C).

Hydralazine and isosorbide dinitrate

Today, their indication is restricted to:

– Patients with EF < 40% or symptomatic HF (FC II-IV, stages C and D) who do not tolerate ACE inhibitors or ARA II (Class IIa. Level of Evidence B).

Digoxin

In chagasic patients, automaticity and conduction disorders associated with malignant (or potentially malignant) ventricular arrhythmias restrict their use. Digoxin may worsen dysautonomia, and rhythm and conduction disorders.

Its use is recommended in:

– Patients with atrial fibrillation (AF) with high ventricular response (Class I. Level of Evidence C).
– Patients with AF of moderate response and moderate to severe HF (FC III-IV, stage D) (Class IIa. Level of Evidence C).
– Patients with sinus rhythm, EF < 40% and moderate to severe HF (FC III-IV, stage D), under treatment with optimal doses of ACE inhibitors or ARA II, BB, AA (Class IIb. Level of Evidence B).
– It should not be used in case of Chagas disease with AF of low response, sinus bradycardia, trifascicular bundle branch block, or second or third degree AV block, unless the patient has a pacemaker working properly (Class III. Level of Evidence B).

Diuretics

– Diuretics should be indicated in patients with HF and signs and symptoms of hydrosaline retention (FC II to IV, stages C and D) (Class I. Level of Evidence B).

Oral anticoagulants and antiplatelet drugs

In chagasic cardiomyopathy, oral anticoagulation is indicated in the following cases:

– Atrial fibrillation (permanent, persistent, or

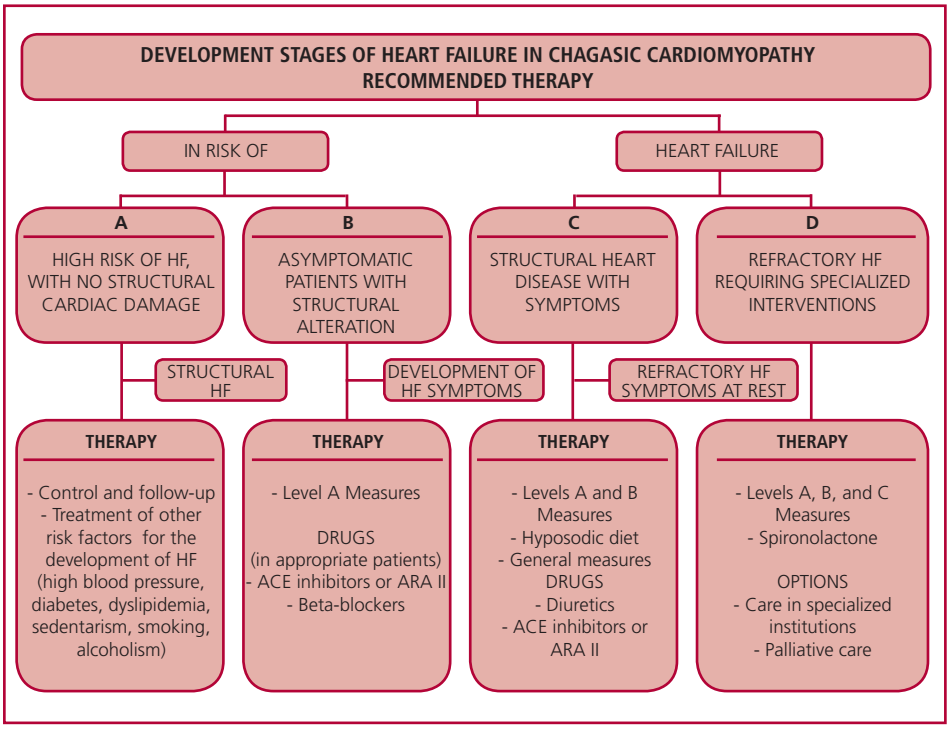


Fig. 5. Number of question by quality value. Exams A and B

paroxysmal) (Class I. Level of Evidence A).
- History of systemic embolism (Class I. Level of Evidence C).
- Evidence by images of intracavitary thrombus (Class I. Level of Evidence C).
- Apical aneurysm with no thrombus evidence (Class IIb. Level of Evidence C).
- Aspirin and other antiplatelet drugs do not have systematic indication in chagasic cardiomyopathy (Class III. Level of Evidence C).

Amiodarone

The GESICA study included 10% of chagasic patients, and it showed a reduction in mortality due to progression of heart failure or sudden death. However, the superiority of BB left aside its indication.
- Amiodarone indication is only justified as treatment of HF in patients with contraindication or intolerance to BB (Class IIb. Level of Evidence B). The drug is usually indicated in cases of arrhythmias.

ANTIPARASITIC TREATMENT

Indicating etiological trypanocidal therapy with benznidazol or nifurtimox in patients with chronic Chagas disease is controversial. The indications are the following:
- Acute chagasic myocarditis on chronic chagasic cardiopathy, as a result of endogenous reinfection in patients with trasplant, with acquired immunodeficiency syndrome (AIDS), or immunodepressed for other reason (Class I. Level of Evidence C).
- Chagasic receptor in organ transplant as profilaxis (Class IIa. Level of Evidence C).
- The indication of antiparasitic treatment is controversial in patients with HF due to chronic chagasic cardiomyopathy (Class IIb. Level of Evidence B).

Summarizing, all patients with HF due to dilated cardiomyopathy of chagasic origin in any of its stages (B, C, or D) should be administered ACE inhibitors (or otherwise ARA II), and BB, provided they are tolerated and there are no contraindications. For symptomatic or with congestive signs patients (stages C and D), general measures and diuretic agents are indicated. For those who have HF in FC III-IV (stage D), an AA is also recommended. Those patients with AF, a history of embolism, or an apical aneurysm with thrombus should be under anticoagulation. Careful digitalization is indicated in AF in cases of high ventricular response. Table 7 shows the doses of the common drugs used in heart failure.

CARDIOVASCULAR REHABILITATION

The main purposes of cardiovascular rehabilitation are to improve life quality and morbimortality, change sedentarism, increase functional capacity, fight stress, reduce anxiety, change risk factors, and promote occupational and social reintegration of patients. Inclusion criteria: patients with chagasic cardiomyopathy in heart failure, classes I, II, and III of the NYHA. Patients in functional class IV of the NYHA, with complex arrhythmias, or history of drug and alcohol addictions should be excluded.

It is important to consider the requirements of energy for daily life and for working activities in order to indicate proper tasks according to the impairment of the patient, as well as take into account the overload that certain physiological acts produce, such as sexual intercourse, excess food, etc. (Figure 5).

ADVANCED HEART FAILURE

According to the Consensus on Heart Failure organized by the Council of Heart Failure of the Argentine Society of Cardiology, "advanced heart failure" is defined as the clinical condition with persistence of symptoms in functional class III-IV of the NYHA, despite the complete and optimized medical treatment (diuretics, BB, ACE inhibitors/ARA II, and AA) in a patient with severe deterioration of ventricular function.

HEART FAILURE. ELECTRICAL TREATMENT

Outcomes of biventricular stimulation, that is, resynchronization, have been good in rare cases, when the patient to be treated has refractory heart failure despite optimal drug therapy, in functional class III-IV with complete left bundle branch block and substantial increase of QRS complex duration (150 msec), and intraventricular and interventricular dyssynchrony and dyskinesia. All large-scale studies were performed in patients with idiopathic or ischemic dilated cardiomyopathy.

Although left bundle branch block is uncommon in chagasic patients, and complete right bundle branch block with anterior hemiblock is highly predominant, some cases have been published which have had a clear benefit through biventricular stimulation.

Like the left bundle branch block, the right bundle branch block has recently been identified as an independent predictor of mortality in patients with congestive heart failure.

Recommendations for a cardiac resynchronizator implantation

Patients with deteriorated left ventricular function and HF present –with a variable frequency– with electrical conduction disorders and contraction dyssynchrony. This dyssynchrony may occur in both ventricles (interventricular), among the different segments of the left ventricle (intraventricular), or may be atrioventricular. It will result in worsening of the ventricular function, with increased ventricular volumes and mitral regurgitation.

The first trials, of physiopathological type, were followed by studies that included endpoints of clinical value (mortality/readmissions).

As a result, the conclusion may be that cardiac resynchronization therapy (CRT) reduces mean mortality in 22% and that readmissions due to heart

failure in 37% of patients with severe deterioration of ventricular function and advanced FC. Mortality reduction is applicable to death both by progression of heart failure and sudden death. In patients with deteriorated ventricular function, sinus rhythm and wide QRS but with poor involvement of functional capacity, two recent studies, MADITCRT and REVERSE, showed that this device improves clinical evolution with no impact on mortality.

It is estimated that 30% of patients with CRT indication are non-responders, that is, with no clinical improvement. This may be due to improper patient selection (absence of mechanical dyssynchrony), necrosis in the site of the left electrode implantation, impossibility to access the site of major dyssynchrony, lack of pacemaker rhythm for long periods, etc. In small studies, some echocardiographic parameters of dyssynchrony have shown effectiveness to identify who will benefit from the transplant, but this has not yet been confirmed in larger multicenter trials. The generalized use of echocardiography is not indicated to select candidates, but it is useful for some patients who are doubtful.

Indications to cardiac resynchronization therapy

Class I

- Patients with chronic HF in FC III-IV (at least 6 month of evolution) under maximal medical] therapy, with EF < 35%, wide sinus rhythm of QRS ≥150 msec (Level of Evidence A).
- Patients with already implanted pacemaker or indication for implantation, and need replacement (probable upgrade), who present with chronic HF in FC III-IV (at least 6 month of evolution) under maximal possible medical therapy, with EF < 35% (Level of Evidence B).
- Patients with indication of CRT, who would also be indicated an ICD:
  - In "secondary prevention": patients with ICD indication (sustained ventricular tachycardia or sudden death) (Level of Evidence A).
  - In "primary prevention", the indication of CRT associated with ICD in young patients who have no severe comorbidities and with a life expectancy > 2 years, particularly with a history of ventricular tachycardia episodes (Level of Evidence C).

Class IIa

- Patients with chronic HF in FC III-IV (at least 6 month of evolution) under maximal medical therapy, with EF < 35%, wide sinus rhythm of QRS between 120-150 msec. It is recommended to evaluate parameters of mechanical dyssynchrony (Level of Evidence B).
- Patients with chronic HF in FC I-II under maximal medical therapy, with EF < 30%, wide sinus rhythm of QRS ≥ 150 msec (Level of Evidence B).

Class IIb

- Patients with chronic HF in FC III-IV (at least 6 month of evolution) under maximal medical therapy, with EF < 35%, with atrial fibrillation and wide sinus rhythm of QRS ≥ 150 msec. It is necessary to produce a pharmacological A-V block, or by ablation of the A-V node, to ensure that most of the heartbeats will be conducted by the resynchronizer (Level of Evidence B).
- Patients with already implanted pacemaker or indication for implantation, and need replacement (probable upgrade) with EF < 35%, but with no clinical evidences of HF. Pacing time required by the patient should be analyzed and, in case it is high, the possibility of CRT may be considered (Level of Evidence C).

Table 7. Doses of the common drugs used in heart failure

Drug	Start dose (mg)	Target dose (mg)
ACE inhibitor		
Captopril	6.25	50-100
Enalapril	2.5	10-20
Lisinopril	2.5-5	20-35
Ramipril	2.5	5
Trandolapril	0.5	4
Perindopril	1.25	5-10
Beta-blockers		
Bisoprolol	1.25	10
Carvedilol	3.125	25-50
Metoprolol	12.5/25	200
Nebivolol	1.25	10
ARA II		
Losartan	25	100
Candesartan	4-8	32
Valsartan	40	160
AA		
Spironolactone	25	25-50
Eplerenone	25	50

ACE inhibitors: Angiotensin-converting enzyme II inhibitors. ARA II: Angiotensin II receptor antagonists. AA: Aldosterone antagonists.

HEART TRANSPLANT

Chagasic cardiomyopathy is no longer a contraindication for heart transplant (HT), since, although it presents difficulties, may be performed successfully.

Recommendations for heart transplant in patients with advanced chagasic cardiomyopathy

Class I

- Patients in cardiogenic shock, under parenteral drugs, MV and/or MCS (Level of Evidence C).
- Patients with advanced HF and high mortality markers (> 30%) within a year, despite the optimal and adjusted medical treatment (Level of Evidence

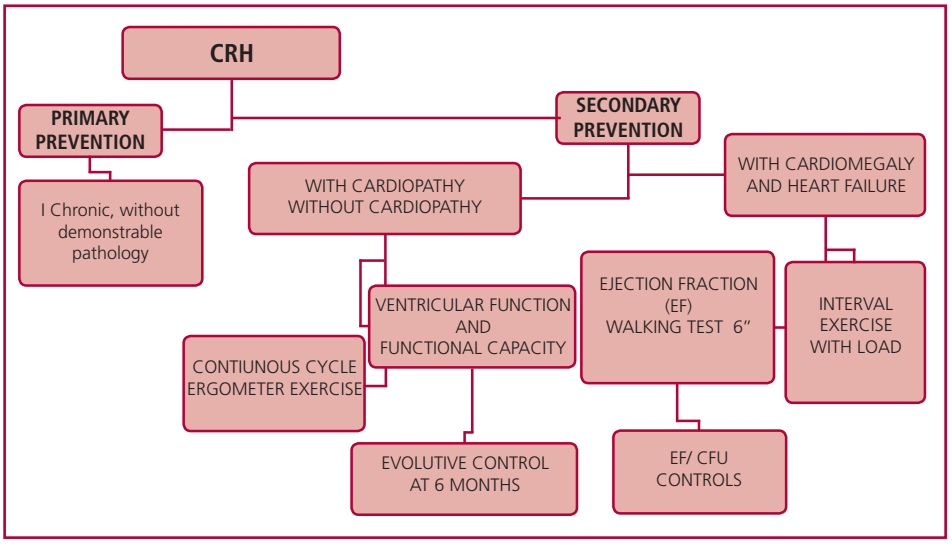


Fig. 6. Cardiac rehabilitation algorithm (CHR) in chagasic disease

C).
- Patients in advanced HF with maximum O2 consumption < 10 ml/kg/min (Level of Evidence C).
- Patients with HF and severe symptomatic ventricular arrhythmia, refractory to antiarrhyth mic treatment and to ICD (Level of Evidence C).

Class IIb
- Patients in HF with maximum O2 consumption between 11 and 14 ml/kg/min: a risk score is proposed to help prognosis stratification (Level of Evidence C).
- Patients with HT indication and relative contraindication (Level of Evidence C).

Class III
- Patients with HF under incomplete medical treatment (Level of Evidence C).
- Patients with absolute contraindications for HT (Level of Evidence C).

SURGERY ALTERNATIVES

The demand of donors for HT fails to satisfy the need for organs, so alternative surgeries have special relevance, not only because they do not require donors but also because their outcomes are comparable to those of transplants.

The scenario offered by the cell therapy with stem cells is encouraging; its procedures are being clinically developed, and promising experiences are being collected, both for ischemic and non-ischemic cardiomyopathy, even in Chagas disease.

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