Diagnosis and management of Chagas disease and cardiomyopathy

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Abstract | Chagas cardiomyopathy is the most severe and life-threatening manifestation of human Chagas disease—a 'neglected' tropical disease caused by the protozoan parasite *Trypanosoma cruzi*. The disease is endemic in all continental Latin American countries, but has become a worldwide problem because of migration of infected individuals to developed countries, mainly in Europe and North America. Chagas cardiomyopathy results from the combined effects of persistent parasitism, parasite-driven tissue inflammation, microvascular and neurogenic dysfunction, and autoimmune responses triggered by the infection. Clinical presentation varies widely according to the extent of myocardial damage, and manifests mainly as three basic syndromes that can coexist in an individual patient: heart failure, cardiac arrhythmia, and thromboembolism. NYHA functional class, left ventricular systolic function, and nonsustained ventricular tachycardia are important prognostic markers of the risk of death. Management of Chagas cardiomyopathy focuses on the treatment of the three main syndromes. The use of β-blockers in patients with Chagas disease and heart failure is safe, well tolerated, and should be encouraged. Most specialists and international institutions now recommend specific antitrypanosomal treatment of patients with chronic Chagas disease, even in the absence of evidence obtained from randomized clinical trials. Further research on the management of patients with Chagas cardiomyopathy is necessary.

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Introduction

Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi*, and is a 'neglected' tropical disease, meaning that it is associated with poverty, neglected by the media and policy makers, and has a major adverse impact on health, quality of life, and socioeconomic development in low-income, developing countries.[1] In the past 3 decades, initiatives in Latin–American countries to minimize infection from vectors and blood transfusions, and appropriately manage patients with Chagas disease, have sharply reduced the incidence of the condition. The WHO estimates that 8–10 million people worldwide currently have Chagas disease.[1,2] Between 1990 and 2009, the estimated annual global mortality from Chagas disease decreased from 45,000 to around 11,000, and the annual incidence of the disease declined from 700,000 to 56,000.[2] However, the infection is no longer confined to Latin America. Individuals with Chagas disease have been identified in nonendemic countries in Europe, the Western Pacific region (mainly Australia and Japan), Canada, and the USA, owing to increased population mobility and migration from endemic countries to the rest of the world.[3] The global spread of the disease increases the risk of parasite transmission through blood transfusion or organ transplantation in countries where screening of blood and organ donors is not obligatory, and a lack of awareness of the disease impedes timely diagnosis and treatment of patients.[2]

Chronic Chagasic heart disease, or Chagas cardiomyopathy, is the most severe and life-threatening manifestation of Chagas disease. Chagas cardiomyopathy eventually affects 20–40% of patients in the chronic phase of the disease, and manifests as heart failure, arrhythmia, heart block, thromboembolism, stroke, and sudden death.[4,5] These abnormalities generally occur in combination, which adds to the complexity and cost of managing these patients. Because Chagas cardiomyopathy affects and incapacitates patients in their most-productive working years, and is associated with high morbidity and mortality, the disease is a major public-health problem in Latin–American countries.[2] Patients with Chagas cardiomyopathy can present in nonendemic countries where knowledge and experience of the disease are limited, which can compromise patient care if Chagas disease is not recognized and appropriately treated.[6] The aim of this Review is to provide a comprehensive and up-to-date overview of the diagnosis and treatment of Chagas disease, focusing on developments and challenges in the management of patients with Chagas cardiomyopathy.

Epidemiology

Chagas disease is a zoonosis transmitted mainly through parasite-laden secretions from blood-sucking triatomine insects ('kissing bugs'), which are found only in the

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American continent from the southern USA to Argentina and Chile.[7] *T. cruzi* can also be transmitted through blood transfusions, which is a matter of concern in nonendemic regions with a substantial Latin–American population, such as in North America and Europe.[8] The disease can also be transmitted from infected donors by organ transplantation, or congenitally from mother to fetus.[9] Oral transmission has gained epidemiological importance after small, sporadic outbreaks of the disease in humans, mostly in the Amazon region, caused by contamination of juices, water, or soup with *T. cruzi* from infected triatomines or other animal hosts.[10] Instances of accidental laboratory transmission of the disease have also been reported.[11]

The disease is endemic in all continental Latin–American countries.[1,7] Figure 1 shows the worldwide distribution of patients with *T. cruzi* infection using the latest official estimates.[1] A coordinated, international program in the Southern Cone countries (Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay) that was launched in 1991 has markedly reduced the transmission of Chagas disease by vectors and via blood transfusion in most countries.[12] Consequently, the incidence of new *T. cruzi* infections across the South American continent has markedly decreased.[13] Similar international initiatives were launched in the Andean countries (Colombia, Ecuador, Peru, and Venezuela) and in Central America (Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama) in 1997, and in the Amazon Basin in 2004. As a result, progress towards the goal of controlling the transmission of Chagas disease has been reported.[13] However, several challenges in the control of Chagas disease in Latin America remain. Active, vector-borne transmission persists in areas of, for example, Argentina, Colombia, El Salvador, and Panama. In addition, several countries including Mexico and Peru either have no national program to control Chagas disease vectors, or have yet to implement one effectively.[14,15] Chagas disease has re-emerged in regions where the disease was previously successfully controlled, such as the Gran Chaco ecoregion that extends primarily over Argentina, Bolivia, and Paraguay, thus reinforcing the need for long-term surveillance and sustainability of prevention programs.[16] Chagas disease has also emerged in regions previously considered to be free from the disease, such as the Amazon Basin, where mainly sylvatic (rather than domestic) vectors transmit the parasite, and oral contamination has been identified as an important route of transmission.[10,17,18] In Brazil, blood-bank screening and vector control over the past 30 years has almost eliminated the acute form of the disease, but 2–3 million patients with chronic infections remain.[13] Because of a cohort effect, Chagas disease is now a public-health problem and a major cause of heart disease, stroke, and death predominantly among elderly individuals (aged >60 years) in the regions in which the disease was historically endemic.[19–21]

The emergence of Chagas disease as a new global challenge has attracted attention from both scientific researchers and health authorities.[7,22–26] In the USA, a few autochthonous, vector-borne infections in humans have been reported in the southern states such as California.[27] However, most individuals in the USA infected with *T. cruzi* are immigrants from endemic areas of Latin America.[24] In 2009, an evaluation of the burden of Chagas disease in the USA estimated that 300,000 individuals were infected with *T. cruzi*, that 30,000–45,000 patients had Chagas cardiomyopathy, and that 63–315 infections were congenital.[23] In Europe, the number of infected individuals is estimated to exceed 80,000. These estimates are made on the basis of approximate numbers of immigrants, many of whom are illegal, and the predicted prevalence of the disease in this population. More than 3,900 laboratory-confirmed infections have been reported during the past 10 years in various European countries, including Belgium, France, Italy, Spain, Switzerland, and the UK.[26]

Key points

- Chagas disease is no longer confined to Latin–American countries and, because of migration of infected patients to developed countries, is now a global problem
- The predominant pathogenic hypothesis is that the persistence of the parasite drives local tissue inflammation, vascular and neurogenic dysfunction, and an autoimmune response, which culminate in progression to Chagas cardiomyopathy
- Several prognostic markers have been described, but NYHA functional class, left ventricular systolic function, and nonsustained ventricular tachycardia have consistently been identified in the majority of studies
- Etiological treatment with trypanocidal drugs for chronically infected adults aged <50 years is recommended by most specialists, although robust evidence of their efficacy obtained from randomized clinical trials remains lacking
- Currently available trypanocidal drugs have substantial toxicity and require careful monitoring; safer and more-effective drugs to treat the infection are desirable
- Studies and clinical trials focused on the management of patients with Chagas cardiomyopathy are required

Pathogenesis

Studies in animals have been crucial in defining the molecular mechanisms associated with the immune response to *T. cruzi* infection.[28] An immune T-lymphocyte type 1 response driven by IL-12, in which IFN-γ production predominates, is critical to the control of acute infection. IFN-γ induces production of several molecules, particularly nitric oxide, which kill parasites in the macrophages. Lytic antibodies also seem to be important in reducing parasite replication during the acute infection.[29] These immune responses eventually control the replication of parasites, but cannot completely eliminate them. Indeed, the persistence of *T. cruzi* throughout the course of infection is an important feature of the chronic disease.[30]

Chronic Chagas disease is characterized by multifocal mononuclear inflammatory infiltrates, varying degrees of fibrosis, constant low-grade tissue parasitism, and low or undetectable parasitemia. Studies in animals have revealed more about acute Chagas disease than chronic forms of the condition. Additionally, no prospective studies of the immune response in humans before disease progression have been reported. Studies of Chagas cardiomyopathy have, in general, involved comparisons between patients who already have the disease (varying

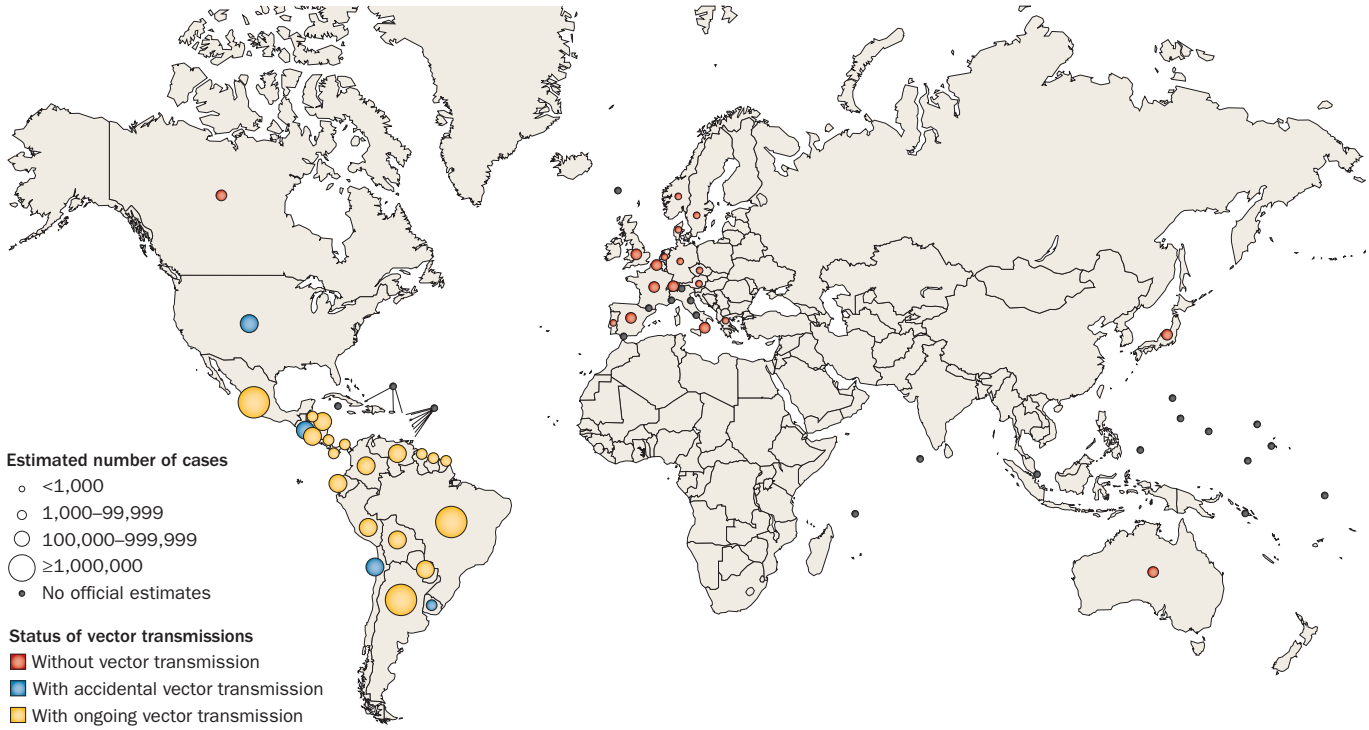

Figure 1 | Global distribution of individuals infected with *Trypanosoma cruzi*. Official estimates of vector transmission between 2006 and 2009; reproduced with permission from the WHO.[1]

severities) with those who do not have the disease, which limits interpretation of the findings.[31] Despite these caveats, several features of chronic Chagas disease have been identified and various hypotheses have been proposed to explain the poor prognosis of some patients. In particular, neurogenic mechanisms,[32] microvascular dysfunction,[33] autoimmunity,[34] and parasite-driven injury[35] might be important contributors to disease progression. These mechanisms are not mutually exclusive, and current thinking is that the persistence of the parasite drives local tissue inflammation, which causes vascular dysfunction, autoimmunity, and neurogenic dysfunction, culminating in severe disease.[35,36] Indeed, the low-grade inflammation and adaptive immune response to the parasite observed in chronic Chagas disease are now accepted to be both necessary and sufficient to control the infection. This phenomenon is demonstrated by the exacerbation of Chagas disease in individuals with HIV or those taking immunosuppressant drugs.[37] Low-grade inflammation causes little damage in the majority of patients with Chagas disease, as indicated by the favorable outcomes of those with the indeterminate form of the disease or with minimal heart damage.[9,38]

In some individuals, Chagas cardiomyopathy (and occasionally esophageal and colonic disease) occurs, which is thought to result from the combined effect of persistent parasitism, parasite-driven tissue inflammation, microvascular and neurogenic dysfunction, and autoimmune responses triggered by the infection.[35] Individuals with Chagas cardiomyopathy have, in general, heightened T-lymphocyte type 1 responses and failure of particular immune control mechanisms, including altered expression of IL-10 and regulatory T cells.[31] Additionally, several autoantibodies have been detected that might contribute to disease progression, but the autoimmune response seems to depend on the continuous presence of parasites.[28,29] The realization that parasite persistence drives the chronic inflammation and autoimmune response has practical consequences for Chagas disease research and treatment of chronic infection. Indeed, the research community has put much effort into identifying targets for vaccine development to prevent infection, and safer and more-effective drugs to treat the disease.[39]

Natural history and symptoms

The natural history of Chagas disease comprises two sequential phases: an initial acute phase, followed by a chronic phase that can be categorized into indeterminate, cardiac, or digestive forms.[9,40] The acute phase is characterized by evident parasitemia observable in direct examination of the blood.[9,40] Symptoms are usually absent or mild; severe acute disease is uncommon.[38] In symptomatic patients, manifestations include entry point signs (inoculation chagoma), fever, generalized adenopathy, edema, hepatosplenomegaly, and myocarditis. Romaña's sign—a unilateral, painless, periorbital swelling—is one of the most-characteristic inoculation chagomas.[41] In endemic areas, the majority of infected individuals are children, in whom mortality from encephalomyelitis or severe cardiac failure is 5–10%.[10] In the setting of acute infections associated with transfusions or transplants, the incubation period can be as long as 4 months, and several factors including immunosuppression can increase the severity of the acute manifestations.[38]

Clinical manifestations of the acute phase of Chagas disease resolve spontaneously after 4–8 weeks. Subsequently, patients enter an indeterminate stage that is defined by a combination of infection (which can be confirmed by either serological or parasitological tests), a normal chest radiograph and electrocardiogram (ECG), a normal barium swallow and enema, and the absence of clinical signs and symptoms of disease.[42] About 50% of individuals infected with *T. cruzi* in endemic areas have the indeterminate form of the disease, and have a life expectancy similar to individuals without Chagas disease.[42,43] However, some patients have abnormal responses when tested by noninvasive cardiac examinations.[42,44] In a study of 505 patients with the indeterminate form of Chagas disease, echocardiography revealed that 13.8% had segmental cardiac lesions.[45] In another study, delayed-enhancement MRI showed areas of cardiac fibrosis in about 20% of patients with the indeterminate form of the disease.[46] Dysautonomia and left ventricular diastolic dysfunction have also been reported.[47–51] The variable degree of subclinical cardiac involvement in patients in the indeterminate stage of the disease is of uncertain prognostic value.

In general, progression from the indeterminate phase to a symptomatic form can take years or even decades.[42–44] In endemic areas, electrocardiographic alterations indicate that 2–5% of patients progress to the cardiac form each year.[52,53] In general, Chagas disease becomes clinically evident 10–30 years after acute infection by affecting specific organs, particularly the heart, esophagus, or colon, which characterizes distinct chronic forms of the disease: cardiac, digestive, or mixed (cardio–digestive).[54] Chagas cardiomyopathy is the most severe and frequent manifestation, affecting 20–40% of individuals with chronic Chagas disease.[9,55] Sudden cardiac arrest and progressive heart failure are well-recognized causes of death in patients with Chagas cardiomyopathy, especially in those with depressed left ventricular systolic function.[54] Stroke related to Chagas cardiomyopathy has also been identified as an important contributor to mortality in endemic areas.[20]

Chronic Chagas cardiomyopathy manifests as three basic syndromes that can coexist in an individual patient: heart failure, cardiac arrhythmia, and thromboembolism.[56] Clinical presentation varies widely according to disease duration and the extent of myocardial damage.[57] Early manifestations of Chagas cardiomyopathy are usually mild, frequently characterized by the presence of asymptomatic abnormalities on the ECG or in other complementary examinations, such as with echocardiography, 24 h Holter monitoring, or MRI.[4] Subsequent manifestations include advanced conduction abnormalities, most frequently the combination of complete right bundle branch block and left anterior fascicular block, and premature ventricular contractions.[58] Usually, the degree of myocardial damage predicts clinical worsening and ventricular arrhythmias.[59] Enlargement of the left ventricle and deterioration in overall systolic function are features of the final stages of the disease, and form a common pathway of all dilated cardiomyopathies.

Box 1 | ECG abnormalities in patients with Chagas cardiomyopathy*

Typical
- Right bundle branch block, with or without associated left anterior fascicular block
- Frequent premature ventricular beats (>1 detected on ECG), polymorphous or repetitive
- Nonsustained ventricular tachycardia
- Second or third degree atrioventricular block
- Sinus bradycardia with heart rate <40 bpm
- Sinus-node dysfunction
- Left bundle branch block
- Atrial fibrillation
- Electrically inactive segment
- Primary alterations of the ST–T wave

Nonspecific
- Sinus bradycardia with heart rate ≥40 bpm
- Low limb voltage‡
- Nonspecific ST–T wave changes
- Incomplete right bundle branch block
- Left anterior fascicular block
- Isolated premature ventricular beats
- First-degree atrioventricular block

*According to the Brazilian Consensus on Chagas disease.[60] ‡QRS peak-to-peak amplitude <5 mm in all beats in each of leads I, II, and III. Abbreviation: ECG, electrocardiogram.

The prevalence of megaesophagus and megacolon (abnormal enlargement and dysfunction of the esophagus or colon, respectively) varies between countries according to the parasite strain. In Brazil, 5–8% of patients with Chagas disease develop chronic esophagopathy, and 4–6% develop chronic colopathy.[57] The prognosis for patients with digestive forms of the disease is generally good, except in those with complications (such as esophageal cancer, or obstruction with torsion and necrosis of the colon).[58]

Diagnosis

The cornerstone of the diagnosis of chronic Chagas disease is the detection of the specific antibodies against *T. cruzi* by various techniques, particularly ELISA, but also indirect immunofluorescence or hemagglutination. Two positive results using different methodologies, or two different antigens in an ELISA, is sufficient to confirm a diagnosis in most patients, especially in the context of a compatible personal history of living in, having lived in, or having visited an endemic area.[60] Serological tests can have some crossreactivity with other protozoan parasites, especially *Leishmania spp.*, but the clinical presentation of leishmaniasis is very different from that of Chagas disease. PCR-based assays to detect *T. cruzi* DNA in blood samples from patients with Chagas disease are not commercially available, and do not seem to be more accurate than serological tests.[61] Currently, therefore, PCR assays should not be used to diagnose chronic Chagas disease in clinical practice.[62] However, PCR can be useful in specific situations, such as suspected congenital Chagas disease, or reactivation of infection in patients who are immunocompromised.[63,64] Hemocultures and direct searches for the parasite are positive in acute Chagas disease, but rarely positive in chronic Chagas disease, except in patients with HIV or who are immunosuppressed.

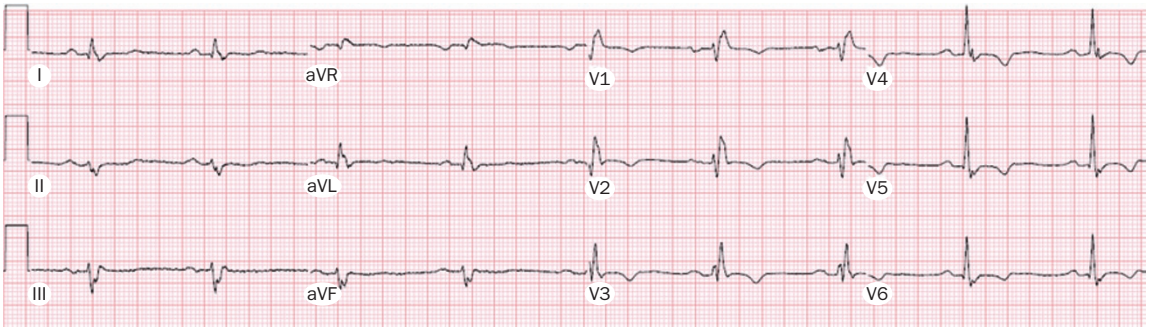

Figure 2 | An electrocardiogram showing typical features of Chagas cardiomyopathy. The patient displays sinus bradycardia with first-degree atrioventricular block, right bundle branch block associated with left anterior hemiblock, and primary T-wave abnormalities in the lateral wall.

ECG-based diagnosis

Electrocardiography is the single most-definitive examination technique for patients with Chagas cardiomyopathy, and several ECG abnormalities are typical of the disease (Box 1 and Figure 2). Several cohort studies have shown that patients with a normal ECG have an excellent prognosis after 5–10 years of follow-up and only very rarely develop severe, global left ventricular dysfunction.[42,43,65] Conversely, the onset of new electrocardiographic alterations can help to identify patients with a substantial decrease (≥5%) in left ventricular ejection fraction.[66] A direct relationship exists between the number of alterations identified in a single ECG and the severity of the myocardial damage and the risk of death during follow-up.[67] Very few instances of sudden death as the first manifestation of Chagas disease have been reported in patients with a normal ECG.[68]

Exercise stress testing can be safely performed in patients with Chagas cardiomyopathy. The test allows the detection of exercise-induced arrhythmias, assessment of the NYHA functional class, and can help to define the type and amount of work that a patient can perform. Exercise-induced nonsustained ventricular tachycardia is of prognostic importance in patients with Chagas cardiomyopathy.[69,70] Chronotropic insufficiency and an abnormal blood-pressure response can impair exercise capacity in patients with Chagas disease.[71,72]

Dynamic ECG recording (Holter monitoring) allows the recognition of clinically relevant, transitory arrhythmias, some with prognostic and therapeutic implications.[73] Episodal, nonsustained ventricular tachycardia during 24-h Holter monitoring is a well-established risk marker in patients with Chagas cardiomyopathy.[70,74,75] The method is also useful to identify potentially lethal arrhythmias—ventricular tachycardia or severe bradycardia from either advanced heart blocks or sick sinus syndrome can indicate the need to implant a cardioverter–defibrillator or pacemaker device, respectively. Holter monitoring can also be used to investigate palpitations and syncope,[73,76] or evaluate the efficacy of device therapy.[77] Invasive electrophysiological study is used to identify the cause of syncope,[76] when noninvasive tests are inconclusive, or to guide the implantation of cardiac pacemakers or defibrillators.[78]

Imaging-based diagnosis

Chest radiography is routinely used to evaluate patients with Chagas disease, and is particularly useful in individuals with advanced disease. An increased cardiothoracic ratio, which indicates cardiomegaly, is not a sensitive marker of left ventricular systolic dysfunction,[79] but is a powerful indicator of poor prognosis in Chagas cardiomyopathy.[74] Pulmonary venous changes are frequently observed on chest radiographs of patients with Chagas cardiomyopathy, but are usually mild.[80]

Echocardiography is extremely useful in the evaluation of patients with Chagas cardiomyopathy. The technique is mainly used to assess ventricular function, which provides key data to guide therapy and prognosis.[81] Advanced cardiac disease is characterized by global cardiac dilatation, often associated with mitral and tricuspid regurgitation, and diffuse hypokinesis.[4] Segmental, left ventricular contractile abnormalities are also typical, but the prevalence varies according to the stage of the disease.[4] In the early stages of cardiac involvement, approximately 10% of patients have segmental, left ventricular wall-motion abnormalities,[45] which can be associated with ventricular arrhythmia.[82] As the disease progresses and cardiac damage worsens with left ventricular dilatation and dysfunction, about half of patients develop segmental wall-motion abnormalities, especially in the apex and inferior–posterior wall.[45] The presence of regional contractility abnormalities identifies the individuals at risk of progressive worsening of left ventricular systolic function.[83] A limited contractile reserve can be detected using dobutamine echocardiography.[84]

Apical aneurysms are a typical finding in patients with Chagas disease, and can be as small as a 'hollow punch', or large and indistinguishable from a myocardial infarction (Figure 3). Wide variation in the prevalence of apical aneurysms exists depending on the population studied and the method used for diagnosis.[45] In studies using 2D echocardiography, the prevalence of apical aneurysm ranged from 8.5% among individuals who were asymptomatic or had mild cardiac damage, to 55.0% in patients with moderate-to-severe cardiac impairment.[85] Left ventricular apical aneurysms are an independent predictor of mural thrombus and stroke,[85–88] and are usually associated with arrhythmogenesis in

Chagas disease,[89] but do not seem to be an independent predictor of mortality.[90,91]

Diastolic dysfunction is an important hallmark of disease severity in patients with Chagas cardiomyopathy.[90] Accumulation of interstitial collagen fibers in chronic Chagas disease can impair ventricular relaxation and progressively reduce myocardial compliance, which increases left atrial pressure.[90] Diastolic abnormalities can be detected early in the course of the disease, but are usually associated with systolic dysfunction.[48,90,92] Echocardiographic parameters of diastolic function are also correlated with levels of B-type natriuretic peptide (BNP).[48,93,94] Left atrial volume, a reliable marker of the duration and severity of diastolic dysfunction, is a powerful predictor of functional capacity[95] and outcome in patients with Chagas cardiomyopathy.[90] The ratio of the early transmitral velocity to the tissue Doppler mitral annular early diastolic velocity (E/e' ratio)—an accepted, noninvasive method to estimate left ventricular filling pressures—is also an independent predictor of mortality in patients with Chagas cardiomyopathy.[90,96] However, an interaction exists between left ventricular ejection fraction and the E/e' ratio in predicting prognosis. The E/e'ratio has a high prognostic value in patients with mild or moderate left ventricular dysfunction, and was inversely associated with mortality in patients with severe systolic ventricular dysfunction.[96]

Right ventricular dysfunction is also considered a typical feature of Chagas cardiomyopathy and can be detected early in the course of the disease by biventricular radionuclide angiography[97] or tissue Doppler imaging.[98] Right ventricular dysfunction is usually evident in association with dilatation and functional impairment of the left ventricle.[99] Right ventricular function is also an important determinant of exercise capacity[100] and prognosis[101] in patients with Chagas disease.

Myocardial perfusion scintillography can be used in patients with precordial pain or with abnormalities on the ECG or in echocardiographic examination that suggest ischemic heart disease. Myocardial perfusion scanning can reveal both transient and irreversible perfusion defects in patients with Chagas cardiomyopathy, and coronary catheterization might be needed to exclude obstructive coronary artery disease.[102,103] Cardiac magnetic resonance is emerging as a useful modality to evaluate cardiac morphology and function in Chagas disease,[104] including to assess myocardial energetics, metabolism,[105] and fibrosis.[46]

Biomarkers

Serum levels of BNP are a reliable indicator of the presence of systolic left ventricular dysfunction in patients with Chagas disease.[106] High levels of BNP are also indicative of ventricular arrhythmia[107] and diastolic dysfunction.[93,94] A strategy combining electrocardiography and measurement of BNP levels to detect left ventricular systolic dysfunction in patients with Chagas disease was more accurate than the conventional approach using electrocardiography and chest radiography, and should, therefore, be considered as a valid option.[108] Moreover,

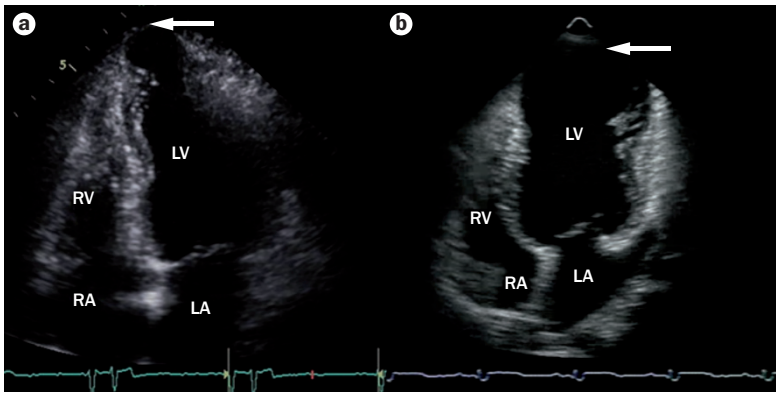

Figure 3 | Left ventricular apical aneurysms in Chagas cardiomyopathy. 2D, four-chamber, apical-view echocardiograms showing **a** | small and **b** | large left ventricular apical aneurysms (arrows). Abbreviations: LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

BNP levels were a strong predictor of the risk of stroke[20] or death[109,110] in longitudinal studies, and might have a role in the clinical evaluation of patients with Chagas cardiomyopathy. Levels of other biomarkers, such as cardiac muscle troponin T[111] and several inflammatory cytokines (tumor necrosis factor and IFN-γ),[112,113] correlate with the severity of cardiac disease and are candidate biomarkers to be used in clinical practice.

Risk stratification and prognosis

Chagas cardiomyopathy is an heterogeneous condition with a wide variation in clinical course and prognosis.[5,91,114] Disease progression is directly and independently associated with mortality. Several classification systems have been proposed,[57,59,60,115,116] but no single system is universally accepted or used. Most clinical classification systems encompass the wide spectrum of the disease. A comprehensive assessment of the current classification systems needs to be performed.[4]

In a systematic review of prognostic factors in patients with Chagas disease, the wide variation in reported annual mortality between studies (varying from 0.2% to 19.2%) was highlighted, and several potential prognostic markers were identified.[74] The principal findings of the outcome studies that have been performed in the past decade are summarized in Table 1. Despite several differences between the studies, NYHA functional class, left ventricular systolic function, and nonsustained ventricular tachycardia have been consistently identified as important prognostic markers.[74] The severity of left ventricular systolic dysfunction—the most well-established predictor of death in Chagas disease—is typically associated with symptoms of heart failure and episodes of nonsustained ventricular tachycardia in the subgroup of patients at the highest risk of death.[5,91]

Several prognostic echocardiographic parameters have also been identified. In particular, left ventricular filling pressure, right ventricular function, and left atrial volume can be useful markers to risk stratify patients with Chagas heart disease.[90,91,96,101,114] Although the independent prognostic value of ECG abnormalities is not certain,[70,74,117]

Table 1 | Predictors of adverse outcome in patients with Chagas disease

Study	Number of patients	Duration of follow-up	End points	Number of events	Prognostic factors
Salles *et al.* (2003)[118]	738	58±39 months	All-cause mortality	62	Age, heart rate, Q waves, QT dispersion, cardiomegaly, LVSD
Basquiera *et al.* (2003)[122]	56	Mean 31 months	Cardiac death, presence of new ECG or echocardiogram abnormalities	12	Presence of parasitic DNA, male sex
Viotti *et al.* (2004)[45]	849	Mean 9.9 years (range 2–23 years)	New ECG abnormalities, change in clinical group or death	150	Change in clinical group, LVSD, LVEF
Viotti *et al.* (2005)[58]	856	8 years	Progression of the disease or death	74	Age, LVSD, intraventricular conduction disorders, sustained ventricular tachycardia, benznidazole treatment
Rassi Jr *et al.* (2006)[70]	424	7.9±3.2 years	All-cause mortality	130	NYHA class, cardiomegaly on radiograph, LVSD, nonsustained ventricular tachycardia, QRS voltage, male sex
Benchimol Barbosa *et al.* (2007)[89]	50	84±39 months	Cardiac death or documented episodes of ventricular tachycardia	20	Apical aneurysm, isolated premature ventricular contractions >614 per 24 h, LVEF <62%
Cardinalli-Neto *et al.* (2007)[175]	90	25±19 months	All-cause mortality	31	Number of shocks per patient by day 30
Ribeiro *et al.* (2008)[75]	184	74±17 months	Cardiovascular death	13	LVEF, nonsustained ventricular tachycardia, prolonged filtered QRS duration (signal-averaged ECG)
Theodoropoulos *et al.* (2008)[180]	127	25±19 months	All-cause mortality	63	No β-blocker use, digoxin use, low serum sodium levels, LVEF, NYHA functional class
Nunes *et al.* (2009)[90]	192	Mean 34 months	Death or cardiac transplantation	66	NYHA functional class, LVEF, right ventricular function, left atrial volume, E/e' ratio
Gonçalves *et al.* (2010)[117]	120	Mean 18.5 years	All-cause mortality	42	Aged ≥39 years, black ethnicity, right bundle branch block and left anterior hemiblock, left bundle branch block, premature ventricular contractions
Lima-Costa *et al.* (2010)[20]	524	Mean 8.9 years	All-cause mortality	233	Levels of B-type natriuretic peptide, ECG (Minnesota code) major abnormalities
Pedrosa *et al.* (2011)[123]	130	Median 9.9 years	Cardiovascular death	33	Exercise-induced ventricular arrhythmia, cardiomegaly on chest radiograph
Ribeiro *et al.* (2011)[120]	113	106±28 months	Cardiovascular death	14	Repolarization variability, LVEF, nonsustained ventricular tachycardia, QRS duration >133 ms
Sarabanda & Marin-Neto (2011)[179]	56	38±16 months	Death caused by Chagas disease	16	LVEF <40%
Bestetti *et al.* (2011)[157]	231	Median 19 months	Death or cardiac transplantation	140	Lack of β-blocker use, need for inotropic support, LVSD
Nunes *et al.* (2012)[96]	232	Mean 3.4 years	Death or cardiac transplantation	107	NYHA functional class, LVEF, right ventricular function, left atrial volume, E/e' ratio and interaction (LVEF and E/e' ratio)

Abbreviations: ECG, electrocardiogram; E/e' ratio, ratio of the early transmitral velocity to the tissue Doppler mitral annular early diastolic velocity; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dimension.

studies have shown that signal-averaged electrocardiography[75] and certain parameters, including QT interval and dispersion,[118] T-wave axis deviation,[119] and T-wave amplitude variability,[120] can give prognostic information. Other prognostic factors, including age,[58,117,121] male sex,[70,122,123] and apical aneurism,[89] have shown inconsistent results.[74] Using a six-item risk score, patients with Chagas cardiomyopathy were accurately classified into groups at low, intermediate, or high risk of death,[70,124] and the scoring system is now the standard prediction model for patients with Chagas disease.[116] Subsequently, other risk scores have been proposed to improve the accuracy of risk stratification, simplify risk prediction in the clinical setting, or both,[75,90,114,125,126] but have not been

externally validated and, consequently, are not ready for clinical use. The search continues for a definitive, accurate, and easy-to-use risk-prediction score for patients with Chagas cardiomyopathy.[114,126]

Treatment

Chagas disease

In the past 10 years, interest in developing and testing new drugs for Chagas disease has increased, and discussion about antitrypanosomal therapy for chronic Chagas disease has reached mainstream medical and scientific journals.[127,128] Most experts now believe that antitrypanosomal treatment should be offered to the majority of patients with chronic *T. cruzi* infection (with or without cardiomyopathy), especially in those aged <50 years.[35,127,129–131] This recommendation, endorsed by national and international institutions,[132,133] is supported by the 'sum of evidence' derived from several experimental, pathological, nonrandomized clinical studies that suggest that etiological treatment can slow progression of the disease.[131,132,134,135] However, some clinicians believe that this indication should be supported by data from prospective, randomized trials, which are not yet available.[136,137] A meta-analysis of the available clinical trials and observational studies showed that the efficacy of antitrypanosomal treatment in late chronic infection is doubtful.[138] This uncertainty is even greater in asymptomatic individuals and those aged >50 years, which challenges the strategy of treating all patients with Chagas disease. Additionally, currently available drugs require a prolonged course, carry a substantial risk of adverse effects, and need careful monitoring.[138] The controversy is now so strong that the experts who wrote the I Latin–American guidelines for the diagnosis and treatment of Chagas cardiomyopathy could not agree which class of indication and level evidence to assign to the treatment of patients who are chronically infected.[116] A multicenter, randomized, double-blind, placebo-controlled trial (BENEFIT)[139] to assess the effects of benznidazole on cardiac outcomes in patients with chronic infection is ongoing and is expected to clarify the role of trypanocidal therapy to prevent cardiac disease progression and death.

The current indications for the treatment of patients with Chagas disease are summarized in Box 2.[139] Etiological treatment of Chagas disease is mandatory for all acute infections caused by vector transmission, oral transmission, congenital infection, laboratory accidents, or organ transplantation, as well as reactivation because of immunosuppression. Additionally, children (aged <12 years or <18 years, depending on the guidelines) with chronic infection should also be treated. Because treatment is expected to reduce the probability of congenital transmission, strong consideration is warranted for women of reproductive age.[140]

Only two drugs are currently available for the treatment of Chagas disease: benznidazole and nifurtimox. The recommended dose of benznidazole is 10 mg/kg daily in children or adults with acute infection, or 2.5 mg/kg twice daily for 60 days in adults with chronic disease. The maximum recommended daily dose is 300 mg. The efficacy and tolerability of benznidazole is inversely related to age.[141] The most-common adverse effect is urticarial dermatitis, which occurs in up to 30% of patients in the first week of treatment, but responds well to antihistamines or corticosteroids. The drug should be discontinued in the event of severe dermatitis, particularly if associated with fever or lymphadenopathy. Other adverse effects include polyneuropathy, which is dose-dependent and occurs most commonly late in the course of treatment. Bone-marrow suppression can occur early during therapy and treatment should be stopped immediately. The complete blood-cell count should be measured every 2–3 weeks during treatment.[141,142]

Nifurtimox is prescribed at a dose of 8–10 mg/kg daily in three doses for 90 days. Adverse effects are frequent and mostly related to gastrointestinal-tract complaints. Toxic effects on the central nervous system include insomnia, irritability, and psychic alterations.[142]

New drugs with improved safety and efficacy would alter the risk–benefit balance considerably and increase the number of individuals who receive treatment.[127] Indeed, several triazole derivatives (inhibitors of ergosterol synthesis, including posaconazole[143] and ravuconazole[144]) and TAK-187[145] (an unapproved antifungal drug) have been successfully tested in animal models of Chagas disease. In ongoing, phase II trials, the efficacy and safety of posaconazole[146] and E1224,[147] a pro-drug of ravuconazole, are being evaluated. Amiodarone, an antiarrhythmic drug used in patients with Chagas disease (discussed below), and dronedarone (an amiodarone derivative) also have intrinsic antiparasitic properties,[148,149] although their clinical usefulness is uncertain. Another candidate drug is the cruzain inhibitor K777, which is being prepared for a phase I safety trial.[150]

Evaluation of whether Chagas disease has been cured is the most-complex aspect of treatment, often yielding inconclusive parasitological and clinical results.[127] The lack of reliable tests to confirm parasite clearance is the main difficulty in evaluating treatment. Moreover, clinical cure is determined by nonspecific markers of long-term disease progression, which have limited value in either the acute or the chronic phases of Chagas disease. Measurement of conventional and nonconventional

Box 2 | Indications for specific treatment of Chagas disease[116,127,132,133]

Accepted

- Acute infections, irrespective of the mechanism of transmission
- Early chronic phase (children aged <18 years)
- High-risk accidental contaminations (for example, cutting or piercing by contaminated instruments or mucous contact with material containing living parasites, samples for culture, infected vectors or laboratory animals, or samples from patients suspected of having high parasitemia)
- Reactivated *Trypanosoma cruzi* infection in patients with AIDS or other immunosuppression
- Congenital infection
- Organ transplantation in which either the donor or the recipient has Chagas disease

Disputed

- Late, chronic phase, including patients with the indeterminate or cardiac forms of Chagas disease

serological titers can be useful to monitor the early impact of treatment. The main criterion of cure is the seronegative conversion of previously reactive serology, which is generally achieved many years after treatment.[151]

PCR has been suggested as an important advance in parasitological control to cure Chagas disease.[152] However, PCR procedures have highly variable levels of sensitivity and specificity, depending on various physical parameters (such as temperature or cycle times) or chemical factors (for example, the template concentration or type of enzyme used). An international collaborative study was launched by experts in laboratories from 16 countries to validate PCR procedures to detect *T. cruzi* in human blood samples.[153]

Parasitological tests are often negative in the chronic phase of the disease, and have limited value in the evaluation of treatment response.[154] Improved serological, parasitological, or molecular assays—especially rapid tests—are needed to monitor the effectiveness of treatment in patients with chronic Chagas disease.

Chagas cardiomyopathy

The management of Chagas cardiomyopathy follows the standard recommendations for treatment of heart failure, despite the fact that most medical interventions for arrhythmias and heart failure have not been specifically validated for treatment of Chagas disease.[4,155] Additionally, patients with Chagas disease have particular features that should be taken into account during treatment.

Heart failure

Heart failure should be routinely managed with a combination of three types of drug: diuretics, β-blockers, and angiotensin-converting-enzyme (ACE) inhibitors (or angiotensin II-receptor blockers). Treatment is initiated with ACE inhibitors at low doses, and then incrementally increased if these doses are well tolerated. Cautious up-titration of ACE-inhibitor dose is safe, hemodynamically well tolerated, and associated with clinical improvement.[156]

β-Blockers have been avoided in patients with Chagas disease because of a perceived risk of worsening bradycardia and atrioventricular blocks. However, new studies indicate that the use of β-blockers should be encouraged.[156] In a double-blind, placebo-controlled, randomized trial, the use of carvedilol in patients with Chagas cardiomyopathy was shown to be safe, well tolerated, and not associated with symptomatic bradycardia.[156] Moreover, the use of β-blockers was associated with increased survival in both an observational study[157] and a subgroup analysis of a randomized trial.[158] A large, long-term, prospective, randomized study is ongoing to evaluate the effects of β-blockade with bisoprolol on cardiovascular mortality and clinical end points in patients with Chagas cardiomyopathy.[159]

Spironolactone is recommended in combination with standard therapy including ACE inhibitors and diuretics for patients with Chagas cardiomyopathy in NYHA class III or IV.[156] Digoxin has long been used in the treatment of patients with Chagas cardiomyopathy, but this drug should be used cautiously because of the risk of worsening bradycardia, and the frequency and complexity of ventricular arrhythmias. The use of digitalis should be considered for patients with left ventricular systolic dysfunction who have persistent symptoms despite standard therapy, and for patients with atrial fibrillation and a rapid ventricular response.[4]

Cardiac transplantation is a feasible treatment option for particular patients with refractory end-stage heart failure.[116] In Brazil, Chagas cardiomyopathy is the third most-common indication for cardiac transplantation.[116] Current indications for cardiac transplantation focus on the identification of patients with severe functional impairment or dependence on intravenous inotropic agents. Recurrent, life-threatening ventricular arrhythmia that is refractory to all currently available treatments is a less-common indication for cardiac transplantation in patients with Chagas disease. Survival after transplant seems to be longer and with a higher quality of life among patients with Chagas disease than in recipients without Chagas disease.[160] The risk of reactivation of Chagas disease is increased by immunosuppression after transplantation, but survival is still improved in these patients.[161]

Over the past decade, stem-cell therapies have been tested as alternative treatments in patients with Chagas cardiomyopathy.[162] However, a clinical trial showed that intracoronary injection of autologous mononuclear cells derived from bone marrow did not improve left ventricular function or quality of life in patients with Chagas cardiomyopathy.[163]

Exercise training for patients with heart failure can also be useful. A randomized, controlled, single-blind trial demonstrated that exercise training was associated with a major improvement in functional capacity and quality of life and might be a useful therapeutic measure in patients with Chagas cardiomyopathy.[164]

Thromboembolism

Prevention of thromboembolism in patients with chronic Chagas heart disease should be guided by standard clinical recommendations. Anticoagulation should be considered in patients with atrial fibrillation, previous embolic events, or mural thrombus, and possibly in those with an apical aneurism. The role of antiplatelet drugs in the prevention of thromboembolic events has yet to be determined in patients with Chagas disease.[116]

Ventricular arrhythmia

Because of the absence of randomized clinical trials or high-quality evidence, the clinical management of ventricular arrhythmias in patients with Chagas disease varies greatly between institutions. Antiarrhythmic therapy is not required in the management of patients with ventricular premature beats or few episodes of nonsustained ventricular tachycardia, which—in the absence of substantial ventricular dysfunction—are benign conditions.[165,166] At the other end of the spectrum, the use of implantable cardioverter–defibrillators (ICDs) is beneficial in patients with malignant, sustained ventricular

tachycardia or those resuscitated from sudden cardiac arrest, especially with a reduced left ventricular ejection fraction.[167,168] Patients with Chagas cardiomyopathy resuscitated from sudden cardiac arrest have a particular arrhythmogenic profile characterized by high-frequency ventricular fibrillation and a high risk of arrhythmia recurrence within a short period of time.[168] Indeed, ICD therapy provides protection by effectively terminating life-threatening arrhythmias in patients with Chagas disease[169] and, because of the high mortality in untreated patients, a specific randomized trial of ICD use for secondary prevention in patients with Chagas cardiomyopathy might not be necessary.[170] In patients presenting with syncope and near-syncope, electrophysiological study can be used to distinguish those with malignant ventricular tachycardia, in whom an ICD is the treatment of choice, from those with a prolonged HV interval and risk of transient atrioventricular block, who have a better prognosis and should be treated by the implantation of a conventional pacemaker.[76,171]

Controversy surrounds the management of patients with Chagas cardiomyopathy, nonsustained ventricular tachycardia, and abnormal left ventricular function. Current guidelines indicate ICD therapy for patients with nonischemic dilated cardiomyopathy who have a left ventricular ejection fraction ≤35% and who are in NYHA class II or III,[172] although its value in Chagas cardiomyopathy has never been tested. A strategy of implanting ICDs for primary prevention in all candidate patients with Chagas cardiomyopathy would be limited by the high cost of this treatment, which would probably exceed the resources of most Latin–American countries. Amiodarone has been widely used in these patients,[173] but strong evidence of its utility to prevent sudden cardiac death is scarce. Moreover, amiodarone has established cardiac and extracardiac toxicity, and can cause bradyarrhythmias, thyroid abnormalities, corneal deposits, dermatological manifestations, and rare life-threatening pulmonary toxicity.[174] Amiodarone seems to be more beneficial to reduce the number of shocks in patients with an ICD, which is useful given that the number of shocks per patient is an independent predictor of mortality in Chagas cardiomyopathy.[175] Patients refractory to high doses of amiodarone (800 mg per day) might be considered for alternative therapies, such as catheter ablation, in tertiary referral centers.[176]

Bradyarrhythmias

Treatment of symptomatic bradyarrhythmias should follow current recommendations for other cardiomyopathies.[173] Advanced atrioventricular block and symptomatic sinus node syndrome are the main indications for the implantation of a permanent pacemaker. Although right ventricular apical pacing can cause ventricular desynchronization, which has been shown to increase the risk of heart failure in patients with other cardiopathies,[177] no robust evidence exists regarding the use cardiac resynchronization therapy in patients with Chagas cardiomyopathy.[155]

Conclusions

More than a century after the initial description of Chagas disease by Carlos Chagas,[178] the condition remains a major public health challenge in Latin America and has become a new concern in many developed countries. Persistent parasitism is now regarded as being of seminal importance in the pathogenesis of chronic Chagas cardiomyopathy and might drive other processes that contribute to disease progression, including inflammation, vascular and neurogenic dysfunction, and autoimmunity. In this context, the recommendation to treat patients with chronic Chagas disease with trypanocidal drugs is now endorsed by many specialists and international institutions, even in the absence of robust evidence obtained from randomized clinical trials. Currently available drugs have substantial toxicity and require careful monitoring, which makes safer and more-effective drugs to treat the infection desirable. Studies must define criteria to assess when patients have been cured to allow the evaluation of treatment efficacy.

Chagas cardiomyopathy is the most common and severe form of chronic Chagas disease and can produce a wide range of clinical manifestations, from asymptomatic abnormalities to severe, intractable heart failure. Several prognostic markers and risk scores have been described that should be helpful in clinical practice. Very few clinical trials have involved patients with Chagas disease, and the current management of Chagas cardiomyopathy relies largely on recommendations transposed from guidelines developed for other cardiopathies. Studies and clinical trials focused on the management of patients with Chagas cardiomyopathy are necessary and to be welcomed.

Review criteria

Literature searches of MEDLINE, LILACS, and SciELO were performed using the term "Chagas disease" alone and in combination with "epidemiology", "pathogenesis", "clinical evaluation", "cardiomyopathy", "heart failure", "diagnosis", "prognosis", "risk stratification", "mortality", "sudden death", "treatment", and "antitrypanosomal therapy". Articles published from 2000 to 1 February 2012 published in English or Portuguese were included. We focused, but did not restrict, the search to publications from the past 5 years. Other pertinent articles, reports, and book chapters were identified through citations in the literature. Recent guidelines by expert committees were also consulted.

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