Chagas Disease: Chronic Chagas Cardiomyopathy

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Abstract: Chagas disease (CD) is a tropical vector-borne infection caused by the protozoan parasite Trypanosoma cruzi (T. cruzi), also known as American Trypanosomiasis. It is considered endemic in all South and Central America and in this past decades its becoming a burden particularly in the United States and Europe due to human migration. The vast majority of patients during the acute phase are asymptomatic, while chronic symptomatic phase appears years later, with around 30% progressing toward detectable organ damage affecting mainly the cardiovascular and digestive systems. Chagas cardiomyopathy is the leading cause of nonischemic cardiomyopathy (NICM) in Latin America and affects around 30% of infected patients. The foremost characteristics are a diffuse myocarditis with focal fibrosis, mainly located in the apex and basal segments of the posterior and inferior wall, leading to a highly arrhythmogenic disease. Treatment can be etiologic during the parasitic infection, without and established efficacy during the advanced chronic symptomatic phase. Chronic Chagas cardiomyopathy treatment consists in guided medical therapy for non-ischemic cardiomyopathy, but more studies are imperative to improve clinical outcomes, some of them already in progress, and hopefully soon refine treatment and recommendations. (Curr Probl Cardiol 2021;46:100507.)

Curr Probl Cardiol 2021;46:100507
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2019.100507

Introduction

Chagas disease (CD), named after Carlos Chagas, a Brazilian doctor who discovered the disease in 1990, is a tropical vector-borne disease caused by the protozoan parasite *Trypanosoma cruzi (T. cruzi)*, also known as American Trypanosomiasis. CD is asymptomatic in the vast majority of patients during the acute phase, but chronic infection will manifest as a multisystem disease affecting mainly the cardiovascular and digestive systems. Chagas cardiomyopathy is the leading cause of non-ischemic cardiomyopathy (NICM) in Latin America and affects around 30% of infected patients.[1,2] The foremost characteristics are a diffuse myocarditis with focal fibrosis, mainly located in the apex and basal segments of the posterior and inferior wall, as well as left ventricular hypertrophy. Chronic Chagas cardiomyopathy (CCC) carries a worse prognosis than other etiologies of NICM, and sudden cardiac death (SCD) is the most common cause of death.[3-5] Despite this, antiarrhythmic therapy is still largely extrapolated from other etiologies of cardiomyopathy.[6]

Epidemiology and Worldwide Distribution

Chagas disease is endemic to all South and Central America including Mexico, but not the Caribbean islands or Puerto Rico. Bolivia has the highest prevalence and incidence rates, but Argentina, Brazil, and Colombia have a higher number of people living with CCC due to their larger population has traditionally been more common in rural areas where poverty is widespread. This distribution is related to the triatomine bug, which thrives in poor housing conditions, but due to economic changes, deforestation and increasing urbanization CD is now emerging in urban and periurban regions.[7] The Pan American Health Organization estimates that 8 million people are infected in historically endemic regions, but in the past 2 decades, CD has spread to other parts of the globe becoming a worldwide burden due to human migration.[5,7] According to the Centers for Disease Control and Prevention there are over 300,000 people infected with *T. cruzi* currently living in the United States[8-10] and 80,000 in Europe.[11,12] A recent European meta-analysis showed a prevalence of positive serological infection of 4.2% among 10,000 Latin American immigrants.[13] Worldwide the WHO estimates there are 56,000 new cases annually, and 12,000 persons die each year from CD.[14]

There is currently no vaccine available for the prevention of CD, but in past years many countries in South America have been able to significantly reduce new infections by interrupting vectorial transmission. Structural improvements to typical rural houses with cracked walls of

mud or mud-brick and thatch roofs can reduce the triatomine bug habitat and its proximity to humans.[15-17] Other important public health measures like educating population at risk and serologic screening of donated blood have helped reduce its transmission.[18] Through these efforts several countries in South and Central America have been certified as free of Chagas disease transmission by domestic vectors, since 1997 in Uruguay and 1999 in Chile. Brazil in 2006 interrupted transmission through the most common vector in South America, *Triatoma infestans*.[14,19,20]

Natural History

The disease is transmitted by various species of bloodsucking triatomine insects, also called kissing bugs, in the reduviid bug family. The insects become infected by sucking blood with circulating trypomastigotes, which multiplicate in the midgut of the insect forming more trypomastigotes that are released in feces/urine during or immediately after blood meals. These trypomastigotes then enter the host's blood stream through the bite wound or mucosal membranes and proliferate intracellularly as amastigotes. Most infections occur in childhood among those <5 years old, without a gender predominance.[2,14,18] *T. cruzi* can also be transmitted through contaminated food, blood transfusions, organ transplantation, congenital transmission, and laboratory contamination.[21] Around 30% will develop either CCC or Chagas gastrointestinal disease.

Clinical Course

Chagas disease can manifest in 2 phases, each one presenting with different clinical syndromes. The acute phase lasts approximately 6-8 weeks and is often asymptomatic or unrecognized due to mild nonspecific symptoms, even though there is a high level of microscopically detectable parasitemia. The initial lesion depends on where the parasite enters the body; an inflammatory nodule (Chagoma) can appear if acquired via insect bite, or a painless unilateral edema of the palpebrae/periocular tissues (Romaña sign) can occur when the conjunctiva is the portal of entry. These signs are accompanied by locally enlarged lymph nodes and fever that may last for several weeks. Other acute symptoms include malaise, anorexia, edema of face and lower extremities, hepatosplenomegaly and generalized lymphadenopathies. Around 5% present with a severe acute phase, predominantly in children <5 year of age, the elderly and immunosuppressed. This more severe form includes fulminant myocarditis resulting in a wide range electrocardiographic and echocardiographic abnormalities, and even death secondary to congestive heart failure (HF).[9,15,18]

If left untreated, symptoms from an acute infection will resolve spontaneously over weeks to months. Once this happens, the person enters an indeterminate phase of Chagas disease, characterized by undetectable parasitemia as the parasites quiescently invade target tissues. Specific antibodies against *T. cruzi* develop, without a clear role in the disease, and for most patients this indeterminate phase is life long.[14]

The chronic symptomatic phase appears years, or even decades later, with around 30% progressing toward detectable organ damage. The most serious and frequent manifestation of chronic CD is cardiac involvement which can be seen in up to 20%-30% of all cases, followed by the gastrointestinal system in 5%-20%, and a mixed form (cardiac and digestive) in 5%-10%.[22,23] The phenotype of Chagas cardiomyopathy is variable. The most common finding is dilated cardiomyopathy accompanied by conduction system abnormalities. Electrical manifestations include a right bundle branch block (RBBB), left anterior fascicular block (LAFB), sinus node dysfunction, and ventricular arrhythmias. Structural abnormalities can include left ventricle aneurysms and secondary embolism as a result of thrombus formation and HF Signs of cell-mediated immune damage to the myocytes and capillary endothelium occur in the acute phase, with hyaline degeneration of muscle fibers, coagulative necrosis of myocytes and surrounding tissues, and involvement of the epicardium and pericardium despite consistently normal epicardial coronary arteries. Prolonged host survival, in the absence of symptoms, permits a chronic inflammation resulting in irreversible lesions of the conduction system and cardiac neural cells. Eventually a diffuse and progressive myocarditis sets in, aggravated by auto-immunity secondary to molecular mimicry and polyclonal activation.[1,15,24-26] Patients ultimately die in early adulthood due to SCD (55%-65%) caused by arrhythmias, mainly sustained ventricular tachycardia (VT) degenerating into ventricular fibrillation. Other causes of mortality include stroke (10%-15%), progressive impairment of global myocardial contraction function (25%-30%), or rupture of left ventricular apical aneurysm.[6,9,10,14,23]

Characteristic changes to the digestive system from chronic CD include enlargement of the esophagus, colon, or both, that result from damage to intramural neurons. The presentation of esophageal disease can range from an asymptomatic motility disorder with mild achalasia, to severe megaesophagus with dysphagia, odynophagia, chest pain, weight loss, esophageal reflux, cough, regurgitation, and aspiration during sleep. Colonic disease can progress to megacolon with chronic constipation that may result in a fecaloma, volvulus or bowel ischemia.[9,14]

Electrocardiogram

The earliest electrocardiogram (ECG) signs of Chagas cardiomyopathy are conduction-system defects (especially RBBB and LAFB, multiform premature ventricular contractions, repolarization abnormalities, Q waves and low QRS voltage.[9,15,22] Chagas cardiomyopathy is highly arrhythmogenic, often presenting with sinus and junctional bradycardias, atrial fibrillation, atrial flutter, atrioventricular blocks, and VTs. Abnormal ECG results, recurrent syncope and cardiac symptoms should motivate further investigation, with echocardiography and a 24-hour Holter being the preferred initial methods to assess for supportive findings of CCC such as chamber dilatation, apical aneurysms, mural thrombus, ventricular dysfunction, and arrhythmias.[22]

Echocardiography

There are a wide range of possible findings in echocardiography because of the inflammatory nature of the disease, ranging from normal wall motion, to localized segmental abnormalities, or a globally dilated cardiomyopathy. In symptomatic acute CD the left ventricular ejection fraction can be depressed but is frequently normal, with the other possible finding of a pericardial effusion seen in 42% in one series.[27] When CCC becomes symptomatic, the findings are predominantly a hypokinetic dilated left ventricle with reduced ejection fraction or biventricular dilation. There are likely subclinical changes happening during the indeterminate phase of the disease, as asymptomatic CD is associated with abnormalities of diastolic function.[28] When segmental abnormalities are apparent, they are located mainly at the left ventricular apex and inferior and inferolateral walls.[15] After cardiomyopathy has developed, left ventricular diameter and ejection fraction are the strongest predictors of mortality, similar to other forms of cardiomyopathy.[29] The presence of ventricular aneurysm predicts the development of mural thrombus and stroke.[10]

Illustration of the most common finding in patients with Chagas cardiomyopathy. ECG: Right bundle branch block (RBBB) and/or left anterior fascicular block (LAFB), other common findings are premature ventricular contractions, Q waves, atrioventricular block, sinus node dysfunction, atrial fibrillation, ventricular tachycardia. Echocardiogram: Enlarged cavities, left ventricle (LV) aneurysm, mural thrombus in apex.

Laboratoy Diagnosis

During the acute phase, parasites (motile trypomastigotes) can be seen by direct examination under microscope, in blood smears with special

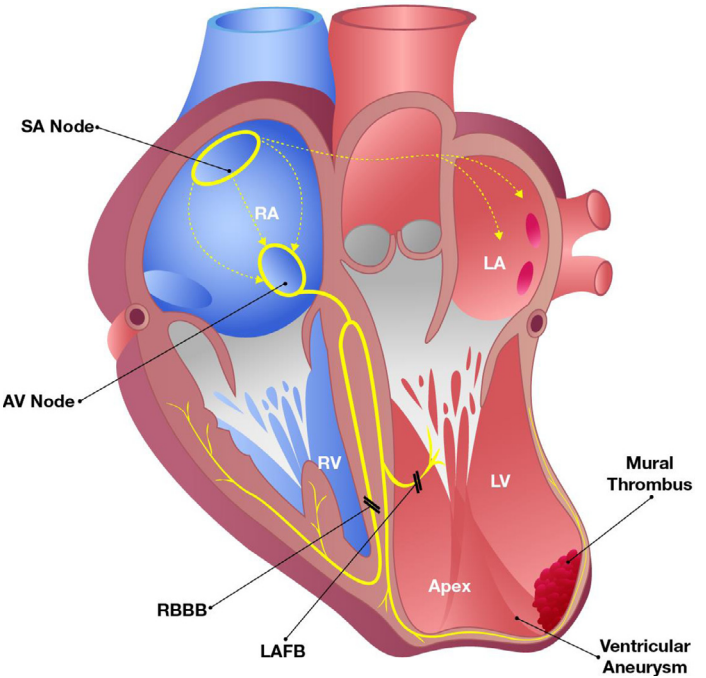


Illustration of the most common finding in patients with Chagas cardiomyopathy. ECG: Right bundle branch block (RBBB) and/or Left anterior fascicular block (LAFB), other common findings are premature ventricular contractions, Q waves, atrioventricular block, sinus node dysfunction, atrial fibrillation, ventricular tachycardia. **Echocardiogram:** Enlarged cavities, Left ventricle (LV) aneurysm, mural thrombus in apex.

stains or a thick blood smear. Thick blood smears are particularly useful in countries with malaria due to the high training in microscopic evaluation for this technique.[30] The Strout method (double centrifugation) is a useful direct examination technique when there is low parasitemia as the concentration facilitates parasitic visualization.[30,31] Polymerase chain reaction has a higher sensitivity than direct examination and is advantageous in many settings including the acute phase of CD, for early detection of infection in organ transplant recipients, for accidental exposure surveillance, and congenital CD. The diagnosis of congenital CD can also be made with microscopic examination of cord blood. When chronic infection is suspected, diagnosis has to be made by immunologic tests that detect specific IgG antibodies; for congenital CD, IgG should be tested at 6-9 months if the initial parasitological studies are negative.[9,18]

For chronic *T. cruzi* infection more than 30 assays for serologic diagnosis are available, most commonly done by enzyme-linked immunosorbent assay, immunofluorescent antibody assay, and indirect hemagglutination. Unfortunately sensitivities and specificities of these assays are not as robust; one reason why the WHO recommend that 2 assays based on different formats should be completed to make clinical decisions.[32] False positive reactions can occur typically with infections caused by leishmaniasis, malaria, and syphilis.[18] Biomarkers are being studied to determine their diagnostic value to distinguish severity of CCC. Echeverría et al found a significant association between NT-proBNP and high-sensitivity cardiac troponin T in determining severity of CCC in a cross-sectional study of 100 patients with established cardiac disease.[33]

Prognosis and Risk Factors

The Prospective Comparison of ARNI With ACE to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) and the Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE) trials included 2552 Latin American patients, and post-hoc analysis were done in these patients for the composite of cardiovascular death or HF hospitalization, its components, or death from any cause. The 195 patients with CCC and reduced ejection fraction, compared to the 1300 with NICM, and 1057 with ICM, were more often female, younger, and had few comorbidities. At the same time those with CCC had a worse quality of life and higher hospitalization and mortality rates compared with other etiologies.[4] Rassi et al retrospectively studied a Brazilian cohort of 424 patients with CCC with a mean follow-up of 7.9 years and identified 6 independent risk factors for mortality. They created a risk score, and each

factor was assigned a number of points proportional to its regression coefficient: New York Heart Association (NYHA) class III or IV (5 points), cardiomegaly on chest radiography (5 points), left ventricular systolic disfunction (3 points), nonsustained VT (NSVT) on 24-hour Holter monitoring (3 points), low QRS voltage on ECG (2 points), and male sex (2 points). Three groups were categorized according to their 10-year mortality rates: low risk (0-6 points) with a 10% 10-year mortality, intermediate risk (7-11 points) with 44%, and high risk (12-20 points) with 84%.[34] Senra et al studied myocardial fibrosis on cardiac magnetic resonance imaging to determine prognostic value independent of the Rassi risk score. They expressed myocardial fibrosis as absolute mass, and found a cut-off point of $\geq$12.3 g to be significantly associated with a combined all-cause mortality, heart transplantation, antitachycardia pacing, or appropriate shock from an implantable cardioverter-defibrillator.[35]

Etiologic Treatment

Treatment can be etiologic treating the parasitic infection, or nonetiologic, treating clinical manifestations of the disease. For the etiologic treatment there are only 2 drugs that have shown efficacy against *T. cruzi* infection: benznidazole and nifurtimox, which are each given as a 60-day monotherapy course. These drugs have been used since the 1970s and there is yet no better drug available, even if there are still many questions about their mode of action and efficacy at different stages of infection. The highest efficacy is during the acute and indeterminate phases, with a cure rate of 65%-80%, approaching 100% in congenital acquired disease. During the indeterminate phase the efficacy in not well established, but neither benznidazole nor nifurtimox are effective during the advanced chronic symptomatic phase, whether cardiac or digestive form.[1,22,36] Both drugs are contraindicated during pregnancy and in patients with severe renal or hepatic insufficiency.[23] Benznidazole, a nitroimidazole derivate, is given as monotherapy and is the drug of choice due to its safety and efficacy profile,[26] but still has a variety of adverse effects like allergic dermatitis affecting 20%-30%, polyneuropathy in 10% and more rarely bone marrow suppression. In the 2015 BENEFIT (Benznidazole Evaluation for Interrupting Trypanosomiasis) trial, 2854 patients with established CCC were given benznidazole or placebo for 80 days and were followed for 5.4 years. Even though twice as many patients had a negative seroconversion in the treatment arm, there was no significant reduction in cardiac clinical deterioration on follow-up.[36] Trials involving new drugs like posaconazole for CCC and E1224 for chronic indeterminate Chagas disease have demonstrated no benefit above benznidazole alone and high long-term treatment failures.[37,38]

Nonetiologic Treatment

Large cohort studies involving CCC patients are not available, but treatment has been inferred from studies involving patients with nonischemic HF due to its resemblance. Guideline-directed medical therapy with renin-angiotensin-aldosterone system blockade, beta blockers and diuretics, the later with a higher dose due its systemic congestive manifestations over signs of pulmonary congestion.[23] Due to the highly arrhythmogenic nature of the disease and high risk of SCD, early initiation of amiodarone is recommended, with the importance of knowing its multiple possible side effects and precautions. Multiple studies have shown its effectiveness reducing ventricular arrhythmias, even though hard endpoints such as SCD have not been demonstrated similar to findings in nonischemic HF.[39,40] A small post hoc analysis of the CCC patients in the SHIFT trial, studying the use of ivabradine, was done by Bocci et al. While there were several differences in baseline characteristics including a higher prevalence of RBBB, lower systemic blood pressure, and higher use of diuretics, they showed a trend toward improved heart rate and functional class among CCC patients treated with ivabradine.[41] An exploratory post hoc analysis of 113 patients with CCC from the PARADIGM-HF trial has also been made, comparing angiotensin receptor neprilysin inhibitors with angiotensin converting enzyme inhibitors. Patients with CCC treated with sacubitril/valsartan, as compared with enalapril, had a lower risk of experiencing cardiovascular death or HF hospitalization, the primary composite endpoint, with an even higher risk reduction than that seen in the entire study population. Understandably, this study is underpowered and cannot be a reliable source to give a clinical recommendation, but this hypothesis is currently being evaluated in the PARACHUTE-HF trial, a phase 4, multicenter, randomized clinical trial with 900 patients with heart failure with reduced ejection fraction caused by CCC.[42-44]

For refractory, hemodynamically unstable sustained VT, ventricular fibrillation, and for prevention of secondary SCD, some cardiologists support implantable cardioverter defibrillator (ICD), even if data specific to CCC is lacking.[9,22,23,45] Catheter ablation is suggested for selected patients with CCC and symptomatic monomorphic VT that recurs despite antiarrhythmic drug therapy, with the primary benefit being improved quality of life, reduced ICD shocks, and reduced hospital admissions for VT.[26] Patients with CD tend to have lower heart rates and bradyarrhythmias, a reason why many cannot tolerate beta blockers, an unfortunate situation given the likely benefit extrapolated from other etiologies of

cardiomyopathy. Bradycardia can also periodically limit use of amiodarone and digoxin.[1,23,46]

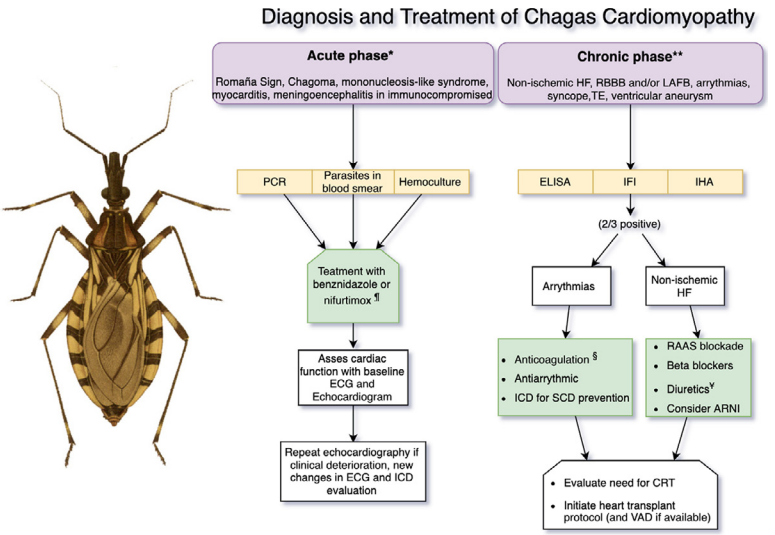
Because of the high prevalence of atrial fibrillation, atrial flutter, and systemic embolism secondary to apical aneurysms and mural thrombus, management with anticoagulation therapy is highly recommended whenever the risk of stroke overweighs the risk of a major bleed.[1,26,47]

Given that Chagas disease is a systemic infection, it has historically been considered a contraindication for any organ transplantation with the belief that the infection could reoccur in the allograft or other native organs after immunosuppression. However large investigational series have since demonstrated similar results when compared to heart transplants of other etiologies, and transplant has been considered the treatment of choice in advanced CCC with endstage HF since 1990. The criteria do not otherwise differ from other etiologies, except for the presence of megaesophagus or megacolon, which are relative contraindications.[10,48,49] Careful monitoring of immunosuppresses and being aware of the risk for CD reactivation is the fundamental, especially in central nervous systems where the most frequent manifestation is meningoencephalitis, which is associated with a poor prognosis. Despite these concerns prophylactic antitrypanosomal therapy is not recommended.[1,14,50] Survival after transplantation at 1 month, 1 year, and 10 years is 83%, 71% and 46%, respectively, comparable if not better than then the general heart transplantation population.[51]

Nonconventional Cardiac Devices

Cardiac resynchronization therapy (CRT) is another form of treatment in patients with reduced systolic HF and left bundle branch block, but fewer data support this therapy in RBBB, which is more common in patients with CCC.[23] Ferreira et al analyzed the clinical outcomes in 72 patients with CCC and NYHA class III-IV despite optimal therapy, a QRS complex greater than 120 ms (36.2% with RBBB), left ventricular ejection fraction (LVEF) less than 35%, and a left ventricle end-diastolic diameter greater than 55 mm, who underwent CRT. At the end of follow-up 87% were now NYHA class I-II, left ventricular ejection fraction ranged from 27.3% to 44.2%, and the group had an overall response of 65%. These findings suggest improvement with this therapy, but other studies contrasting CRT in CCC with CRT in other etiologies in HF have shown comparatively worse long term outcomes in the CCC population.[52,53]

Ventricular assist device or mechanical circulatory support may be an option as a bridge therapy to heart transplant. Six cases of extracorporeal



* Patients in endemic regions or who have recently traveled to endemic regions, 1-2 weeks of exposure
** Patients born or who have lived in endemic regions, who received blood or platelet transfusion in regions that include immigrants from endemic regions
¶ Monotherapy during 60 days
§ In atrial fibrillation (according to CHA2DS2-VASc score), previous thromboembolic events, cardiac thrombus detected on echocardiography
¥ Consider an aldosterone receptor antagonist for patients with functional class NYHA II to IV and LVEF $\leq$35%
HF: Heart failure; RBBB: Right bundle branch block; LAFB: Left anterior fascicular block; TE: Thromboembolism; PCR: Polymerase chain reaction; ELISA: Enzyme-linked immunosorbent assay; IFI: Immunofluorescent antibody assay; IHA: Indirect hemagglutination; RAAS: Renin-angiotensin-aldosterone system; ARNI: Angiotensin receptor neprilysin inhibitors; CRT: Cardiac resynchronization therapy; VAD: Ventricular assist device; NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; ECG: Electrocardiogram; ICD: Implantable Cardioverter Defibrillator; SCD: Sudden cardiac death

membrane oxygenation (ECMO) in vector-mediated diseases have been published, 2 of them were diagnosed with severe acute Chagas myocarditis and were successfully treated with venoarterial ECMO for progressive ventricular dysfunction.[54] Still this is a limited therapy in South America because of financial limitations, as such there is not sufficient information and experience to make a broader recommendation. Successful cases of a left ventricular assist device have been reported as well, with and without biventricular support.[48,55-57] Support with total artificial heart may be reasonable when there is predominantly right ventricular failure, left ventricular apical aneurysms, and mural thrombi.[58,59]

Summary and Conclusions

CD is well known in Latin America due to its prevalence; doctors are more sensitive to this disease and a diagnosis can be made earlier when looking for causes of NICM. However, in the past 2 decades CD has spread to other parts of the globe, as such it must now be considered in the differential diagnosis in non-endemic areas, particularly in the United States and Europe.

It is crucial that doctors around the world not only think of this disease as a possible alterantive, but also have an understanding of how to make the diagnosis and initiate treatment. NICM with symptoms of HF in typically younger patients should at least trigger a review of epidemiologic history and ECG abnormalities such as a RBBB and/or LAFB, atrioventricular block, sinus bradycardia, and multiform premature ventricular contractions. When clinical suspicion exists work up should consist of serologic testing, echocardiogram and a 24-hour Holter. Supportive findings of CCC include chamber dilatation, apical aneurysms, mural thrombus, ventricular dysfunction, and arrhythmias.

According to the stage of the disease, therapy will consist either of etiologic treatment such as benznidazole in the acute and indeterminate phase or guideline-directed medical therapy for NICM in the advanced chronic symptomatic phase. Other potential therapies for specific indications include antiarrhythmic medications, VT ablation, ICD implantation, anticoagulation for mural thrombus, ventricular assist device in severe ventricular dysfunction, and heart transplant for appropriate patients.

The development of more accurate biomarkers to diagnose and guide treatment according the stage of disease and to evaluate therapeutic response is imperative. Also needed are specific clinical trials to better assess the effectiveness of antitrypanosomal therapy and refine treatment recommendations.

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