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Guidelines for Diagnosis and Treatment of Chagas Disease

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ABSTRACT

Chagas' disease is caused by the flagellate protozoa Trypanosoma cruzi. It has 3 different stages acute, indeterminate and chronic phase. 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.
Treatment with antitrypanosomal drugs can cure CD in acute, congenital, and early chronic cases and provides improved clinical outcomes for chronic indeterminate cases. This treatment should be offered as early as possible, before advanced CCM develops.

Keywords: Chagas disease; Trypanosoma cruzi; diagnosis; neglected diseases.

INTRODUCTION

Chagas' disease or American trypanosomiasis, is a potentially lethal parasitic zoonosis prevalent and endemic only in Latin America. The entity constitutes and important public health problem in most of the Latin American countries. The illness is caused by the flagellate protozoa Trypanosoma cruzi (T. cruzi). This parasite belongs to the Kinetoplastida order and the Trypanosomatidae family. It has several vulgar names: vinchuca, barbeiro, kissing bug, conenosed bug, chupança, chinchorro.[1]

Transmission to humans in rural areas is the result of the conjunction of several factors, including the density of sylvatic and domestic animal reservoirs, the density and rate of infection of the triatomine bugs, and the housing and living conditions of the people (WHO, 1991). Trans- mission may also occur through blood transfusion or transplacentally, and there is evidence suggestingtransmission as the result of the ingestion of the insufficiently cooked meat of infected animals.[2]

Chagas disease is clinically silent in most patients (mainly in the acute phase, but also during the chronic phase), and the diagnosis should be confirmed by the results of laboratory tests. Very often the diagnosis is made fortuitously; for example, when individuals donate blood, during health screening examination, during self-referral testing, and in patients with a strong positive family history or epidemiological antecedents[3].

PHASES OF DISEASE: Chagas disease is characterized by an acute and a chronic phase of infection. In the acute phase most patients have the unapparent (asymptomatic) form, while the remaining infected individuals usually show a

nonspecific febrile disease. In the chronic phase two well-defined forms of disease are distinguished: indeterminate (latent, preclinical) and determinate (clinical), which is subdivided into cardiac, digestive (usually expressed as megaesophagus and/or megacolon), and cardiodigestive forms. Cardiac disease is further classified into stages, and esophageal Chagas disease into groups.[3]

ACUTE PHASE: Clinical manifestations appear around 8-10 days after the penetration of the parasite [7]. In transfusion-transmitted Chagas disease this period may be longer (20-40 days). The acute phase is not clinically recognized in most cases. Romania's sign is the most typical sign of portal of entry of the parasite. It is characterized by a painless swelling of one or both eyelids of one eye . The eyelids turn a bluish color, and conjunctival congestion and hypertrophy of satellite lymph nodes (usually preauricular) frequently occur. Fever is a constant sign, frequently accompanied by malaise, asthenia, anorexia, and headache. ECG and radiological alterations are not frequently observed during the acute phase if compared with the histopathological findings. . Xenodiagnosis with an early examination of the parasites (5-10 days after the blood meal) and the search for specific IgM class antibodies by indirect immunofluorescence are alternative methods.

INTERMEDIATE PHASE: Indeterminate stage or latent phase A majority of the patients with Chagas' disease remain in the latent phase of disease for 10 to 30 years or even for life. The indeterminate stage begins between eight to ten weeks after the initial infection and may last for many years.[1] In this stage people do not have symptoms and can carry the parasite for years without knowing it. About 20–30% of those infected will go on to develop the chronic form of the disease up to 10 or 30 years after they first contracted it. The ajmaline test and the endomyocardial biopsy are, probably, the most sensitive methods to unmask latent forms of chagasic myocarditis during the indeterminate stage[8]

CHRONIC PHASE: The chronic phase begins 2-3 months after the initial infection when the clinical manifestations (if any) of the acute phase disappear, and parasitemia falls to undetectable levels. In most cases, the chronic phase presents as an indeterminate form, which may evolve to the cardiac, digestive, or cardiodigestive forms after years or decades. The diagnosis is made by serological tests, such as indirect hemagglutination, indirect immunofluorescence, and ELISA, all of which have high sensitivity and acceptable specificity. The historical complement fixation reaction (Guerreiro-Machado) is no longer used because of its complexity and because it is no more sensitive or specific than the other tests[3].

Microvascular disturbances including necrotizing microvascular arteritis that leads to platelet thrombosis and subsequent hypoperfusion and foci of myocytolytic necrosis, which progressively destroy both myocardial contractile cells (myocytolysis) and the pacemaking/ /conduction system.

Immune-mediated myocardial injury due to cross-over autoimmune reaction, triggered against the MXT antigen of T. cruzi, which is homologous to myosin of cardiac structures

Autonomic nervous system derangements of focal character, irregular distribution, variable and unpredictable.

Extra-cardiac manifestations include visceromegalies that are the most important digestive system manifestations of Chagas disease and characterized by motor disorders and dilation of organs such as esophagus.

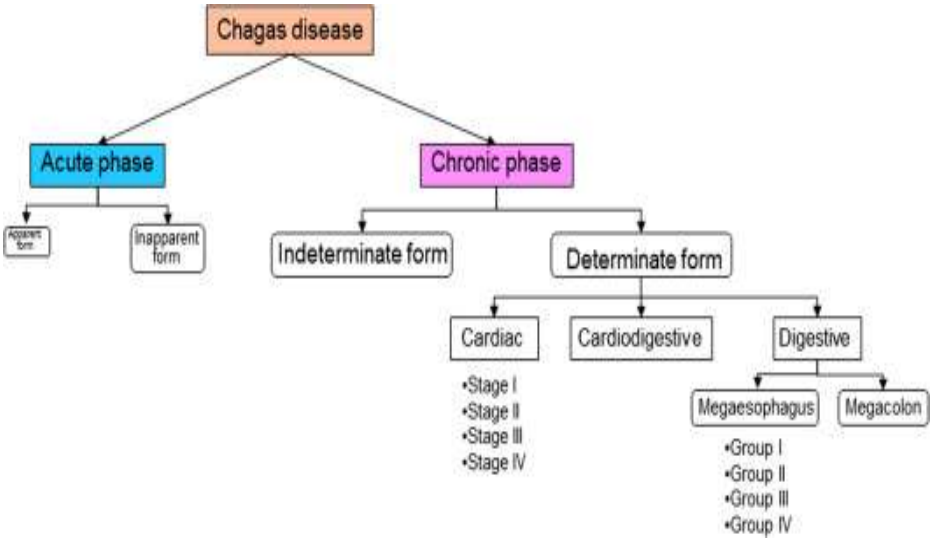


Figure 1(SOURCE:https://www.sciencedirect.com/science/article/pii/B9780128010297000290)

LIFECYCLE OF T. CRUZI:

The life cycle of T. cruzi begins when the triatomine vector ingests circulating trypomastigotes in a blood meal from an infected mammalian host. Trypomastigotes transform into epimastigotes, the main invertebrate replicating stage, in the midgut of the vector. Epimastigotes migrate to the hindgut and differentiate into infective metacyclic trypomastigotes, which are excreted with the feces of the vector.

Metacyclic trypomastigotes enter through a bite wound or through an intact mucous membrane of the mammalian host and invade many types of nucleated cells. In the cytoplasm, trypomastigotes differentiate into the intracellular amastigote form, which replicates with a doubling time of approximately 12 hours over a period of 4 to 5 days[9]. At the end of this period, the amastigotes transform into trypomastigotes, the host cell ruptures, and the trypomastigotes are released into the circulation. The circulating parasites can then invade new cells and initiate new replicative cycles and are available to infect vectors that feed on the host[4]

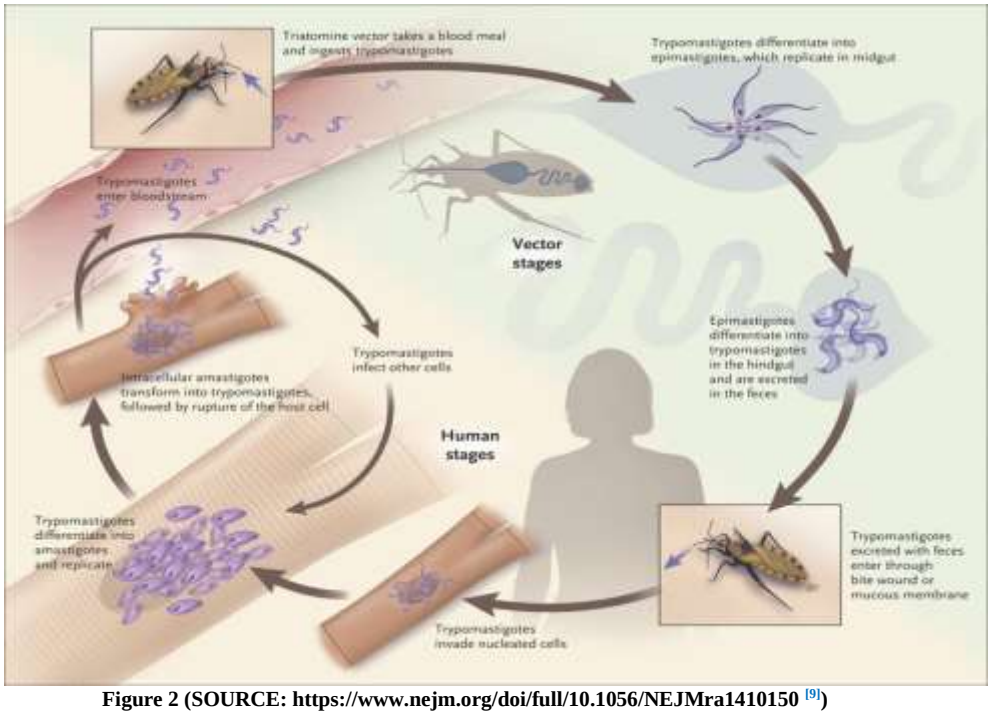


Figure 2 (SOURCE: https://www.nejm.org/doi/full/10.1056/NEJMra1410150 [9])

EPIDEMIOLOGICAL ASPECTS:

The disease is endemic in Latin America, from the north of Mexico to the South of Argentina and Chile. The number of people with Chagas' disease worldwide is estimated to be about 16–18 million in 18 countries of Latin America. There are 90,000,000 exposed and 120,000 new cases per year diagnosed in Latin America. Mortality is around 45.000 to 50.000 people/ /year and the main cause of mortality is cardiac cardiomyopathy[1]

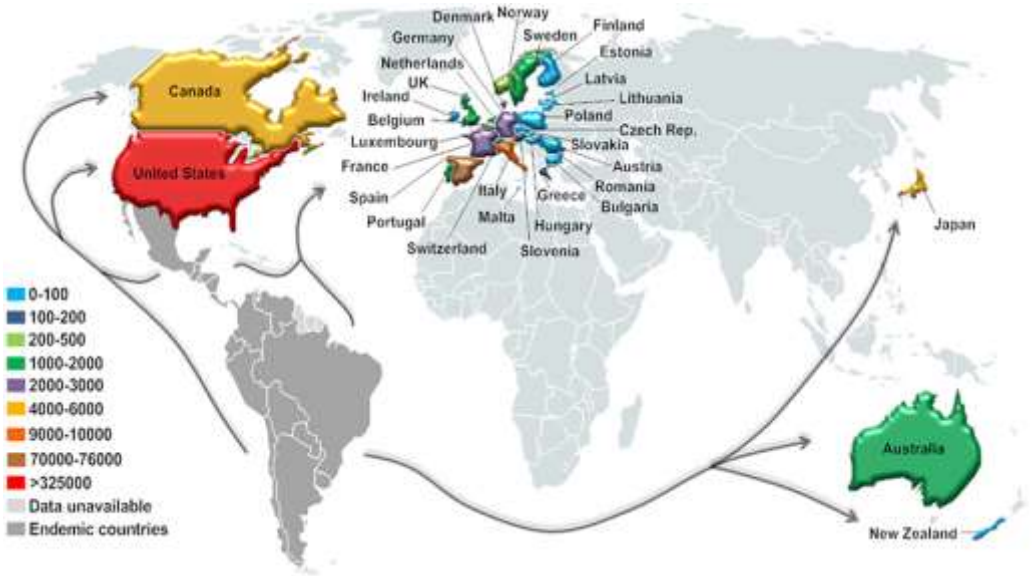


Figure 3 (SOURCE:www.frontiersin.org/articles/10.3389/fpubh.2019.00166/full)

DIAGNOSIS OF CHAGAS DISEASE:

Laboratory tests

Microscopic examination or parasitological diagnosis (utility in the acute phase):

—Fresh anticogulated blood,

—Tthin and thick blood smears stained with Giemsa,

— Inoculation into mice,

— Culture in specialized media (NNN, LIT),

— Xenodiagnosis;

Immunodiagnostic test:

— Complement fixation test, Guerreiro- -Machado reaction: an indirect method of laboratory diagnosis of American trypanosomiasis. When positive, this test remains so throughout life, thus being a good indicator of previous infection,

— Indirect hemaglutination,

— Indirect fluorescent assay (IFA),

— Radio-immunoassay (RIA),

— Enzyme-linked immunosorbent assay (ELISA).

— Molecular biology techniques: polymerase chain reaction (PCR): it is a diagnostic tool for congenital Chagas' disease. Comparative analysis between both parasitological methods, on samples taken at birth, showed a higher sensitivity of PCR as compared to the microhematocrit [10]

Specific tests :

Non-invasive cardiologic test:

— Electrocardiogram,

— Vectorcardiogram

— Chest X-ray,

— Ambulatory ECG recording,

— Cardiopulmonary metabolic exercise test,

— Signal-averaged electrocardiogram,

— Heart rate variability (HRV) or 24-hour HRV,

— QT-interval dispersion (QTd) [11,12]

— T-wave alternans (TWA),

— Transthoracic echocardiogram (TTE),

— Transesophageal echocardiography (TEE) [13]

— Real-time three-dimensional (3D) echocardiography (RT3DE),

— Cardiac magnetic resonance imaging (MRI), gallium-67 myocardial uptake: it is an accurate and alternative method for the diagnosis of inflammatory process associated with chronic Chagas' cardiomyopathy[14]

Invasive cardiologic tests:
— electrophysiologic study with His Bundle recording. In chronic Chagasic cardiomyopathy among the electrophysiological findings, only the HV interval ≥ 70 ms is associated with cardiovascular events [15]
— electrophysiological programmed stimulation (EPS),
— endomyocardial biopsy (EMB).

Non-invasive non-cardiologic test:
— Radiographic contrast study of the esophagus,
— Radiographic study of the colon,
— Radiographic contrast studies of the colon,
— Esophageal endoscopy and manometry.

Screening and Diagnosis in Immunosuppressed Patients:
Immunosuppressed hosts with acute T. cruzi infection (eg, donor-derived infection) are at risk for severe manifestations such as meningoencephalitis or acute myocarditis. Recipients of blood components, organ, or tissue from an infected donor should be monitored by serial polymerase chain reaction (PCR) in blood weekly during months 1–2, every 2 weeks during months 3–4, monthly during months 5–6 posttransfusion or transplant, then based on the clinical scenario[16]

TREATMENT OF CHAGAS DISEASE:
In the acute phase, CD can be diagnosed through direct observation of T. cruzi in peripheral blood. However, patients will typically need testing in the chronic phase when detection of the parasite is more difficult. Clinical diagnosis relies on positive serology on a minimum of two tests with different antigenic principles.[17] For chronic cases, recent Brazilian guidelines recommend using a test with high sensitivity such as a totalantigen enzyme-linked immunosorbent assay (ELISA) or indirect immunofluorescence assay as an initial test, followed by a highly specific method such as an indirect hemagglutination assay [18]

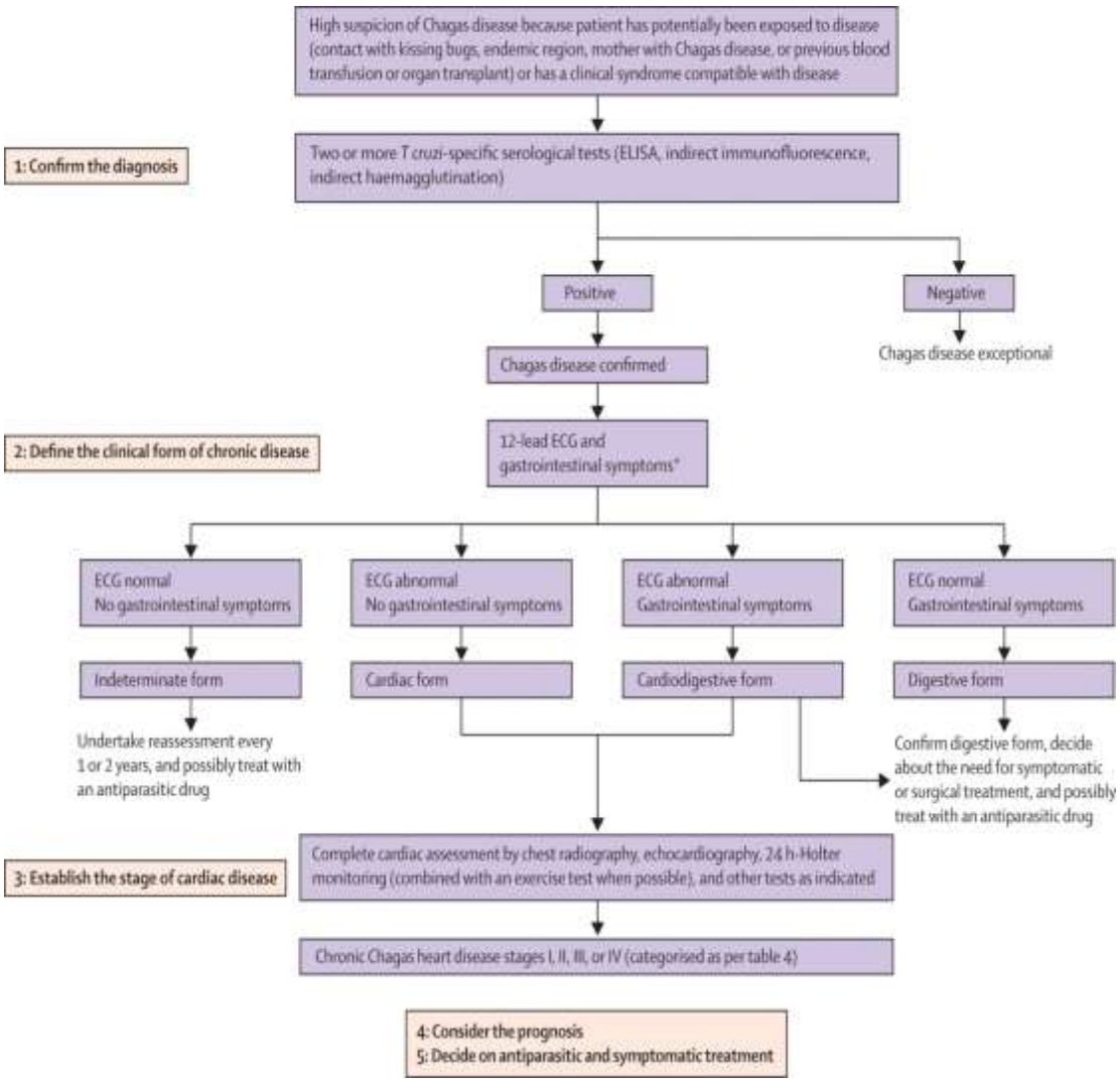
Antitrypanosomal therapy:
Benznidazole, a nitroimidazole derivative (N-Benzil 2 Nitro 1- Imidazolacetamide), and nifurtimox, a nitrofuran compound, both developed over 40 years ago, are currently the only drugs available for treating CD. Benznidazole is often considered the first-line therapy because of its better tolerability, but both drugs produce significant side effects. These nitroheterocyclic drugs inhibit the parasite's ability to replicate DNA, and are effective against the trypomastigote and amastigote forms [19] .Effectiveness is higher for both drugs if administered as soon as possible after infection. Reported cure rates are as high as 96% for congenitally infected infants [20] , 76% for acute infections [21] , 62% for chronically infected children [22] , and 37% for chronically infected adult[23].
DOSAGE : The recommended adult dosage for benznidazole is 5 mg/kg divided into two daily doses, not exceeding 300 mg in 1 day for 60 days. The recommended dose for children is 5-7 mg/kg daily divided into two doses. Benznidazole is ideally taken after meals to avoid gastrointestinal discomfort. For nifurtimox, the adult dosage is 8–10 mg/kg daily divided into three daily doses and administered over 60 days. The length of treatment was previouslyrecommended as 90 days, but this has been reduced in recent international guidelines[24]

Medical treatment of chronic Chagasic heart failure:
In patients with chronic Chagas' cardiomyopathy, optimization of treatment with angiotensin-converting enzyme inhibitors, furosemide, spironolactone and subsequent addition of carvedilol are safe and associated with benefits in cardiac function and clinical status. Larger trials are

needed to show effects on mortality and/or hospitalization. Cardiac transplantation is a feasible treatment option for particular patients with refractory end-stage heart failure[25]. In Brazil, Chagas cardiomyopathy is the third most-common indication for cardiac transplantation. Current indications for cardiac transplantation focus on the identification of patients with severe functional impairment or dependence on intravenous inotropic agents.

Treatment of gastrointestinal complications:

Dysphagia and regurgitation could be indicative of esophageal involvement, while volvulus, constipation, or irregular bowel movements can result from colonic damage. In cases where there is clinical suspicion of gastrointestinal complications from CD, a barium enema and radiological study are recommended. Early-stage gastrointestinal manifestations are not necessarily a contraindication for etiological treatment, [26] but more advanced cases of megaesophagus or megacolon may require surgical correction before any contemplation of antitrypanosomal treatment. [5]



SOURCE:https://www.thelancet.com/journals/lancet/article/PIIS014067361060061X/fulltext

CONCLUSION

Chagas' disease remains an important cause of illness and premature death. Better drug regimens and rigorously conducted drug trials are needed to enable the effective management of chronic T. cruzi infection in the millions of people who have it. Progress has been made in the past 5 years toward improving the evidence base for the treatment of Chagas' disease in adults. Two randomized, double-blind trials of new drug candidates have been completed, and they have validated the use of molecular methods as timely indicators of treatment failure; the search for a true test of cure continues.

There are no known markers of disease progression. Patients with ECG changes consistent with Chagas heart disease should undergo a routine cardiac assessment to establish the stage of disease. Ambulatory 24-h Holter monitoring is used to detect arrhythmias; combined chest radiography and 2D echocardiography refine the assessment of cardiac size and function, and provide additional prognostic. If complaints of dysphagia or constipation are present, the routine contrasted X-rays are indicated.

Declaration by Authors

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Conflict of Interest: The authors declare no conflict of interest.

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