American Trypanosomiasis (Chagas Disease)

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KEYWORDS

• Chagas disease • Chagas heart disease • American trypanosomiasis
• *Trypanosoma cruzi* • Epidemiology • Treatment

KEY POINTS

- Chagas disease still represents a major public health challenge in Latin America, where 8 to 10 million people are infected. Because of growing population movements, the disease has also spread to other continents.
- The disease is caused by the protozoan parasite *T cruzi* and transmitted to humans usually by the faeces of triatomine bugs or occasionally by nonvectorial mechanisms, such as blood transfusion and mother to fetus.
- Chagas disease has 2 phases, acute and chronic. Acute-phase disease is often asymptomatic. Up to 40%-50% of chronically infected patients develop progressive cardiomyopathy and/or motility disturbances of the esophagus and colon.
- The disease, in both phases, is curable with the available antitrypanosomal drugs (benznidazole and nifurtimox). The sooner the treatment is initiated after infection, the greater the chance of cure.
- In patients with established chronic disease, several pharmacologic and nonpharmacologic interventions are available and may prevent or delay disease complications.

Chagas disease, or American trypanosomiasis, is caused by the parasite *Trypanosoma cruzi*, and was discovered in 1909 by the Brazilian physician Carlos Chagas (1879–1934).[1] While still at a young age he described the etiologic agent, vectors, principal reservoirs, and mechanism of infection, as well as the acute clinical manifestations of the first human case. However, Chagas disease is most likely an ancient disease: *T cruzi* DNA has been recorded in tissue specimens of mummies in pre-Colombian Andean countries from as early as 9000 years ago (~7050 BC).[2]

T cruzi is a protozoan of the *Sarcomastigophora* phylum, *Mastigophora* subphylum, *Kinetoplastida* order, and Trypanosomatidae family (**Fig. 1**). It has a flagellum and its

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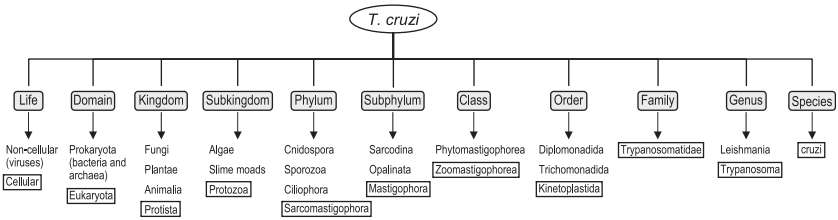

Fig. 1. Taxonomy of *Trypanosoma cruzi*. Eukaryota, cell organisms that have a cell nucleus and specialized organelles; Protista, a group of eukaryotic organisms (usually microorganisms), without the cardinal characteristics of plants and animals, also known as lower forms of plants and animals; Protozoa, the lowest form of animal life ("first animals"), typically unicellular; Sarcomastigophora, protozoa that locomote by flagellae, pseudopodia, or both; Mastigophora, use flagella for motility; Zoomastigophora, animal-like flagellates; Kinetoplastida, order of protozoa characterized by the possession of a kinetoplast (a region rich in DNA within the mitochondrion of the cell); *Trypanosoma*, name derived from the Greek *trypano* (auger, drill) and *soma* (body) because of their corkscrew-like motion; *cruzi*, species of *Trypanosoma* discovered by Carlos Chagas and named in honor of Dr Oswaldo Cruz, his mentor and a famous Brazilian bacteriologist.

single mitochondrion contains the kinetoplast, an extranuclear DNA network corresponding to the parasite's mitochondrial genome, which is localized near the flagellate's basal body.

This review discusses mechanisms of transmission and the life cycle of *T cruzi*, its epidemiology, pathogenesis, clinical manifestations, diagnosis, and treatment, with an emphasis on the effectiveness of antiparasitic treatment in the chronic phase of the disease.

MECHANISMS OF TRANSMISSION

Vector Transmission

Chagas disease is transmitted to human beings and to more than 150 species of domestic and wild mammals mainly by large, bloodsucking insects of the *Arthropoda* phylum, *Hexapoda* subphylum, *Hemiptera* order, Reduviidae family, and Triatominae subfamily. Although some 140 species of triatomines (kissing or cone-nosed bugs) have been identified, only a few are competent vectors for *T cruzi.* The main vectors are *Triatoma infestans, Triatoma brasiliensis*, and *Panstrongylus megistus* in the Southern Cone countries, *Rhodnius prolixus* and *Triatoma dimidiata* in the Andean Pact countries and parts of Central America, and *T dimidiata* and *Triatoma barberi* in Mexico.[3] Birds, reptiles, and amphibians are refractory to *T cruzi*; however, in some situations birds (mainly chickens) are important sources of blood meals for triatomines, which are strictly hematophagous.

Other Mechanisms of Transmission

Chagas disease can be transmitted to man by nonvector mechanisms: blood transfusion and congenital transmission are the main causes of infestation in urban zones and nonendemic countries. The risk of Chagas disease after transfusion of 1 unit of blood from an infected donor is as high as 10% to 20%.[4] Because trypomastigotes are predominantly separated into the platelet fraction during centrifugation, the transmission risk has been reported to be higher for transfusion of platelets than for other blood components. Congenital transmission occurs in at least 5% of pregnancies in chronically infected women in some regions of Bolivia, Chile, and Paraguay, and in 1% to 2% or less in most other endemic countries.[4]

Transmission can also occur from transplantation of a solid organ or bone marrow from a chronically infected donor, which has been well documented in Latin America. Furthermore, Chagas disease can be orally transmitted by ingestion of food or liquid contaminated with *T cruzi*. Such transmission is usually responsible for regional outbreaks of acute infection in areas devoid of domiciled insect vectors. More rarely, *T cruzi* can be transmitted through laboratory accidents to people who work with live parasites.

LIFE CYCLE OF *T CRUZI*

The life cycle of *T cruzi* is complex, with several developmental forms in insect vectors and mammalian hosts.[4] The insects become infected by sucking blood from animals or human beings who have circulating parasites (trypomastigote forms). In the digestive tract of triatomines, the trypomastigotes differentiate into epimastigotes (multiplicative form) and then to metacyclic trypomastigotes in the final portion of the intestine. Infection of mammals occurs when they come into contact with the infective metacyclic forms of the parasite that are eliminated with the feces of triatomines after feeding. This contact occurs through the mucosa or through injury, either preexistent or resulting from the bite of the bug.

Once in the vertebrate host, the metacyclic trypomastigotes invade the local reticuloendothelial and connective cells, and differentiate into amastigotes that begin replicating by binary fission. When the cell is swollen with amastigotes, they transform back into trypomastigotes by growing flagellae. The trypomastigotes lyse the cells, invade adjacent tissues, and spread via the lymphatics and bloodstream to distant sites, mainly muscle cells (cardiac, smooth, and skeletal) and ganglion cells, where they undergo further cycles of intracellular multiplication. The cycle of transmission is completed when circulating trypomastigotes are taken up in blood meals by vectors.[4]

EPIDEMIOLOGY AND GEOGRAPHIC DISTRIBUTION

T cruzi is restricted to South America, Central America, and parts of North America (Mexico and southern United States). The Caribbean islands are free of Chagas disease. In rural Latin America, poor housing conditions favor vector infestation and acute Chagas disease usually occurs in children younger than 12 years. Historically transmission and morbidity were concentrated in this region, but migration has brought chronic infected individuals to cities both in and outside of Latin America, making Chagas disease a public health problem of global concern. According to estimates by the Pan American Health Organization (PAHO)[5] and the World Health Organization (WHO),[6] 7.7 to 10 million people are chronically infected with *T cruzi*, and 10,000 to 14,000 deaths per year are caused by Chagas disease.

It is notable that as a result of successful programs involving vector control, blood bank screening, and education of at-risk populations, both of these estimates are substantially lower than a few decades ago. A major program, begun in 1991 in the Southern Cone nations of South America (Uruguay, Paraguay, Bolivia, Brazil, Chile, and Argentina), has provided the framework for much of this progress.[7] Uruguay and Chile were certified free of transmission by the main domiciliary vector species (*T infestans*) in the late 1990s, and Brazil was declared transmission-free in 2006. In addition, blood donor screening has steadily increased, with coverage now approaching 100% in most endemic countries.

The highest prevalences of Chagas disease have been reported from Bolivia (6.8%), Argentina (4.1%), El Salvador (3.4%), Honduras (3.1%), and Paraguay (2.5%).

However, 2 remaining countries with prevalences of about 1% (Brazil and Mexico), together with Argentina, are home to almost 60% of all people infected with *T cruzi* in Latin America.[4]

CHAGAS DISEASE IN THE UNITED STATES AND OTHER NONENDEMIC COUNTRIES

Acute Chagas disease is rare in the United States.[8] Six human cases of autochthonous transmission and 5 instances of transmission by blood transfusion have been reported. Furthermore, 3 infected donors transmitted *T cruzi* to 5 recipients of solid organs, 2 of whom received cardiac transplants. The rarity of autochthonous vector-borne transmission is presumably due to better housing conditions and less efficient vectors, but many infections probably go undetected. The 2 principal vectors in the United States (*Triatoma sanguisuga* and *Triatoma gerstaeckeri*) have relatively low infection rates (25% and 45%, respectively), display different feeding habits, and often defecate 30 minutes or more after feeding, making them likely to be somewhat inefficient at stercorarian transmission to hosts.[9]

By contrast, the prevalence of chronic *T cruzi* infections in the United States has increased substantially in the past 20 years. An estimated 23 million immigrants from endemic countries live in the United States, about 17 million of whom are Mexicans.[10] The United States ranks seventh worldwide for the total number of people infected with *T cruzi*: in 2009 an estimated 300,167 infected people lived in the United States.[11] Screening of United States blood donations for *T cruzi* infection began in January 2007, and now covers most of the blood supply. About 1 in 28,000 donors has *T cruzi* infection, and so far more than 1400 infected donors have been identified and deferred permanently from donation.[8]

The southern states of the United States have an active sylvatic transmission cycle involving many wild animal reservoirs. Recent serologic and parasitologic surveys suggest that raccoons, opossums, and woodrats are the main hosts, with prevalence of infections of 38.7%, 28.0%, and 33.2%, respectively.[9]

Many individuals with Chagas disease have emigrated from Latin America to countries other than the United States, such as Canada, Australia, Japan, France, Italy, Sweden, Switzerland, and England. But by far the largest population of these infected immigrants lives in Spain (47,000–67,000), with most originating from Ecuador, Argentina, Bolivia, and Peru.[12] Nonendemic countries with large immigrant populations have also begun to establish interventions to prevent transfusion-associated *T cruzi* infection. European legislation prevents people with a history of Chagas disease from donating blood. However, most infected people are asymptomatic and unaware of their status.

PATHOGENESIS

Chagas disease occurs in 2 phases: acute and chronic. Initial infection at the site of parasite entry is characterized by the presence of infective trypomastigotes in leukocytes and cells of subcutaneous tissues, and by the development of interstitial edema, lymphocytic infiltration, and reactive hyperplasia of adjacent lymph nodes. After dissemination through the lymphatic system and the bloodstream, parasites concentrate mainly in the muscles (including the myocardium) and ganglion cells. The characteristic pseudocysts that are present in some tissues are intracellular aggregates of multiplying forms (amastigotes).

Chagas disease is the most severe parasitic infection of the heart,[13] and the heart is the organ most often affected in individuals with chronic *T cruzi* infection.[14] Changes include thinning of the ventricular walls, biventricular enlargement, apical aneurysms,

and mural thrombi. Widespread destruction of myocardial cells, diffuse fibrosis, edema, lymphocytic infiltration of the myocardium, and scarring of the conduction system are often apparent, but parasites are difficult to find in myocardial tissue by conventional histologic methods. In chronic Chagas disease of the gastrointestinal tract, the esophagus and colon can be dilated to varying degrees. On microscopic examination, focal inflammatory lesions with lymphocytic infiltration are seen, and the number of neurons in the myenteric plexus might be markedly reduced.

Evidence accumulated with highly powerful and sensitive methods, such as immunohistochemistry and polymerase chain reaction (PCR), indicates that myocardial damage in chronic *T cruzi* infection is due to the persistence of parasites and the accompanying chronic inflammation, rather than autoimmune mechanisms. Cardiac denervation (mainly parasympathetic), and abnormalities in the coronary microvasculature might also contribute to the pathogenesis of chronic lesions.[15]

CLINICAL MANIFESTATIONS

Acute Chagas Disease

In most individuals, irrespective of the mechanism of transmission, acute Chagas infection is asymptomatic, which is probably because the parasite load is fairly small.[4,10] Symptoms that develop at around 8 to 10 days after invasion by the parasites, or at 20 to 40 days after transfusion of *T cruzi*–infected blood, include prolonged fever, malaise enlargement of the liver, spleen, and lymph nodes, and subcutaneous edema (localized or generalized). In vector-borne transmission, there are signs of portal of entry of *T cruzi*: entry through the skin produces the chagoma, an indurated area of erythema and swelling, whereas entry via the ocular mucous membranes produces Romaña's sign, the classic finding in acute Chagas disease, which consists of unilateral painless edema of the palpebrae and periocular tissues. Severe myocarditis develops rarely; most deaths in acute Chagas disease are due to heart failure. Neurologic signs are not common, but meningoencephalitis occurs occasionally, especially in children younger than 2 years.[4,10]

An electrocardiogram (ECG) might show sinus tachycardia, first-degree atrioventricular block, low QRS voltage, or primary T-wave changes; and a chest radiograph might show variable degrees of cardiomegaly. Repetition of the ECG and chest radiograph is crucial for detection of these abnormalities.[16]

Echocardiography was recently introduced, which explains the lack of information about its performance during the acute phase because most of such cases were reported before this method was available. Nevertheless, variable degrees of pericardial effusion, mitral or tricuspid valve regurgitation, and concentric hypertrophy of the left ventricle have been described, with more than one abnormality often seen in the same patient.[17]

Chronic Chagas Disease

The chronic phase begins 2 to 3 months after initial infection, when the clinical manifestations (if present) of the acute disease will have resolved in virtually all infected individuals even if the infection has not been treated with trypanocidal drugs.[4] About 60% to 70% of these patients will have the indeterminate form of chronic Chagas disease, which has no clinical symptoms. This form is characterized by positivity for antibodies against *T cruzi* in serum, a normal 12-lead ECG, and normal radiologic examination of the chest, esophagus, and colon. The remaining patients (30%–40%) will develop a determinate form—cardiac, digestive (mainly megaesophagus and megacolon), or cardiodigestive—usually 10 to 30 years after initial infection.[4]

Reactivation of Chagas disease can also occur in chronically infected patients who become immunologically compromised, for example, from coinfection with human immunodeficiency virus (HIV) or immunosuppressive drugs. Fever, myocarditis, panniculitis, and skin lesions are common in recipients of solid-organ or bone marrow transplants, whereas the most common manifestations of reactivation in patients with AIDS are meningoencephalitis and lesions of the central nervous system that resemble the lesions of cerebral toxoplasmosis.

Cardiac form

The cardiac form is the most serious and frequent manifestation of chronic disease.[14] This form develops in 20% to 30% of individuals and typically leads to abnormalities of the conduction system, bradyarrhythmias and tachyarrhythmias, apical aneurysms, cardiac failure, thromboembolism, and sudden death. The most common ECG abnormalities are right bundle branch block, left anterior fascicular block, ventricular premature beats, ST-T changes, abnormal Q waves, and low QRS voltage. The combination of right bundle branch block and left anterior fascicular block is very typical in Chagas heart disease.[4,13,14] Frequent, complex ventricular premature beats, including couplets and runs of nonsustained ventricular tachycardia, are a common finding on Holter monitoring or stress testing.[18]

Sustained ventricular tachycardia is another hallmark of the disease, and seems to result from an intramyocardial or subepicardial reentry circuit that is usually located at the inferior-posterior-lateral wall of the left ventricle.[4,14,18]

Heart failure is often a late manifestation of Chagas heart disease. Such failure is usually biventricular with a predominance of right-sided failure at advanced stages, with peripheral edema, hepatomegaly, and ascites more prominent than pulmonary congestion. Isolated left-sided failure can occur in the early stages of cardiac decompensation.[4,14] Heart failure of chagasic etiology is associated with higher mortality than is heart failure from other causes.[19] Systemic and pulmonary embolisms arising from mural thrombi in the cardiac chambers are frequent.

Sudden cardiac death accounts for nearly two-thirds of all deaths in Chagas heart disease, followed by refractory heart failure (25%–30%) and thromboembolism (10%–15%).[20] Sudden death can occur even in patients who were previously asymptomatic. It is usually associated with ventricular tachycardia and fibrillation or, more rarely, with complete atrioventricular block or sinus node dysfunction. **Fig. 2** summarizes the common findings associated with chronic Chagas heart disease.

Digestive form

The digestive form of Chagas disease is characterized by alterations in the motor, secretory, and absorptive functions of the esophagus and the gastrointestinal tract.[21] Lesions of the enteric nervous system are pivotal in the pathogenesis of Chagas digestive megasyndromes. The structure most often affected is the myoenteric plexus of Auerbach, which is located between the longitudinal and circular muscular layers of the digestive tract. Although most damage to the neurons of this plexus and the nervous fibers occurs during acute infection, further neuronal loss occurs slowly throughout the chronic phase. Denervation occurs to variable degrees, is irregular and noncontinuous, and probably depends on both parasitic and host factors. The esophagus and the distal colon, because of their physiology, are the most frequently compromised segments. Denervation leads to loss of motor coordination and achalasia of the sphincters, preventing these segments from emptying semisolid material, thereby causing dilatation; this is the pathophysiologic mechanism underlying chagasic megaesophagus and megacolon.

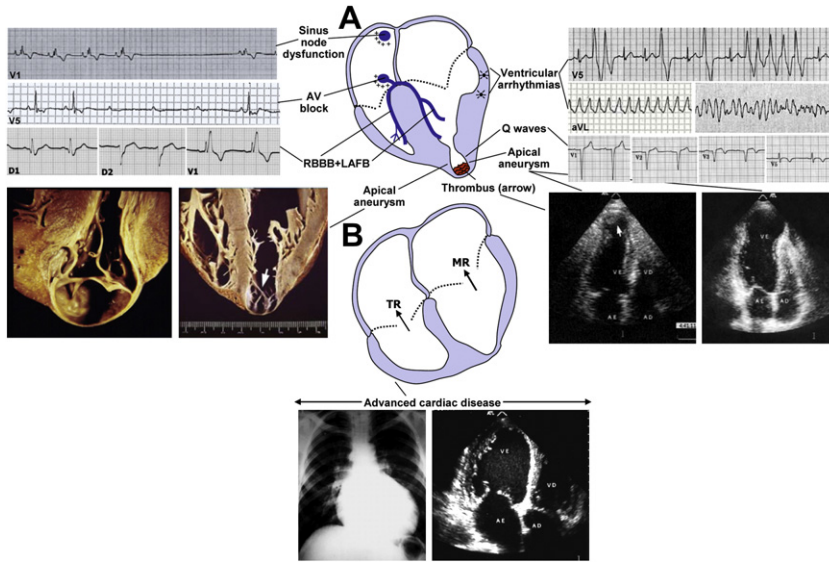

Fig. 2. Common findings in chronic Chagas heart disease. (*A*) Cardiac segmental form. (*B*) Cardiac global dilated form. AV, atrioventricular; LAFB, left anterior fascicular block; MR, mitral regurgitation; RBBB, right bundle branch block; TR, tricuspid regurgitation. (*Adapted from* Rassi A Jr, Rassi A, Marin-Neto JA. Chagas disease. Lancet 2010;375:1395; with permission.)

The digestive form is seen almost exclusively south of the Amazon basin (mainly in Brazil, Argentina, Chile, and Bolivia), and is rare in northern South America, Central America, and Mexico. This geographic distribution is probably due to differences in parasite strains. Gastrointestinal dysfunction (mainly megaesophagus, megacolon, or both) develops in about 10% to 15% of chronically infected patients.[4,21]

The megaesophagus causes dysphagia, regurgitation, and esophageal pain. Other less frequent symptoms are hiccups, pyrosis, and hypersalivation accompanied by parotid hypertrophy. Malnutrition occurs with progression of the disease. Radiologic examination, which is essential to confirm the diagnosis and stage of disease from the morphofunctional characteristics of the esophagus, identifies 4 groups and is very important for the selection of the most appropriate therapy (**Box 1**).[21]

Most cases of megacolon are associated with megaesophagus. The most common symptoms are constipation, meteorism, dyskinesia and, less often, abdominal colicky pain. Constipation can be absent in 25% to 30% of individuals who have radiologic dilatation of the colon. On physical examination, an increase in the abdominal volume is observed. Because the distal colon is the most affected segment, the distended sigmoid occupies a large part of the abdominal cavity and can be localized by palpation and percussion outside its normal topography. Prolonged retention of feces in the distal colon leads to formation of fecaloma, which can be diagnosed by simple abdominal palpation as an elastic tumor that can be molded by pressure. Rectal examination will detect a fecaloma at the rectal ampulla.[21]

Other segments and organs of the digestive system might be compromised in Chagas disease, causing functional and morphologic alterations that can be detected by different investigative methods, but with a much lower prevalence and impact than the lesions involving esophagus and colon.[21]

Nearly 20% of patients with megaesophagus have gastric involvement. The main changes are rapid gastric emptying for liquids and delayed emptying for solids,

Box 1
Classification of megaesophagus according to findings of radiologic examination

Group I
- Normal diameter
- Minimal contrast retention
- Presence of a residual air column above the contrast

Group II
- Moderate dilatation
- Some contrast retention
- Increase in uncoordinated motor activity
- Relative hypertony of the inferior third of the esophagus

Group III
- Large increase in diameter
- Great contrast retention
- Hypotonic esophagus with weak or absent motor activity

Group IV
- Large increase in volume
- Atonic, elongated esophagus, lying on the right diaphragmatic dome

reduced adaptive relaxation of the stomach in response to distension, altered gastric electric rhythm, chronic gastritis, and hypertrophy of pyloric muscle (pylorus achalasia). On radiologic examination the gastric volume is extremely variable, and patients with advanced megaesophagus typically do not have air in the stomach.[21]

Duodenum is, after the esophagus and colon, the segment that most often shows dilatation. Megaduodenum is nearly always associated with other visceromegaly. The dilatation can be localized only at the bulb (megabulb) or at the second and third segments, or can affect the entire duodenal arcade. Even when no dilatation is present, dyskinesia and hyperreactivity to cholinergic stimuli are common because of enteric denervation. Symptoms caused by megaduodenum can be confused with dyspepsia of gastric origin, of the dysmotility type.[21]

Findings of histopathologic studies have shown less denervation at the small intestine than at the esophagus and colon. Dilatation of jejunum or ileum, characterizing megajejunum or megaileum, is rare, with few published cases.[21]

An intrinsic denervation of the gallbladder might also be observed, leading to motor alterations in gallbladder filling and emptying. Manometric alterations have also been recorded at the Oddi sphincter. Nevertheless, cholecystomegaly and choledochodilatation are not frequent. An increased prevalence of cholelithiasis has been reported in chagasic patients with megaesophagus or megacolon, or both.[21]

Salivary glands, mainly parotids, are hypertrophic in patients with megaesophagus, a common finding in any obstructive esophageal disease because the esophageal-salivary reflex produces hypersalivation.[21] Patients with megaesophagus also have an increased prevalence of cancer of the esophagus. Conversely, an increased frequency of colorectal cancer has not been reported in patients with chagasic megacolon. The gastrointestinal manifestations of chronic Chagas disease are shown in **Fig. 3**.

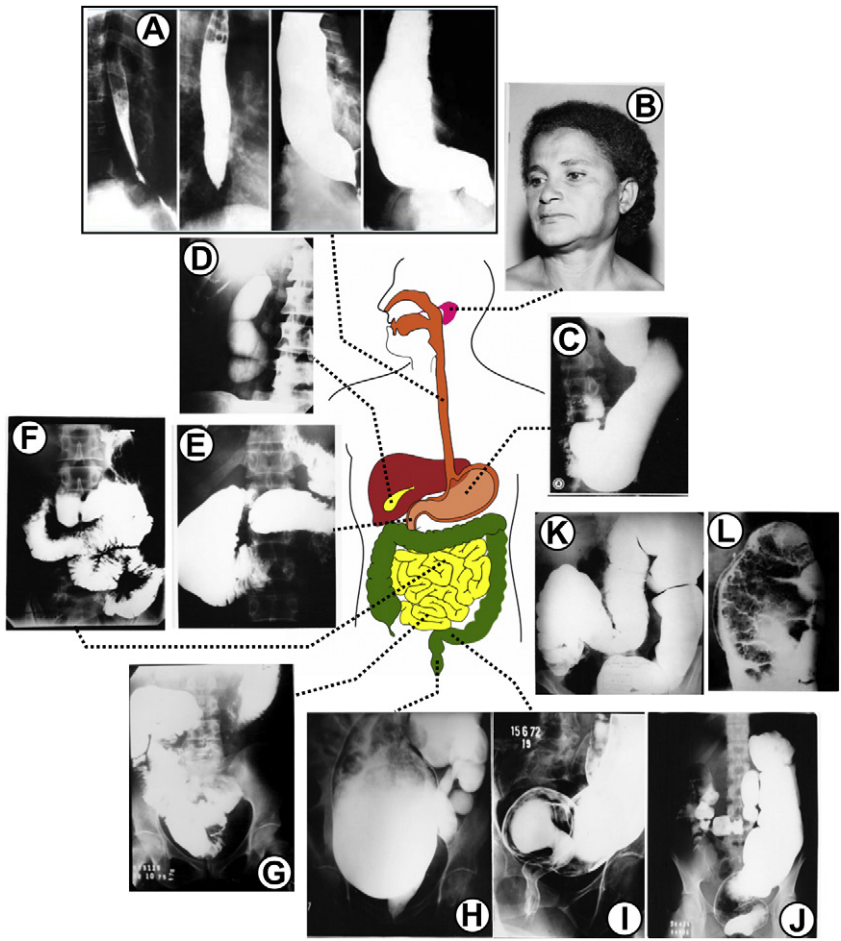

Fig. 3. Gastrointestinal manifestations of chronic Chagas disease. (*A*) Megaesophagus (groups, I, II, III, and IV). (*B*) Hypertrophic parotids in a patient with megaesophagus. (*C*) Megastomach associated with megaesophagus group IV. (*D*) Cholecystomegaly. (*E*) Megaduodenum. (*F*) Megajejunum. (*G*) Megaileum. (*H*) Megarectum. (*I*) Megasigmoid. (*J*) Megarectosigmoid. (*K*) Total megacolon. (*L*) Fecaloma. *C*, *D*, *E*, *F*, and *G* are rare manifestations.

Cardiodigestive form

The cardiodigestive form is a combination of heart disease with megaesophagus or megacolon, or both. In most countries, the development of megaesophagus usually precedes heart and colon disease, but the exact prevalence of the cardiodigestive form is not known because few appropriate studies have been done.

DIAGNOSIS

Diagnosis of acute infection is based on parasite detection (**Fig. 4**A). Microscopic examination of fresh anticoagulated blood or the buffy coat is the simplest way to see motile trypomastigotes. Parasites can also be seen in Giemsa-stained thin and thick blood smears.[4,10] Microhematocrit can be used for the same purpose, and is the method of choice to identify congenital infection because of its heightened

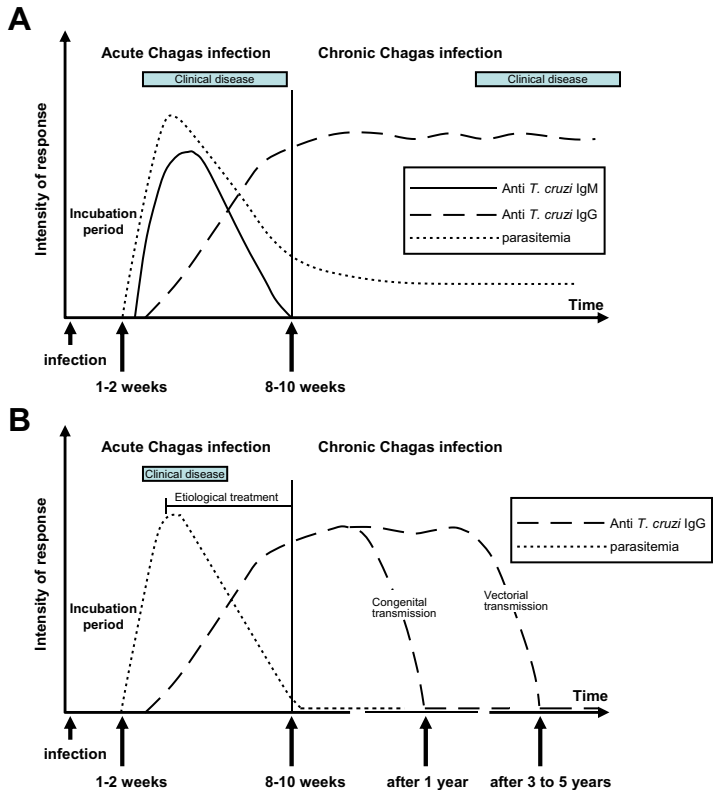

Fig. 4. Serologic and parasitologic evolution in acute Chagas infection. (*A*) Untreated patients. One to 2 weeks after infection with *T cruzi*, individuals undergo an acute phase that lasts approximately 2 months, and is characterized by intense parasitemia, high levels of anti *T cruzi* IgM antibodies, and increasing levels of immunoglobulin G (IgG) antibodies; with the resolution of the acute infection, parasitemia becomes extremely low and IgG antibodies reach their maximum level, persisting elevated and lifelong. (*B*) Treated and cured patients. Cure at the acute phase is accompanied by clearance of parasitemia, which occurs immediately after etiologic treatment, and by seronegative conversion, which occurs after about 1 year for congenital Chagas disease and after 3 to 5 years for vector-borne Chagas disease. Treated and uncured patients present a response that is similar to that of untreated patients.

sensitivity and the small amount of blood needed. Microscopic examination of cord blood or peripheral blood of the neonate by this technique is strongly recommended during the first month of life. Serologic testing is not helpful in diagnosing acute Chagas disease. Although the detection of anti–*T cruzi* immunoglobulin M (IgM) could be used (see **Fig. 4**A), IgM serology assays are not widely available and standardized.[4,10]

In the chronic phase, because of low and probably intermittent parasitemia, diagnosis relies on serologic detection of specific immunoglobulin G (IgG) antibodies that bind to *T cruzi* antigens (see **Fig. 4**A). Enzyme-linked immunosorbent assay, indirect immunofluorescence, and indirect hemagglutination are most common methods used. Two positive results from any of these 3 conventional techniques are recommended for a final diagnosis.

PCR is not helpful in routine diagnosis because of poor standardization, potential DNA cross-contamination, variable results across laboratories and countries, and

the need for specific laboratory facilities. However, PCR has higher sensitivity than do other parasitologic methods, and therefore could be useful to confirm diagnosis in cases of inconclusive serology and as an auxiliary method to monitor treatment. PCR can identify treatment failure from positive detection of *T cruzi* DNA, but not treatment success, because even repeated negative PCR results do not necessarily indicate parasitologic cure. At best, such results indicate the absence of parasite DNA at the time of the test.[4,10]

Low parasitemia during the chronic phase means that hemoculture and xenodiagnosis have low sensitivity for parasite detection. However, these methods could be used to confirm diagnosis in rare cases of serologically doubtful results or to identify treatment failures at specialized centers when PCR is not available.[4,10]

Initial assessment of a patient newly diagnosed with chronic *T cruzi* infection includes a complete medical history and physical examination, and a resting 12-lead ECG.[4,22] Asymptomatic patients with a normal ECG have a favorable prognosis and should be followed up annually or biannually. Patients with ECG changes consistent with Chagas cardiomyopathy should undergo a routine cardiac assessment, including ambulatory 24-hour Holter monitoring (together with an exercise test whenever possible) to detect arrhythmias and assess functional capacity, chest radiography and 2-dimensional echocardiography to assess ventricular function, and other cardiologic tests as indicated. The results of these tests should be used to stratify individual patients by risk and implement appropriate therapy.[23–25] Barium swallow and enema are indicated for patients with symptoms of the digestive form.

TREATMENT

The aim of treatment is to cure infection in acute Chagas disease, to prevent organ damage in chronic asymptomatic infection, and to limit incapacity and prevent morbidity and mortality once the disease is already clinically manifested.[26] In patients with chronic long-standing *T cruzi* infection, research has not elucidated whether the parasite has to be eliminated from the body, or if only a reduction in the parasite burden is sufficient to prevent or delay disease progression.

Antitrypanosomal Treatment

Only 2 drugs, benznidazole and nifurtimox, are recommended for the treatment of Chagas disease. Benznidazole (a nitroimidazole derivative) has been more extensively investigated in clinical studies and has the better safety and efficacy profile, and therefore is usually used for first-line treatment. Children should be given 5 to 10 mg/kg benznidazole in 2 or 3 divided doses per day for 60 days, or 15 mg/kg nifurtimox in 3 divided doses per day for 60 to 90 days; both drugs should preferably be given after meals. For adults the recommended doses are 5 mg/kg benznidazole per day or 8 to 10 mg/kg nifurtimox per day, for the same duration as for children.[27]

The most common adverse effect of benznidazole is a generalized or, sometimes, localized allergic dermatitis, which affects about 20% to 30% of patients and consists of pruritic and nonbullous polymorphous erythematous rashes, often followed by desquamation. This dermatitis is autolimited, usually of mild to moderate intensity, and begins 8 to 10 days after treatment starts (occasionally later); the dose does not need to be reduced or interrupted in most patients. Another adverse effect, which occurs in about 5% to 10% of patients usually late in the treatment course, is a dose-dependent peripheral sensitive neuropathy, affecting mainly the distal parts of the lower limbs; in such cases, treatment should be stopped. Polyneuropathy is nearly always reversible but can take months to resolve. It is not relieved by the

administration of B-complex vitamins, but might respond to systemic corticosteroids. Rare serious adverse events include leukopenia with granulocytopenia or agranulocytosis (sometimes followed by fever and tonsillitis), and thrombocytopenic purpura. Bone marrow suppression usually occurs by the third week of therapy, or eventually later, and should trigger immediate treatment interruption. Leukopenia usually resolves a few days after discontinuation of benznidazole, and tonsillitis should be treated with antibiotics. Additional reported side effects include nausea, vomiting, anorexia, weight loss, insomnia, loss of taste, and onycholysis.[26,28]

Nifurtimox is associated with various adverse effects that usually resolve when treatment is stopped. Gastrointestinal symptoms are the most common side effects reported in clinical studies, occurring in about 50% of patients, and include anorexia leading to weight loss, nausea, vomiting, abdominal discomfort, and occasionally diarrhea. Other common side effects include symptoms of central nervous system toxicity, such as insomnia, irritability, and disorientation. Polyneuropathy, paresthesias, and peripheral neuritis are more serious but less common adverse effects. Additional side effects include headache, myalgia, arthralgia, dizziness or vertigo, and mood changes.[26,28] In general, children treated with benznidazole or nifurtimox have fewer adverse effects than adults.

In acute Chagas disease, antitrypanosomal treatment clears the parasitemia, as shown by conversion to negative serologic and parasitologic tests, reduces the severity and duration of symptoms, and decreases mortality (**Fig. 4**B). Cure rates of up to 81% have been reported,[16] and treatment is mandatory for all patients with acute infection (vector borne, oral, or accidental), congenital infection, or reactivated infection from immunosuppressive treatment (eg, after organ transplantation) or coinfection with HIV.[29]

In children aged 6 to 12 years, findings of 2 randomized placebo-controlled trials showed that benznidazole cured about 60% of asymptomatic infections, as measured by conversion of IgG serologic tests to negative at 3 to 4 years after treatment completion.[30,31] Together with growing favorable anecdotal experiences of individual clinicians across Latin America, these studies prompted the WHO to recommend early diagnosis and antitrypanosomal treatment for all children with chronic *T cruzi* infection[32]; this recommendation was extended to children aged up to 18 years in the United States guidelines.[22]

Whether adults with the indeterminate or chronic symptomatic form of Chagas disease should be treated with benznidazole or nifurtimox has been debated for years. Some researchers argue that both drugs have frequent and unpleasant side effects, might be carcinogenic, need to be taken for a long period, and lack efficacy, as shown by low seroconversion rates.[33,34] However, none of these arguments is solid or compelling.[35] To improve benznidazole tolerability, the authors have adopted 3 strategies. First, the daily dose should not exceed 300 mg; in patients weighing more than 60 kg, a fixed daily dose of 300 mg should be given for a total number of days equal to the patient's weight in kilograms, resulting in a total dose that is equivalent to 5 mg/kg per day for 60 days.[26] Second, patients with mild to moderate allergic dermatitis should be treated immediately with low-dose systemic corticosteroids (eg, 20 mg/d prednisolone orally for 10 days, followed by 10 mg/d for 10 days), without the need for benznidazole interruption.[26,28] Third, in patients with severe dermatitis, the authors have achieved a tolerance rate of 72% by retreating 25 patients with benznidazole and prednisolone (20 mg/d during the first 14 days followed by 10 mg/d for the remaining days of treatment) at the same time (Rassi A, unpublished data, 2010).

Seroconversion might not be the most appropriate criterion to monitor drug efficacy after chemotherapy at a late stage of chronic infection. Contrary to parasitologic testing, serologic test results can take decades to convert from positive to negative

in cured individuals (**Fig. 5**),[28] and drug-induced reduction (not necessarily eradication) of the parasite load could be sufficient to arrest evolution of the disease and avert the irreversible long-term consequences.[36] Moreover, even assuming that seroconversion is quite low after antitrypanosomal treatment in the late chronic phase (about 10%–20%), for every 10 patients treated, 1 or 2 will be cured. Therefore, thousands of infected individuals could derive some clinical benefit from treatment lasting 60 to 90 days,[35] which is a fairly short treatment period for a lifelong disease.

In several observational studies done in the past decades,[36–38] benznidazole treatment slowed the development and progression of cardiomyopathy in adults with long-standing chronic infection. In the largest study, 566 adults (aged 30–50 years) with chronic infection but without advanced heart disease were assigned, in alternating sequences, to receive benznidazole or no treatment.[36] After a median follow-up of 9.8 years, significantly fewer treated patients had a progression of disease or developed ECG abnormalities, despite seroconversion occurring in only 15% of patients.

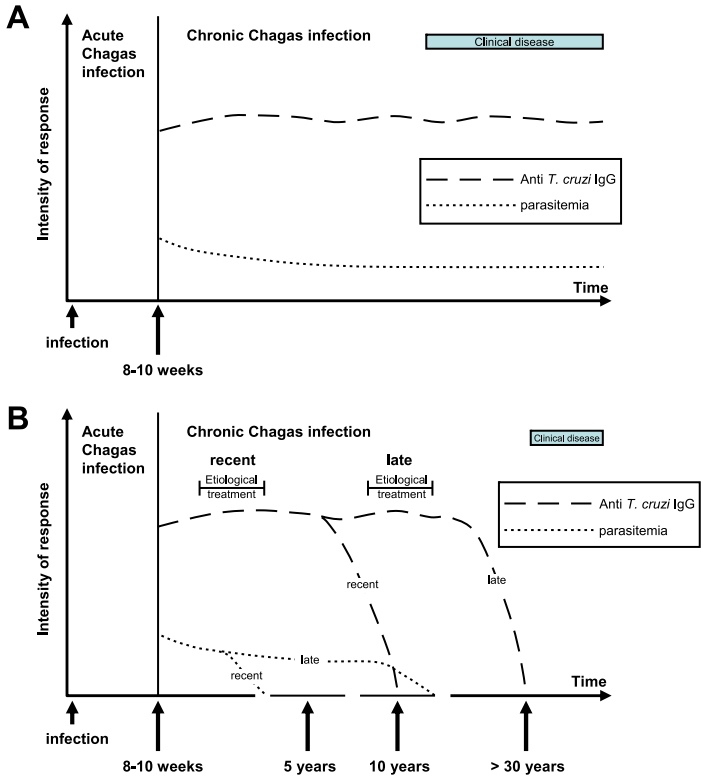

Fig. 5. Serologic and parasitologic evolution in chronic Chagas infection. (*A*) Untreated patients have low levels of circulating parasites and high levels of IgG antibodies directed against the antigens of *T cruzi*. (*B*) Treated and cured patients. Cure at the chronic phase is accompanied by clearance of parasitemia, which occurs immediately after etiologic treatment, and by seronegative conversion, which occurs after 5 to 10 years for those treated with less than 10 years after the initial infection (recent chronic infection), and after at least 20 years for those treated with more than 10 years after the initial infection (late chronic infection). Treated and uncured patients present a response that is similar to that of untreated patients.

Based on these results, in 2006 a panel of experts convened by the US Centers for Disease Control and Prevention[22] recommended that treatment be offered to adults younger than 50 years with presumably long-standing indeterminate *T cruzi* infections or even those with mild to moderate disease. In patients older than 50 years, treatment is optional because of the lack of data. By contrast, treatment is contraindicated during pregnancy and for patients with severe renal or hepatic insufficiency, and should generally not be offered to patients with advanced chagasic cardiomyopathy or megaesophagus with significantly impaired swallowing. A large, multicenter, randomized trial (BENEFIT)[39] has been designed to assess the parasitologic and clinical efficacy of benznidazole in adults (aged 18–75 years) with chronic Chagas heart disease (without advanced lesions), and is under way in Brazil, Argentina, Colombia, Bolivia, and El Salvador. The trial is expected to provide a more solid basis for treatment decisions in this group of patients.

Alternatives to benznidazole and nifurtimox, including allopurinol and itraconazole,[40,41] have had mostly unsuccessful results, with the exception of a small report from Chile[42] and anecdotal use of allopurinol to treat reactivation in patients after cardiac transplantation in Brazil. According to studies in vitro and in animal models, several triazoles that inhibit ergosterol synthesis (including posaconazole and ravuconazole) have curative activity against *T cruzi*, and are now undergoing phase 2 trials.[43]

Treatment of cardiac and gastrointestinal symptoms

Patients who develop cardiac or gastrointestinal disease in association with *T cruzi* infection should be referred to appropriate specialists for further assessment and treatment.

Cardiac transplantation is an option for patients with end-stage chagasic cardiomyopathy. The survival rate in patients with Chagas disease who receive cardiac transplants seems to be higher than that in people receiving cardiac transplants for other reasons.[44] This better outcome might be because lesions are limited to the heart in most patients with symptomatic chronic Chagas disease. By contrast, in the first placebo-controlled randomized trial of treatment with autologous bone marrow–derived mononuclear cells for patients with Chagas heart disease and severe heart failure, cell therapy failed to show any additional benefit compared with standard therapy.[45]

SUMMARY

The control, diagnosis, and treatment of Chagas disease have improved substantially lately, but much still needs to be done. Despite recent encouraging results with available chemotherapy, drugs need to be more effective and better tolerated. Although treatment is now recommended for a wide range of patients, conclusive data are still lacking for certain subgroups of patients, such as those with the indeterminate form or those in the chronic phase who have manifest heart disease and are older than 50 years.

The pathogenesis of Chagas disease is not completely understood. If autoimmunity participates in the development of cardiac lesions, antitrypanosomal treatment after the acute phase could be unsuccessful. However, if parasite persistence is the major pathogenic mechanism, the likelihood of curing a patient with treatment during the chronic phase would be greatly increased. In this regard, there is a great need to find better techniques to assess cure in chronically infected patients. Finally, whether a substantial reduction in parasite load from trypanocidal therapy, instead of parasitologic cure, is sufficient to prevent or delay progression of the disease needs to be rigorously evaluated.

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