REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Chagas' Disease

Caryn Bern, M.D., M.P.H.

From Global Health Sciences, Department of Epidemiology and Biostatistics, University of California, San Francisco, School of Medicine, San Francisco. Address reprint requests to Dr. Bern at the Department of Epidemiology and Biostatistics, UCSF, 550 16th St., San Francisco, CA 94158, or at caryn.bern2@ucsf.edu.

N Engl J Med 2015;373:456-66.
DOI: 10.1056/NEJMra1410150

Chagas' disease is caused by the protozoan parasite *Trypanosoma cruzi*, which is transmitted when the infected feces of the triatomine vector are inoculated through a bite site or through an intact mucous membrane of the mammalian host (Fig. 1).[2] Vectorborne transmission is limited to areas of North America, Central America, and South America. Both in endemic and in nonendemic areas, other infection routes include transfusion, organ and bone marrow transplantation, and congenital transmission. Outbreaks attributed to contaminated food or drink have been reported in northern South America, where transmission cycles involving wild vector populations and mammalian reservoir hosts are prominent.[3] Infection is lifelong in the absence of effective treatment. The most important consequence of *T. cruzi* infection is cardiomyopathy, which occurs in 20 to 30% of infected persons.[4]

Epidemiology

The global epidemiologic profile of Chagas' disease is the result of two major forces: domestic vectorborne transmission over the lifetime of the current population of Latin America and large-scale rural-to-urban migration over the past 50 years (Fig. 2).[2,4] The most epidemiologically important vectors live in the cracks in mud walls and thatched roofs of rustic rural houses. Inhabitants of infested houses are repeatedly exposed to the vector and parasite over many years. Stercorarian transmission (i.e., transmission through the feces of an infected vector) is relatively inefficient: the incidence of *T. cruzi* infection is generally estimated to be less than 1% per year.[6,7] The highest estimated incidence is 4% per year, in the hyperendemic Bolivian Chaco.[8] In an endemic setting, continued transmission over time results in a pattern of increasing prevalence of both infection and cardiomyopathy with increasing age.[8,9] Over the past several decades, millions of infected persons have moved from endemic rural villages to Latin American cities, and hundreds of thousands now live in the United States, Spain, and other countries outside Latin America.[10,11]

Latin America has made substantial progress toward the control of Chagas' disease.[4] The estimated global prevalence of *T. cruzi* infection declined from 18 million in 1991, when the first regional control initiative began, to 5.7 million in 2010.[2,4,5] The Pan American Health Organization has certified the interruption of transmission by domestic vectors in several countries in South America and in Central America.[12,13] Serologic screening for *T. cruzi* is conducted in most blood banks in endemic Latin American countries and the United States, and some countries have systematic screening for congenital Chagas' disease. Nevertheless, Chagas' disease remains the most important parasitic disease in the Western Hemisphere, with an estimated disease burden, as measured by disability-adjusted life-years, that is 7.5 times as great as that of malaria.[14]

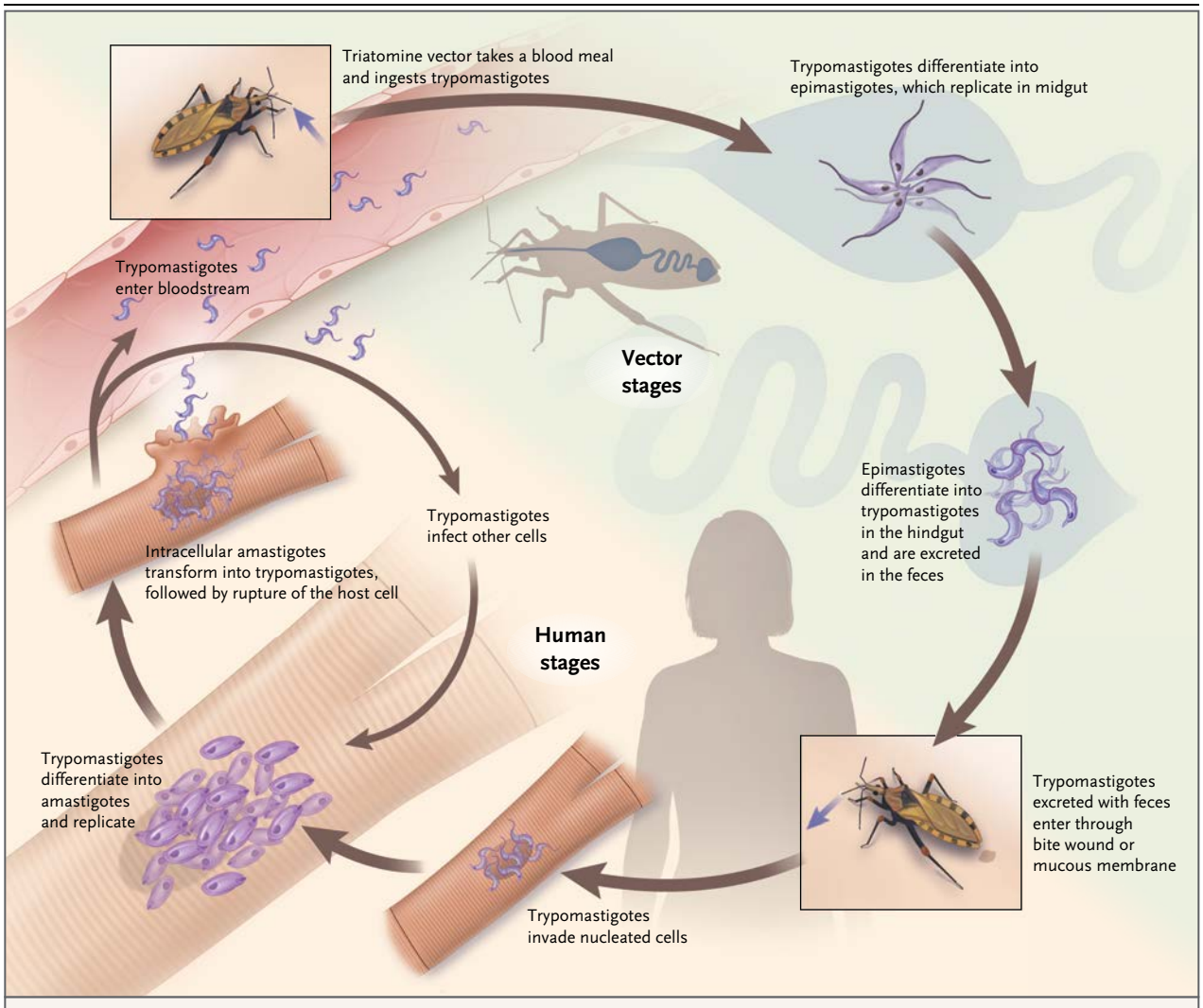

Figure 1. Life Cycle of *Trypanosoma cruzi*.

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. 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. The figure is from Bern.[1]

Although the United States has established enzootic cycles across the southern states, with infected vectors and mammalian hosts such as raccoons, opossums, wood rats, and domestic dogs, the majority of infected U.S. residents are Latin American immigrants who were infected in their home countries.[10,15] On the basis of the size of the Latin American immigrant population and the estimates of *T. cruzi* prevalence in their home countries, it is estimated that 300,000 infected immigrants reside in the United States.[10] Locally acquired vectorborne infection has been documented in a handful of cases over the past 60 years and has been inferred in blood donors for whom acquisition of the infection in Latin America has been ruled out or judged to be unlikely.[15-17] Direct assessments of prevalence in the United States are sparse and have been restricted to small-scale sur-

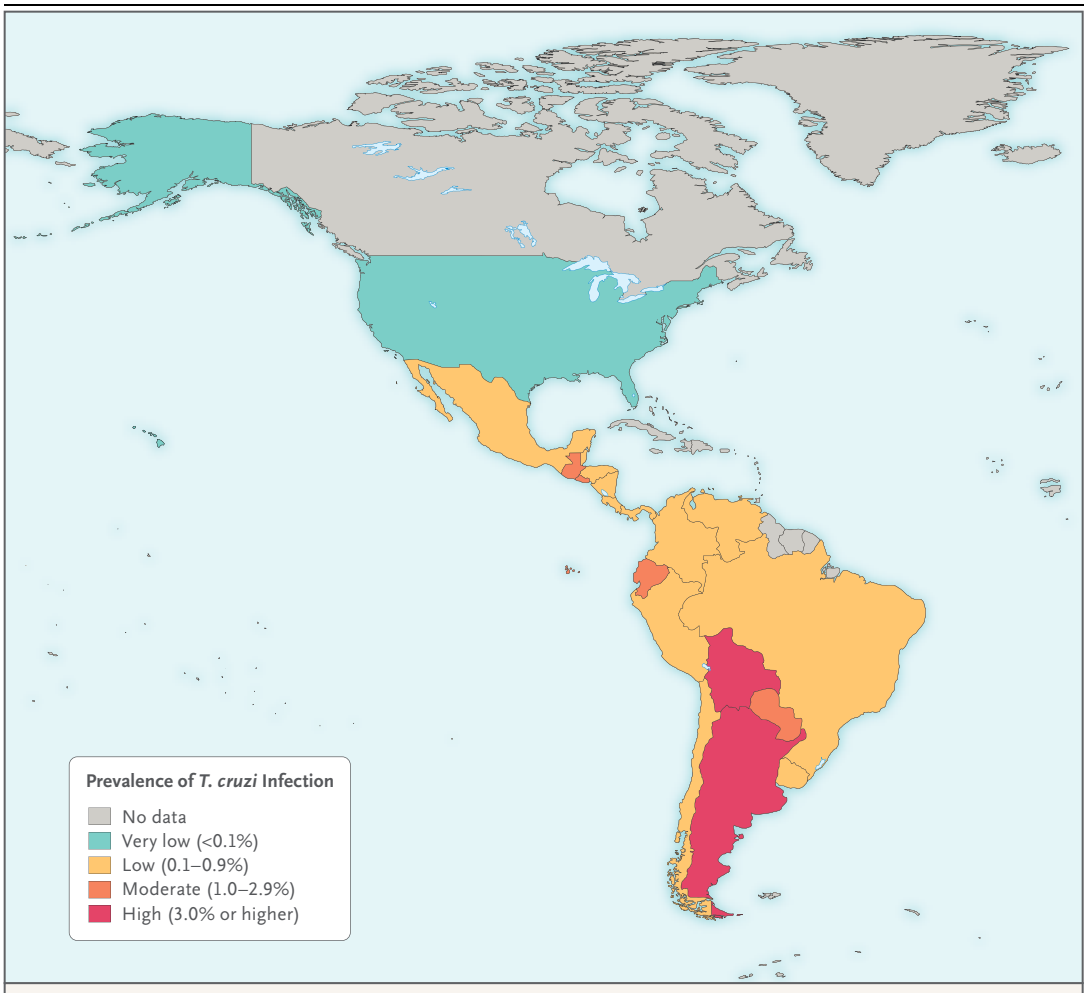

Figure 2. Estimated Prevalences of *Trypanosoma cruzi* Infection.

Shown are the prevalences at the national level, calculated on the basis of published data.[5] Transmission is concentrated in areas with domestic vector infestation and therefore shows strong spatial clustering. However, because infection is lifelong in the absence of treatment, the prevalence reflects past transmission over decades and human migration patterns. Existing data are insufficient to allow mapping at the subnational level.

veys or case series in populations chosen because of an anticipated high risk (e.g., Latin American immigrants with nonischemic heart disease).[18,19] Because of low levels of awareness among health care providers, cases of Chagas' cardiomyopathy are underrecognized, and women at risk for congenital transmission to their infants are rarely screened.[20,21]

CLINICAL FEATURES AND PATHOGENESIS

The incubation period after vectorborne transmission is 1 to 2 weeks (Fig. 3).[4] The hallmark of the acute phase is microscopically detectable parasitemia (Table 1). Symptoms are usually mild and nonspecific and include fever, malaise, hepatosplenomegaly, and atypical lymphocytosis. In rare cases, a skin nodule (chagoma) or painless prolonged eyelid edema (Romaña's sign) may indicate the site of inoculation. The vast majority of acute infections are never detected. In less than 1% of infections, the acute phase is severe and life-threatening because of meningoencephalitis or myocarditis.[23] Outbreaks of orally transmitted *T. cruzi* infection (i.e., transmitted in food or drink that is contaminated with vector feces) appear to be associated with a higher incidence of myocar-

ditis and a higher case-fatality rate than vector-borne infections.[3]

In persons who survive the acute phase, the cell-mediated immune response controls parasite replication, symptoms resolve spontaneously, and patent parasitemia disappears in 4 to 8 weeks.[4] Persons then pass into the chronic phase of *T. cruzi* infection. Most persons remain asymptomatic but are infected for life. It is estimated that 20 to 30% of infected persons have progression over the course of years to decades to chronic Chagas' cardiomyopathy.[4,24] The earliest signs are typically conduction-system defects, especially right bundle-branch block or left anterior fascicular block.[24] Multiform premature ventricular contractions are another early sign, but they may be missed without ambulatory electrocardiographic (ECG) monitoring. Chagas' cardiomyopathy is highly arrhythmogenic and is characterized by sinus and junctional bradycardias, atrial fibrillation or flutter, atrioventricular blocks, and nonsustained or sustained ventricular tachycardia.[2,4,24] Affected patients eventually have progression to dilated cardiomyopathy and congestive heart failure. Left-ventricular aneurysms are common in advanced Chagas' cardiomyopathy.[25] Patients may have strokes or other thromboembolic events as a result of thrombus formation in the dilated left ventricle or aneurysm.[25] Infected persons without overt cardiomyopathy may have subtle abnormalities on echocardiography or autonomic testing, but the prognostic value of these signs is unknown. Retrospective cohort data from infected blood donors in Brazil showed an annual rate of progression to cardiomyopathy of 1.85% per year.[26]

Although the pathogenesis of Chagas' cardiomyopathy is incompletely understood, a consensus has emerged that parasite persistence is central to the disease, which lends a new urgency to the search for antitrypanosomal treatment with high efficacy during the chronic phase.[2,27,28] Evidence suggests that the inflammatory immune response of the host is the most important determinant of progression, with *T. cruzi* strain virulence and tissue tropism as possible contributory factors.[27,29] A range of autoantibodies have been detected in patients with cardiomyopathy, but the role of these autoantibodies in pathogenesis is unknown.[30] Survival during the acute phase requires an inflammatory response involving innate immune cells and macrophages activated by interferon-γ and tumor necrosis factor α, and in the chronic phase, T-cell–mediated immunity maintains parasite replication in check.[31] However, a failure to down-regulate the inflammatory response, maintained by parasite persistence and influenced by both host and parasite factors, appears to play a pre-

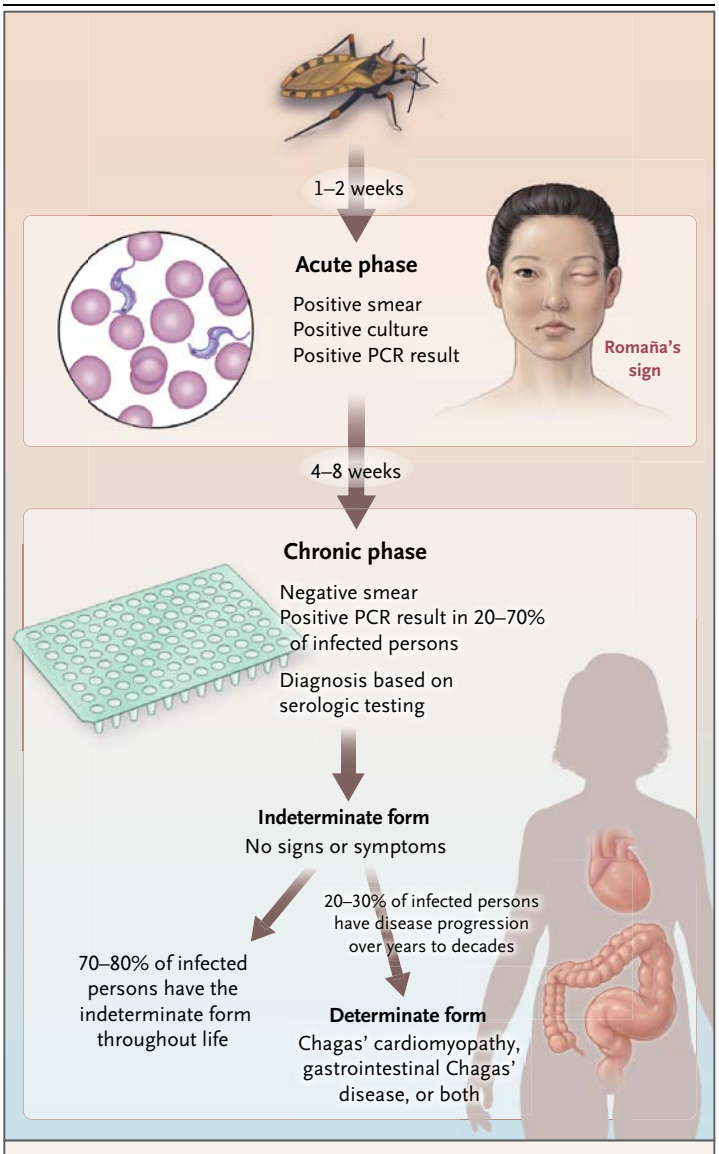

Figure 3. Phases of *Trypanosoma cruzi* Infection.

The acute phase of *T. cruzi* infection is characterized by microscopically detectable parasitemia lasting 8 to 12 weeks. Diagnosis during the chronic phase of infection relies on serologic assays. Persons with chronic *T. cruzi* infection but without signs or symptoms of Chagas' disease are considered to have the indeterminate form of the disease. It is estimated that 20 to 30% of people who initially have the indeterminate form of Chagas' disease have progression over a period of years or decades to clinically evident cardiac disease, gastrointestinal disease, or both. The figure is adapted from Bern.[1]

Table 1. Diagnosis and Management of Chagas' Disease.*

Phase or Form	Clinical Features	Diagnosis of Infection	Antitrypanosomal Drug Efficacy†	Other Management
Acute infection	Usually mild, nonspecific symptoms; myocarditis or meningoencephalitis in rare cases	Positive blood smear or PCR; >99% of infections are undetected	80–100% (AIII)	Supportive; severe disease is more frequent in young infants and in persons with immunosuppression, and when transmission is oral
Congenital infection	Asymptomatic or mild, nonspecific symptoms; myocarditis, meningoencephalitis, or respiratory distress in rare cases	Positive blood smear or PCR; positive IgG serologic test (performed only at 9 months or later)	80–100% (AII)	Supportive as needed
Early chronic infection (children ≤18 yr of age)	Asymptomatic; ECG usually shows no abnormalities suggestive of Chagas' cardiomyopathy	Positive IgG serologic test; PCR often positive	Estimated 60% (AI [<12 yr of age]; AIII [12–18 yr of age])	Yearly cardiac evaluation
Chronic infection (adults)	Asymptomatic; ECG shows no abnormalities suggestive of Chagas' cardiomyopathy	Positive IgG serologic test; PCR variably positive	Unknown; may decrease progression to cardiomyopathy (CIII)	Yearly cardiac evaluation, monitor for gastrointestinal symptoms
Chagas' cardiomyopathy	ECG abnormalities suggestive of Chagas' cardiomyopathy, arrhythmias, syncope, left-ventricular dysfunction, congestive heart failure	Positive IgG serologic test; PCR variably positive	Unknown; may decrease progression (CIII in absence of advanced disease)	Effective cardiac management improves survival and quality of life; heart transplantation for end-stage disease
Gastrointestinal Chagas' disease	Dysfunction followed by dilatation of esophagus, colon, or both	Positive IgG serologic test; PCR variably positive	No evidence of efficacy; may decrease progression to cardiomyopathy (CIII)	Yearly cardiac evaluation; medical management for mild to moderate disease, surgical management for advanced disease
Reactivation in hosts with immunosuppression	Acute myocarditis, CNS abscesses, skin chagomas, atypical manifestations	Positive blood smear or increasing parasite load detected by means of qPCR in serial specimens	Curative efficacy unknown but presumed low; decreases parasitemia and symptoms, prolongs survival (AII)	Serial monitoring after transplantation; provide most effective available antiretroviral or immunosuppressive regimen

* CNS denotes central nervous system, ECG electrocardiography, PCR polymerase chain reaction, and qPCR quantitative PCR.

† Grades reflecting an assessment of the strength and quality of the treatment recommendations are provided in parentheses; the grades are in accordance with recommendations published by the Centers for Disease Control and Prevention and are expressed with the use of Infectious Diseases Society of America quality-of-evidence standards.[22] The strength of the evidence is indicated with a letter grade: a grade of "A" indicates that strong evidence of both efficacy and substantial clinical benefit supports recommendation for use, and the treatment should always be offered; a grade of "C" denotes that evidence for efficacy is insufficient to support a recommendation for or against use or that evidence for efficacy might not outweigh adverse consequences or cost of treatment under consideration, and the treatment should be considered optional. The quality of evidence is graded on a scale of I to III. I denotes evidence from at least one properly designed, randomized clinical trial; II denotes evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments; and III denotes evidence from the opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports from expert committees.

dominant role in pathogenesis.[28,29,31] Investigators have observed that the prevalence of severe Chagas' cardiomyopathy has fallen in areas with effective vector control and postulate that repeated superinfection due to ongoing vector exposure sustains the tissue antigen load and the consequent inflammatory response at a higher chronic level, which promotes cardiac damage.[32] In an experimental model, mice superinfected with the same or a different parasite strain had more frequent severe ECG changes than those infected only once.[33]

Gastrointestinal Chagas' disease predominantly affects the esophagus, colon, or both and results from damage to intramural neurons.[34,35] The manifestations of esophageal disease range from asymptomatic motility disorders and mild achalasia to severe megaesophagus, with symptoms including dysphagia, odynophagia, esophageal reflux, weight loss, aspiration, cough, and regurgitation.[34] Megacolon is characterized by prolonged constipation and may give rise to fecaloma, volvulus, and bowel ischemia. Gastrointestinal Chagas' disease is less frequent than Chagas' cardiomyopathy and is more common in the Southern Cone of South America (Argentina, Bolivia, Chile, Paraguay, Uruguay, and parts of Brazil) than in northern South America, Central America, and Mexico. This geographic pattern is thought to result from differences in the predominant *T. cruzi* genotypes.[36] However, within individual study sites, no strain differences have been detected between infections with and infections without gastrointestinal manifestations.[37]

T. CRUZI IN THE IMMUNOCOMPROMISED HOST

Acute infection in organ recipients has several distinctive features, including a prolonged incubation period and a more severe clinical spectrum that can include acute myocarditis and congestive heart failure.[38] Reactivation of chronic *T. cruzi* infection occurs primarily in patients who have undergone organ transplantation[39] and in adults with human immunodeficiency virus (HIV)–*T. cruzi* coinfection.[40] In both these populations, the risk of reactivation is related to the severity of immunosuppression.

In a longitudinal study involving patients with HIV coinfection, approximately 20% had reactivation, most commonly meningoencephalitis, brain abscesses, or both.[40] The second most commonly reported manifestation is acute myocarditis, which is sometimes superimposed on preexisting chronic cardiomyopathy. Less common manifestations include skin lesions and parasitic invasion of the peritoneum, stomach, or intestine.

The survival of patients who undergo heart transplantation for end-stage Chagas' cardiomyopathy is equal to or longer than that of patients who undergo transplantation for idiopathic or ischemic cardiomyopathy, and in prospectively monitored patients who have undergone transplantation, *T. cruzi* reactivation is a rare cause of death.[41,42] *T. cruzi* reactivation should be considered in the differential diagnosis of febrile episodes and apparent rejection crises. In addition to fever and acute myocarditis in the transplanted heart, symptoms may include panniculitis. Central nervous system involvement is much less frequent among transplant recipients with reactivation than among patients with HIV–*T. cruzi* coinfection.[43]

LABORATORY DIAGNOSIS

In the acute phase, motile trypomastigotes can be detected by means of microscopic examination of fresh anticoagulated blood or buffy coat. Parasites may also be visualized on blood smears stained with Giemsa or other stains and can be grown with the use of hemoculture in a specialized medium. Polymerase chain reaction (PCR) is a sensitive diagnostic tool in the acute phase and is the best test for early detection of infection in the recipient of an organ from an infected donor or after accidental exposure.[44] Early in life, congenital Chagas' disease is an acute infection, and similar diagnostic methods are used.[23] Sampling on several occasions during the first months of life increases sensitivity but may not be acceptable to parents. For at-risk infants in whom Chagas' disease has not been diagnosed at birth, conventional serologic testing is recommended after 9 months, when transferred maternal antibody has disappeared.[23]

The diagnosis of chronic infection relies on IgG serologic testing, most commonly with the use of an enzyme-linked immunosorbent assay (ELISA) or immunofluorescent antibody assay (IFA). No single assay for chronic *T. cruzi* infection has high enough sensitivity and specificity to be used alone; positive results of two tests,

preferably based on different antigens (e.g., whole-parasite lysate and recombinant antigens), are required for confirmation.[4,45] Inevitably, a proportion of persons tested will have discordant results of the two assays and will need further testing to determine their infection status. A number of reference laboratories are located in Latin America and Europe. In the United States, the Centers for Disease Control and Prevention (CDC) offers reference laboratory testing (contact information is provided below).

T. cruzi PCR is increasingly used as a research and monitoring tool. The sensitivity of PCR in the chronic phase of Chagas' disease is highly variable and depends on specimen volume and processing, population characteristics, and PCR primers and methods.[46] Negative PCR results do not prove that infection is absent. Systematic monitoring by means of PCR of serial blood specimens is required for the early recognition of acute organ-derived *T. cruzi* infection; timely treatment can be lifesaving.[44] Quantitative PCR assays are useful in monitoring for reactivation (e.g., after heart transplantation); a positive PCR result does not prove that reactivation has occurred, but a rising parasite load over time is the earliest and most sensitive indicator.[47,48] Rigorously standardized quantitative PCR has been used recently as a primary outcome in two clinical trials of new drug candidates.[49,50]

ANTITRYPANOSOMAL TREATMENT

Nifurtimox and benznidazole, the only drugs with proven efficacy against *T. cruzi* infection, are not currently approved by the Food and Drug Administration but can be obtained from the CDC and used under investigational protocols. Consultations should be sought through the Parasitic Diseases Public Inquiries line (404-718-4745, or parasites@cdc.gov), the CDC Drug Service (404-639-3670), or the CDC Emergency Operations Center (770-488-7100). Access varies outside the United States; questions can be addressed to the World Health Organization (www.who.int/chagas/home_treatment/en/).

Benznidazole, a nitroimidazole derivative, is considered to be the first-line treatment, on the basis of a better side-effect profile than nifurtimox, as well as a more extensive evidence base for efficacy.[22] The most frequently observed adverse effects are dermatologic — usually mild rashes that respond to antihistamines (Table 2).[51-55] Severe or exfoliative dermatitis or dermatitis associated with fever and lymphadenopathy should prompt immediate interruption of treatment. A dose-dependent peripheral neuropathy sometimes occurs late in the course of therapy and necessitates immediate cessation of treatment; it is nearly always reversible, but it may last for months. Bone marrow suppression is rare and should prompt immediate interruption of treatment.

Nifurtimox, a nitrofuran, inhibits pyruvic acid synthesis and disrupts *T. cruzi* carbohydrate metabolism. Gastrointestinal side effects (anorexia, weight loss, nausea, and vomiting) occur in up to 70% of patients.[56,57] Neurologic toxic effects include irritability, insomnia, disorientation, and tremors. Rare but more serious side effects include paresthesias, polyneuropathy, and peripheral neuritis. Both nifurtimox and benznidazole have a better side-effect profile in young children than in adolescents or adults.[60,61] A recent pharmacokinetic study showed significantly faster benznidazole elimination in younger age groups than in older patients, which led to lower drug levels in the younger patients.[62] The good efficacy of the drug in children despite the lower levels in blood raises the possibility that lower benznidazole doses in adolescents and adults might maintain efficacy while decreasing serious side effects.[62]

In patients with acute Chagas' disease and in those with early congenital Chagas' disease, both benznidazole and nifurtimox reduce the severity of symptoms, shorten the clinical course of illness, and reduce the duration of parasitemia; the cure rate in the acute phase is estimated to be 80 to 90%.[63] Until the 1990s, only the acute phase of the infection was thought to be responsive to antiparasitic therapy. However, in the 1990s, two placebo-controlled trials of benznidazole involving children with chronic *T. cruzi* infection showed cure rates of approximately 60%, on the basis of conversion to negative serologic test results 3 to 4 years after treatment.[60,61] Follow-up studies have suggested that the earlier in life children are treated, the higher the rate of conversion from positive to negative results of serologic assays (negative seroconversion).[64,65] Together with growing clinical experience across Latin America, these studies prompted a major change in management of the infection in children, making early diagnosis and antitrypanosomal drug therapy the standard of care throughout the region.

Over the past 15 years, there has been a growing movement toward broader treatment of chronically infected adults, including those with early cardiomyopathy.[22,66-68] Most experts now believe that the majority of patients with chronic *T. cruzi* infection should be offered treatment, with exclusion criteria such as an upper age limit of 50 or 55 years and the presence of advanced irreversible cardiomyopathy.[45,67,68] This change in standards of practice is based in part on nonrandomized, nonblinded longitudinal studies that have shown significantly decreased progression of cardiomyopathy and a trend to decreased mortality among adults treated with benznidazole, as compared with untreated patients.[53,69] The Benznidazole Evaluation for Interrupting Trypanosomiasis (BENEFIT) trial (ClinicalTrials.gov number, NCT00123916), a large, multicenter, double-blind, randomized, placebo-controlled trial of benznidazole for the treatment of patients with mild-to-moderate Chagas' cardiomyopathy, is nearing completion in 2015. The primary outcome measure in the BENEFIT trial is clinical progression of cardiomyopathy.[70] Observational studies have also confirmed that women treated before pregnancy are significantly less likely than untreated women to transmit the infection to their offspring, which provides additional impetus for the treatment of girls and nonpregnant women of reproductive age.[22,71]

Trials of new drug candidates have been sparse and impeded by the lack of a sensitive, practical test of cure.[45,68,72] Conventional serologic markers respond very slowly after treatment; the time to negative seroconversion is measured in years to decades and is said to be inversely proportional to the pretreatment duration of infection (for which age is often used as the proxy).[63] In the two trials involving children, negative seroconversion, as assessed with the use of conventional tests, had not occurred in any treated children by the end of the 3-year and 4-year follow-up periods; the assessment of primary end points relied on experimental assays that measured lytic antibodies.[60,61] These assays are technically challenging and are not currently available for clinical use. Recent randomized clinical trials of two related azole compounds in the treatment of *T. cruzi*–infected adults used quantitative PCR results as the primary end point.[49,50] In a trial of the antifungal drug posaconazole, the enrollment criteria included positive pretreatment PCR results.[49]

Table 2. Dosage Regimens and Frequencies of Adverse Effects Associated with Benznidazole and Nifurtimox Use.

Benznidazole
Dosage regimen*
Age <12 yr: 5–7.5 mg/kg per day orally in 2 divided doses for 60 days
Age ≥12 yr: 5–7 mg/kg per day orally in 2 divided doses for 60 days
Side effects in adults†
Allergic dermatitis (frequent: 29 to 50%)‡
Paresthesia (frequent: 0 to 30%)
Peripheral neuropathy (frequent: 0 to 30%)§
Anorexia and weight loss (frequent: 5 to 40%)
Nausea or vomiting (infrequent: 0 to 5%)
Leukopenia (rare: <1%)§
Thrombocytopenia (rare: <1%)§
Early discontinuation because of side effects (frequent: 7 to 20%)
Nifurtimox
Dosage regimen¶
Age ≤10 yr: 15–20 mg/kg per day orally in 3 or 4 divided doses for 90 days
Age 11–16 yr: 12.5–15 mg/kg per day orally in 3 or 4 divided doses for 90 days
Age ≥17 yr: 8–10 mg/kg per day orally in 3 or 4 divided doses for 90 days
Side effects in adults†
Anorexia and weight loss (very frequent: 50 to 75%)
Nausea (frequent: 15 to 50%)
Vomiting (frequent: 15 to 26%)
Abdominal discomfort (frequent: 12 to 40%)
Headache (frequent: 13 to 70%)
Dizziness or vertigo (frequent: 12 to 33%)
Mood changes (frequent: 10 to 49%)
Insomnia (frequent: 10 to 54%)
Myalgia (frequent: 13 to 30%)
Peripheral neuropathy (infrequent: 2 to 5%)§
Decreased short-term memory (infrequent: 6 to 14%)
Leukopenia (rare: <1%)§
Early discontinuation because of side effects (frequent: 6 to 40%)

* This is the standard regimen in published recommendations.[22] Some investigators treat adults with 300 mg per day for 60 days, regardless of body weight,[49] whereas others use an upper limit of 300 mg per day but prolong treatment to complete the total dose corresponding to 5 mg per kilogram per day for 60 days.[24]

† The frequencies (in parentheses) are based on published data.[51-57]

‡ If the dermatitis is severe, exfoliative, or associated with fever, discontinue treatment with the drug. The Stevens–Johnson syndrome has been reported in association with benznidazole treatment.

§ The symptom necessitates discontinuation of treatment with the drug.

¶ There are no published recommendations regarding an upper dose limit. The standard nifurtimox dosing schedule for human African trypanosomiasis is 15 mg per kilogram per day for 10 days (in combination with efluornithine).[58] Dosing regimens of up to 30 mg per kilogram per day in multiple 21-day cycles have been used in trials for neuroblastoma involving children.[59] Some adverse effects appear to be related to length of treatment rather than daily dose; regimens from 60 days to 120 days have been used.[56,57] Because of the side effects, only 50 to 60% of adult patients complete the entire treatment course.[56]

Parasitemia was suppressed at the end of posaconazole treatment, but it returned to detectable levels in 80% (high-dose group) to 90% (low-dose group) of patients at 12 months. In contrast, only 6% of patients who completed the 60-day benznidazole course had positive PCR results at any time after treatment. Similar results have been reported from a trial of the ravuconazole prodrug E1224 (ClinicalTrials.gov number, NCT01489228), in which the frequency of positive PCR results after 12 months was substantially higher among patients who received the ravuconazole prodrug than it was among patients who received benznidazole.[50] These results, although disappointing in terms of new drug candidates, provide strong support for the use of quantitative PCR as an outcome measure in clinical trials: although negative results do not constitute proof of cure, positive results provide timely, unequivocal evidence of treatment failure. Debate continues regarding other potential tests of response to treatment, including lytic antibody assays, other novel serologic tests, and cellular immune assays.[68,72,73]

MANAGEMENT OF THE CHRONIC SEQUELAE OF *T. CRUZI* INFECTION

Yearly cardiac evaluations, including 12-lead ECG, are recommended for all persons with *T. cruzi* infection, regardless of whether they have completed a course of antitrypanosomal treatment.[22] Cardiac symptoms or ECG abnormalities should prompt a more in-depth cardiac workup, including echocardiography, ambulatory ECG monitoring, and electrophysiological studies, as appropriate.[4,24] In general, management follows the established practices for other causes of heart disease.[74] Sinus node dysfunction and high-grade atrioventricular blocks occur frequently in Chagas' cardiomyopathy and may be indications for pacemaker implantation. Although trial data are lacking, most cardiologists with expertise in Chagas' disease prefer amiodarone as the first-line drug for ventricular arrhythmias and support a role for implantable cardioverter–defibrillators as an additional method of treatment in these patients.[4,74,75] Congestive heart failure is managed in accordance with standard guidelines.[4,74] Because of the bradyarrhythmias that are common in Chagas' cardiomyopathy, careful monitoring is required when digoxin or beta-blockers are used. Cardiac transplantation is an effective method of managing Chagas' cardiomyopathy with refractory heart failure; systematic posttransplantation PCR monitoring enables early diagnosis and treatment of *T. cruzi* reactivation.[42]

The management of gastrointestinal Chagas' disease is similar to that for idiopathic achalasia or megacolon.[34] Esophageal symptoms may be mitigated by drugs that relax the sphincter or by laparoscopic myotomy. The early stages of colonic involvement may respond to high-fiber diets and laxatives or enemas. The late stages of megaesophagus and megacolon may mandate surgical resection.[34] Antitrypanosomal treatment is not thought to influence the progression of gastrointestinal Chagas' disease.[22]

CONCLUSIONS

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.

Despite progress in the control of domestic vector infestation since 1991, difficult challenges remain. New strategies are needed for the most highly endemic areas, especially the Gran Chaco, where rapid domestic reinfestation is the rule and resistance to insecticides is increasingly evident.[76] In areas with extensive sylvatic infestation, such as the Amazon Basin, elimination of the vectors is impossible, and new methods need to be implemented and maintained to prevent vectorborne and oral transmission.[77]

Dr. Bern reports receiving consulting fees from Chemogroup. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

REFERENCES

1. Bern C. Antitrypanosomal therapy for chronic Chagas' disease. N Engl J Med 2011;364:2527-34.
2. Rassi A Jr, Rassi A, Marin-Neto JA. Chagas disease. Lancet 2010;375:1388-402.
3. Shikanai-Yasuda MA, Carvalho NB. Oral transmission of Chagas disease. Clin Infect Dis 2012;54:845-52.
4. Rassi A Jr, Rassi A, Marcondes de Rezende J. American trypanosomiasis (Chagas disease). Infect Dis Clin North Am 2012;26:275-91.
5. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. Wkly Epidemiol Rec 2015;90:33-43.
6. Feliciangeli MD, Campbell-Lendrum D, Martinez C, Gonzalez D, Coleman P, Davies C. Chagas disease control in Venezuela: lessons for the Andean region and beyond. Trends Parasitol 2003;19:44-9.
7. Nouvellet P, Dumonteil E, Gourbière S. The improbable transmission of Trypanosoma cruzi to human: the missing link in the dynamics and control of Chagas disease. PLoS Negl Trop Dis 2013; 7(11):e2505.
8. Samuels AM, Clark EH, Galdos-Cardenas G, et al. Epidemiology of and impact of insecticide spraying on Chagas disease in communities in the Bolivian Chaco. PLoS Negl Trop Dis 2013;7(8): e2358.
9. Maguire JH, Mott KE, Lehman JS, et al. Relationship of electrocardiographic abnormalities and seropositivity to Trypanosoma cruzi within a rural community in northeast Brazil. Am Heart J 1983; 105:287-94.
10. Bern C, Montgomery SP. An estimate of the burden of Chagas disease in the United States. Clin Infect Dis 2009;49(5): e52-e54.
11. Gascon J, Bern C, Pinazo MJ. Chagas disease in Spain, the United States and other non-endemic countries. Acta Trop 2010;115:22-7.
12. Schofield CJ, Jannin J, Salvatella R. The future of Chagas disease control. Trends Parasitol 2006;22:583-8.
13. Hashimoto K, Schofield CJ. Elimination of Rhodnius prolixus in Central America. Parasit Vectors 2012;5:45.
14. Global burden of disease estimates for 2000–2012. Geneva: World Health Organization, 2014 (http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html).
15. Bern C, Kjos S, Yabsley MJ, Montgomery SP. Trypanosoma cruzi and Chagas' disease in the United States. Clin Microbiol Rev 2011;24:655-81.
16. Cantey PT, Stramer SL, Townsend RL, et al. The United States Trypanosoma cruzi Infection Study: evidence for vector-borne transmission of the parasite that causes Chagas disease among United States blood donors. Transfusion 2012; 52:1922-30.
17. Garcia MN, Aguilar D, Gorchakov R, et al. Evidence of autochthonous Chagas disease in southeastern Texas. Am J Trop Med Hyg 2015;92:325-30.
18. Kapelusznik L, Varela D, Montgomery SP, et al. Chagas disease in Latin American immigrants with dilated cardiomyopathy in New York City. Clin Infect Dis 2013;57(1):e7.
19. Edwards MS, Rench MA, Todd CW, et al. Perinatal screening for Chagas disease in southern Texas. J Pediatr Infect Dis Soc 2015;4:67-70.
20. Stimpert KK, Montgomery SP. Physician awareness of Chagas disease, USA. Emerg Infect Dis 2010;16:871-2.
21. Verani JR, Montgomery SP, Schulkin J, Anderson B, Jones JL. Survey of obstetrician-gynecologists in the United States about Chagas disease. Am J Trop Med Hyg 2010;83:891-5.
22. Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: a systematic review. JAMA 2007;298:2171-81.
23. Bern C, Martin DL, Gilman RH. Acute and congenital Chagas disease. Adv Parasitol 2011;75:19-47.
24. Rassi A Jr, Dias JC, Marin-Neto JA, Rassi A. Challenges and opportunities for primary, secondary, and tertiary prevention of Chagas' disease. Heart 2009;95: 524-34.
25. Acquatella H. Echocardiography in Chagas heart disease. Circulation 2007; 115:1124-31.
26. Sabino EC, Ribeiro AL, Salemi VM, et al. Ten-year incidence of Chagas cardiomyopathy among asymptomatic Trypanosoma cruzi-seropositive former blood donors. Circulation 2013;127:1105-15.
27. Marin-Neto JA, Cunha-Neto E, Maciel BC, Simões MV. Pathogenesis of chronic Chagas heart disease. Circulation 2007; 115:1109-23.
28. Tarleton RL. Parasite persistence in the aetiology of Chagas disease. Int J Parasitol 2001;31:550-4.
29. Dutra WO, Menezes CA, Magalhães LM, Gollob KJ. Immunoregulatory networks in human Chagas disease. Parasite Immunol 2014;36:377-87.
30. Tarleton RL. Chagas disease: a role for autoimmunity? Trends Parasitol 2003; 19:447-51.
31. Machado FS, Dutra WO, Esper L, et al. Current understanding of immunity to Trypanosoma cruzi infection and pathogenesis of Chagas disease. Semin Immunopathol 2012;34:753-70.
32. Pinto Dias JC. Natural history of Chagas disease. Arq Bras Cardiol 1995;65: 359-66. (In Portuguese.)
33. Bustamante JM, Rivarola HW, Fernández AR, et al. Trypanosoma cruzi reinfections in mice determine the severity of cardiac damage. Int J Parasitol 2002;32: 889-96.
34. de Oliveira RB, Troncon LE, Dantas RO, Menghelli UG. Gastrointestinal manifestations of Chagas' disease. Am J Gastroenterol 1998;93:884-9.
35. Pinazo MJ, Cañas E, Elizalde JI, et al. Diagnosis, management and treatment of chronic Chagas' gastrointestinal disease in areas where Trypanosoma cruzi infection is not endemic. Gastroenterol Hepatol 2010;33:191-200.
36. Miles MA, Cedillos RA, Póvoa MM, de Souza AA, Prata A, Macedo V. Do radically dissimilar Trypanosoma cruzi strains (zymodemes) cause Venezuelan and Brazilian forms of Chagas' disease? Lancet 1981;1:1338-40.
37. del Puerto R, Nishizawa JE, Kikuchi M, et al. Lineage analysis of circulating Trypanosoma cruzi parasites and their association with clinical forms of Chagas disease in Bolivia. PLoS Negl Trop Dis 2010;4(5):e687.
38. Huprikar S, Bosserman E, Patel G, et al. Donor-derived Trypanosoma cruzi infection in solid organ recipients in the United States, 2001-2011. Am J Transplant 2013;13:2418-25.
39. Bacal F, Silva CP, Pires PV, et al. Transplantation for Chagas' disease: an overview of immunosuppression and reactivation in the last two decades. Clin Transplant 2010;24(2):E29-E34.
40. Sartori AM, Ibrahim KY, Nunes Westphalen EV, et al. Manifestations of Chagas disease (American trypanosomiasis) in patients with HIV/AIDS. Ann Trop Med Parasitol 2007;101:31-50.
41. Bocchi EA, Fiorelli A. The paradox of survival results after heart transplantation for cardiomyopathy caused by Trypanosoma cruzi. Ann Thorac Surg 2001; 71:1833-8.
42. Kransdorf EP, Czer LS, Luthringer DJ, et al. Heart transplantation for Chagas cardiomyopathy in the United States. Am J Transplant 2013;13:3262-8.
43. Fiorelli AI, Stolf NA, Honorato R, et al. Later evolution after cardiac transplantation in Chagas' disease. Transplant Proc 2005;37:2793-8.
44. Chin-Hong PV, Schwartz BS, Bern C, et al. Screening and treatment of Chagas disease in organ transplant recipients in the United States: recommendations from the Chagas in Transplant Working Group. Am J Transplant 2011;11:672-80.
45. Tarleton RL, Reithinger R, Urbina JA,

Kitron U, Gürtler RE. The challenges of Chagas Disease — grim outlook or glimmer of hope? PLoS Med 2007;4(12):e332.
46. Schijman AG, Bisio M, Orellana L, et al. International study to evaluate PCR methods for detection of Trypanosoma cruzi DNA in blood samples from Chagas disease patients. PLoS Negl Trop Dis 2011;5(1):e931.
47. Duffy T, Bisio M, Altcheh J, et al. Accurate real-time PCR strategy for monitoring bloodstream parasitic loads in chagas disease patients. PLoS Negl Trop Dis 2009;3(4):e419.
48. Diez M, Favaloro L, Bertolotti A, et al. Usefulness of PCR strategies for early diagnosis of Chagas' disease reactivation and treatment follow-up in heart transplantation. Am J Transplant 2007;7:1633-40.
49. Molina I, Gómez i Prat J, Salvador F, et al. Randomized trial of posaconazole and benznidazole for chronic Chagas' disease. N Engl J Med 2014;370:1899-908.
50. Chatelain E. Chagas disease drug discovery: toward a new era. J Biomol Screen 2015;20:22-35.
51. Pinazo MJ, Muñoz J, Posada E, et al. Tolerance of benznidazole in treatment of Chagas' disease in adults. Antimicrob Agents Chemother 2010;54:4896-9.
52. Coura JR, de Abreu LL, Willcox HP, Petana W. Comparative controlled study on the use of benznidazole, nifurtimox and placebo, in the chronic form of Chagas' disease, in a field area with interrupted transmission. I. Preliminary evaluation. Rev Soc Bras Med Trop 1997;30:139-44. (In Portuguese.)
53. Viotti R, Vigliano C, Lococo B, et al. Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment: a nonrandomized trial. Ann Intern Med 2006;144:724-34.
54. Pérez-Molina JA, Pérez-Ayala A, Moreno S, Fernández-González MC, Zamora J, López-Velez R. Use of benznidazole to treat chronic Chagas' disease: a systematic review with a meta-analysis. J Antimicrob Chemother 2009;64:1139-47.
55. Tornheim JA, Lozano Beltran DF, Gilman RH, et al. Improved completion rates and characterization of drug reactions with an intensive Chagas disease treatment program in rural Bolivia. PLoS Negl Trop Dis 2013;7(9):e2407.
56. Jackson Y, Alirol E, Getaz L, Wolff H, Combescure C, Chappuis F. Tolerance and safety of nifurtimox in patients with chronic Chagas disease. Clin Infect Dis 2010;51(10):e69-e75.
57. Wegner DH, Rohwedder RW. Experience with nifurtimox in chronic Chagas' infection: preliminary report. Arzneimittelforschung 1972;22:1635-41.
58. Priotto G, Kasparian S, Mutombo W, et al. Nifurtimox-eflornithine combination therapy for second-stage African Trypanosoma brucei gambiense trypanosomiasis: a multicentre, randomised, phse III, non-inferiority trial Lancet 2009;374:56-64.
59. Saulnier Sholler GL, Bergendahl GM, Brard L, et al. A phase 1 study of nifurtimox in patients with relapsed/refractory neuroblastoma J Pediatr Hematol Oncol 2011;33:25-30.
60. de Andrade AL, Zicker F, de Oliveira RM, et al. Randomised trial of efficacy of benznidazole in treatment of early Trypanosoma cruzi infection. Lancet 1996;348:1407-13.
61. Sosa Estani S, Segura EL, Ruiz AM, Velazquez E, Porcel BM, Yampotis C. Efficacy of chemotherapy with benznidazole in children in the indeterminate phase of Chagas' disease. Am J Trop Med Hyg 1998;59:526-9.
62. Altcheh J, Moscatelli G, Mastrantonio G, et al. Population pharmacokinetic study of benznidazole in pediatric Chagas disease suggests efficacy despite lower plasma concentrations than in adults. PLoS Negl Trop Dis 2014;8(5):e2907.
63. Cancado JR, Brener Z. Terapeutica. In: Brener Z, Andrade Z, eds. Trypanosoma cruzi e doença de Chagas. Rio de Janeiro: Guanabara Koogan, 1979:362-424.
64. Andrade AL, Martelli CM, Oliveira RM, et al. Short report: benznidazole efficacy among Trypanosoma cruzi-infected adolescents after a six-year follow-up. Am J Trop Med Hyg 2004;71:594-7.
65. Streiger ML, del Barco ML, Fabbro DL, Arias ED, Amicone NA. Longitudinal study and specific chemotherapy in children with chronic Chagas' disease, residing in a low endemicity area of Argentina. Rev Soc Bras Med Trop 2004;37:365-75. (In Portuguese.)
66. Gascón J, Albajar P, Cañas E, et al. Diagnosis, management and treatment of chronic Chagas' heart disease in areas where Trypanosoma cruzi infection is not endemic. Rev Esp Cardiol 2007;60:285-93. (In Spanish.)
67. Sosa-Estani S, Segura EL. Etiological treatment in patients infected by Trypanosoma cruzi: experiences in Argentina. Curr Opin Infect Dis 2006;19:583-7.
68. Viotti R, Alarcón de Noya B, Araujo-Jorge T, et al. Towards a paradigm shift in the treatment of chronic Chagas disease. Antimicrob Agents Chemother 2014;58:635-9.
69. Villar JC, Perez JG, Cortes OL, et al. Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection. Cochrane Database Syst Rev 2014;5:CD003463.
70. Marin-Neto JA, Rassi A Jr, Avezum A Jr, et al. The BENEFIT trial: testing the hypothesis that trypanocidal therapy is beneficial for patients with chronic Chagas heart disease. Mem Inst Oswaldo Cruz 2009;104:Suppl 1:319-24.
71. Fabbro DL, Danesi E, Olivera V, et al. Trypanocide treatment of women infected with Trypanosoma cruzi and its effect on preventing congenital Chagas. PLoS Negl Trop Dis 2014;8(11):e3312.
72. Pinazo MJ, Thomas MC, Bua J, et al. Biological markers for evaluating therapeutic efficacy in Chagas disease, a systematic review. Expert Rev Anti Infect Ther 2014;12:479-96.
73. Requena-Méndez A, López MC, Angheben A, et al. Evaluating Chagas disease progression and cure through blood-derived biomarkers: a systematic review. Expert Rev Anti Infect Ther 2013;11:957-76.
74. Ribeiro AL, Nunes MP, Teixeira MM, Rocha MO. Diagnosis and management of Chagas disease and cardiomyopathy. Nat Rev Cardiol 2012;9:576-89.
75. Gali WL, Sarabanda AV, Baggio JM, et al. Implantable cardioverter-defibrillators for treatment of sustained ventricular arrhythmias in patients with Chagas' heart disease: comparison with a control group treated with amiodarone alone. Europace 2014;16:674-80.
76. Gürtler RE, Kitron U, Cecere MC, Segura EL, Cohen JE. Sustainable vector control and management of Chagas disease in the Gran Chaco, Argentina. Proc Natl Acad Sci U S A 2007;104:16194-9.
77. Dias JC. Elimination of Chagas disease transmission: perspectives. Mem Inst Oswaldo Cruz 2009;104:Suppl 1:41-5.