Chagas’ Disease

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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). 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. 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.

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). 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. The highest estimated incidence is 4% per year, in the hyperendemic Bolivian Chaco. In an endemic setting, continued transmission over time results in a pattern of increasing prevalence of both infection and cardiomyopathy with increasing age. 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.

Latin America has made substantial progress toward the control of Chagas’ disease. 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. The Pan American Health Organization has certified the interruption of transmission by domestic vectors in several countries in South America and in Central America. 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.
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. 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. 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. Direct assessments of prevalence in the United States are sparse and have been restricted to small-scale sur-

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**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

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veys or case series in populations chosen because of an anticipated high risk (e.g., Latin American immigrants with nonischemic heart disease). 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). 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. 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 myocard-

Figure 2. Estimated Prevalences of Trypanosoma cruzi Infection.

Shown are the prevalences at the national level, calculated on the basis of published data. 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.

Prevalence of T. cruzi Infection
- No data
- Very low (<0.1%)
- Low (0.1–0.9%)
- Moderate (1.0–2.9%)
- High (3.0% or higher)
Chagas’ disease and a higher case-fatality rate than vectorborne 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-
Table 1. Diagnosis and Management of Chagas’ Disease.*

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

* 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. 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 from 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 transplantation39 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. 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. 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 or- tifications should be sought through the Parasitic Administration but can be obtained from the CDC

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. 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. 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. Rigorously standard-ized quantitative PCR has been used recently as a primary outcome in two clinical trials of new drug candidates.

**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. The most frequently observed adverse effects are dermatologic — usually mild rashes that respond to antihistamines (Table 2). 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. 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. 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. 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.

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%. 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. 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). 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.49,67,68 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.22,69 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).22 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

<table>
<thead>
<tr>
<th>Dosage regimen*</th>
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<tbody>
<tr>
<td>Age &lt;12 yr: 5–7.5 mg/kg per day orally in 2 divided doses for 60 days</td>
</tr>
<tr>
<td>Age ≥12 yr: 5–7 mg/kg per day orally in 2 divided doses for 60 days</td>
</tr>
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</table>

**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%)
- Early discontinuation because of side effects (frequent: 7 to 20%)

### Nifurtimox

<table>
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<tr>
<th>Dosage regimen¶</th>
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<tbody>
<tr>
<td>Age ≤10 yr: 15–20 mg/kg per day orally in 3 or 4 divided doses for 90 days</td>
</tr>
<tr>
<td>Age 11–16 yr: 12.5–15 mg/kg per day orally in 3 or 4 divided doses for 90 days</td>
</tr>
<tr>
<td>Age ≥17 yr: 8–10 mg/kg per day orally in 3 or 4 divided doses for 90 days</td>
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</table>

**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, 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.44
† The frequencies (in parentheses) are based on published data.31,32
‡ 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 efuornithine).34 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.29 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.35,36 Because of the side effects, only 50 to 60% of adult patients complete the entire treatment course.46.
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. 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.

**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. Cardiac symptoms or ECG abnormalities should prompt a more in-depth cardiac workup, including echocardiography, ambulatory ECG monitoring, and electrophysiological studies, as appropriate. In general, management follows the established practices for other causes of heart disease. 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. Congestive heart failure is managed in accordance with standard guidelines. 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.

The management of gastrointestinal Chagas’ disease is similar to that for idiopathic achalasia or megacolon. 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. Antitrypanosomal treatment is not thought to influence the progression of gastrointestinal Chagas’ disease.

**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. 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.

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.
The future of Chagas disease control.

45. Tarleton RL, Reithinger R, Urbina JA,


