Evaluation and Treatment of Chagas Disease in the United States

A Systematic Review

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Context Because of population migration from endemic areas and newly instituted blood bank screening, US clinicians are likely to see an increasing number of patients with suspected or confirmed chronic *Trypanosoma cruzi* infection (Chagas disease).

Objective To examine the evidence base and provide practical recommendations for evaluation, counseling, and etiologic treatment of patients with chronic *T cruzi* infection.

Evidence Acquisition Literature review conducted based on a systematic MEDLINE search for all available years through 2007; review of additional articles, reports, and book chapters; and input from experts in the field.

Evidence Synthesis The patient newly diagnosed with Chagas disease should undergo a medical history, physical examination, and resting 12-lead electrocardiogram (ECG) with a 30-second lead II rhythm strip. If this evaluation is normal, no further testing is indicated; history, physical examination, and ECG should be repeated annually. If findings suggest Chagas heart disease, a comprehensive cardiac evaluation, including 24-hour ambulatory ECG monitoring, echocardiography, and exercise testing, is recommended. If gastrointestinal tract symptoms are present, barium contrast studies should be performed. Antitrypanosomal treatment is recommended for all cases of acute and congenital Chagas disease, reactivated infection, and chronic *T cruzi* infection in individuals 18 years or younger. In adults aged 19 to 50 years without advanced heart disease, etiologic treatment may slow development and progression of cardiomyopathy and should generally be offered; treatment is considered optional for those older than 50 years. Individualized treatment decisions for adults should balance the potential benefit, prolonged course, and frequent adverse effects of the drugs. Strong consideration should be given to treatment of previously untreated patients with human immunodeficiency virus infection or those expecting to undergo organ transplantation.

Conclusions Chagas disease presents an increasing challenge for clinicians in the United States. Despite gaps in the evidence base, current knowledge is sufficient to make practical recommendations to guide appropriate evaluation, management, and etiologic treatment of Chagas disease.

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CHAGAS DISEASE IS CAUSED BY *Trypanosoma cruzi*, a protozoan parasite usually transmitted by infected triatomine bugs. Transmission also occurs through transfusion or organ transplantation, from mother to infant, and rarely by ingestion of contaminated food or drink.[1-3] Vector-borne transmission occurs exclusively in the Americas, where an estimated 8 million to 10 million people have Chagas disease.[4,5] Historically, transmission has occurred predominantly in rural areas of Latin America, where poor housing conditions have promoted contact with infected vectors. Successful programs

See also Patient Page.

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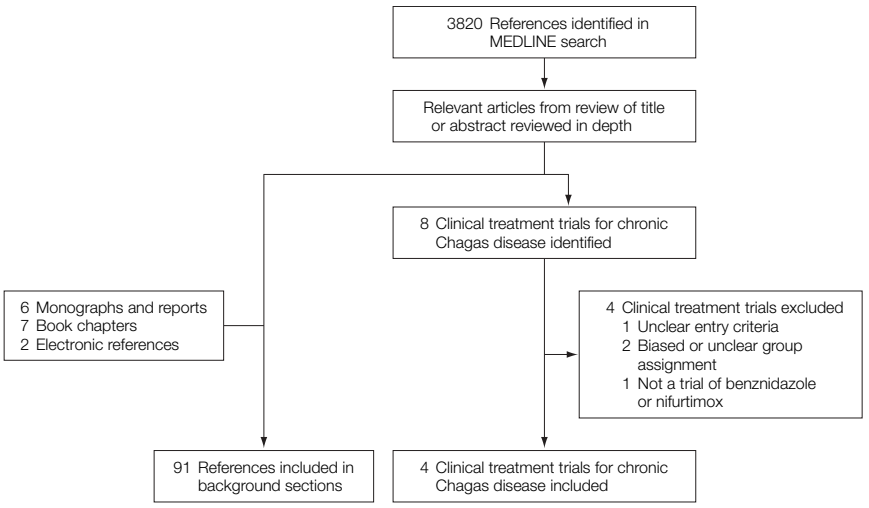
Figure 1. Study Selection



to reduce vector- and blood-borne transmission, as well as migration within and beyond endemic countries, have changed the epidemiology of the disease.[4,6,7]

In endemic settings, *T cruzi* infection is usually acquired in childhood. The vectors defecate during or immediately after feeding; the parasite is present in large numbers in the feces of infected bugs and enters the human body through the bite wound, conjunctiva, or other mucous membrane. An estimated 100 000 infected persons live in the United States; most acquired the disease while residing in endemic areas.[8] However, *T cruzi*–infected vectors and animals are found in many parts of the United States,[9,10] and rare cases of autochthonous transmission have been documented.[11,12] Better housing conditions and less efficient vectors may explain the low risk of vectorial transmission; transfusion, organ transplantation, and mother-to-infant transmission are more likely infection routes in the United States.

On December 13, 2006, the US Food and Drug Administration approved a Chagas disease screening assay for donated blood.[13] As of September 6, 2007, 193 donations confirmed positive had been reported.[14] Blood donor screening is also likely to lead to heightened awareness and increased requests for diagnostic testing in the wider community. Nearly all *T cruzi* infections in newly diagnosed patients will be in the chronic phase, and most will be asymptomatic. Appropriate management of patients with Chagas disease requires specialized clinical expertise, laboratory diagnostic support, and access to antitrypanosomal drugs, all of which are limited in the United States.

This article aims to provide clinicians with practical guidance for the evaluation, management, and etiologic treatment of Chagas disease, with a primary focus on the chronic phase. The detailed management of Chagas cardiac[15-17] and gastrointestinal tract[18] disease is beyond the scope of this article; primary care clinicians should consult with experienced subspecialists. This article is based on a comprehensive systematic literature review supplemented by extensive input from experts and the experience of the US Centers for Disease Control and Prevention (CDC) and takes into account the drugs and medical technology available in the United States.

EVIDENCE ACQUISITION

The literature was reviewed based on MEDLINE searches using the term *Chagas disease* with the subheadings *evaluation*, *diagnosis*, *prognosis*, *treatment*, *congenital*, *gastrointestinal*, *transplant*, *HIV*, *nifurtimox*, *benznidazole*, *clinical trials*, *adverse effects*, and the limiter *human*. Articles published from 1966 through July 1, 2007, in English, Spanish, and Portuguese were included. These searches yielded 3820 potentially relevant articles (FIGURE 1). Other pertinent articles, reports, monographs, and book chapters were located through citations in the literature or suggested by experts. Recent guidelines by expert committees in Brazil, Argentina, and Spain were also consulted.[19-21] We reviewed titles, abstracts, or both to determine relevance to this article. Observational studies were cited if the design and outcome measures were clearly described and appropriate. Prospective drug treatment trials were included if criteria for patient inclusion and group allocation were clearly described and unbiased and if outcome measures were well defined and appropriate. Trials of drugs other than benznidazole and nifurtimox were excluded, because no other drugs have been demonstrated to have efficacy in human *T cruzi* infection.

EVIDENCE SYNTHESIS

Clinical Aspects of Chagas Disease

Most *T cruzi*–infected persons pass through the acute phase with mild symptoms or a nonspecific febrile illness; most acute infections are unrecognized.[1] Severe manifestations, such as acute myocarditis or meningoencephalitis, are rarely detected.[1] The acute phase lasts 4 to 8 weeks. Infected individuals then enter the chronic phase and, in the absence of successful treatment, remain infected for life. Persons with chronic infection but without signs or symptoms are considered to have the indeterminate form of Chagas disease. The strict definition of the indeterminate form requires positive anti–*T cruzi* serology results, no symptoms or physical examination abnormalities, normal 12-lead electrocardiogram (ECG) findings, and normal findings on radiological examination of the chest, esophagus, and colon.[20]

Approximately 70% to 80% of infected individuals remain in the indeterminate form throughout their

lives, whereas as many as 20% to 30% of those who initially have the indeterminate form progress over a period of years to decades to clinically evident disease, most commonly affecting the heart.[22,23] Affected patients have a chronic inflammatory process that involves all heart chambers, conduction system damage, and often an apical aneurysm. The pathogenesis is hypothesized to involve parasite persistence in cardiac tissue and immune-mediated myocardial injury.[24] The earliest manifestations are usually conduction system abnormalities, most frequently right bundle-branch block or left anterior fascicular block and segmental left ventricular wall motion abnormalities.[23] Later manifestations include (1) complex ventricular extrasystoles and nonsustained and sustained ventricular tachycardia; (2) sinus node dysfunction, usually leading to sinus bradycardia; (3) high-degree heart block; (4) pulmonary and systemic thromboembolic phenomena due to thrombus formation in the dilated left ventricle or aneurysm; and (5) progressive dilated cardiomyopathy with congestive heart failure.[17] These abnormalities lead to palpitations, presyncope, syncope, and a high risk of sudden death.[15] Often there are both bradyarrhythmias and tachyarrhythmias. A substantial proportion of patients have atypical chest pain, hypothesized to be related to microvascular perfusion defects.[24] Several classification schemes for Chagas heart disease are used in Latin America (BOX).[20,25-28] The most important discriminating factors are ECG status and presence or absence of congestive heart failure. One system incorporates the recently updated American College of Cardiology/American Heart Association staging of congestive heart failure.[27,28]

Box. Classification Schemes to Grade Presence and Severity of Chagas Cardiomyopathy

Modified Kuschnir Classification[25]

0: Normal ECG findings and normal heart size (usually based on chest radiography)

I: Abnormal ECG findings and normal heart size (usually based on chest radiography)

II: Left ventricular enlargement

III: Congestive heart failure

Brazilian Consensus Classification[20]

A: Abnormal ECG findings, normal echocardiogram findings, no signs of CHF

B1: Abnormal ECG findings, abnormal echocardiogram findings with LVEF >45%, no signs of CHF

B2: Abnormal ECG findings, abnormal echocardiogram findings with LVEF <45%, no signs of CHF

C: Abnormal ECG findings, abnormal echocardiogram findings, compensated CHF

D: Abnormal ECG findings, abnormal echocardiogram findings, refractory CHF

Modified Los Andes Classification[26]

IA: Normal ECG findings, normal echocardiogram findings, no signs of CHF

IB: Normal ECG findings, abnormal echocardiogram findings, no signs of CHF

II: Abnormal ECG findings, abnormal echocardiogram findings, no signs of CHF

III: Abnormal ECG findings, abnormal echocardiogram findings, CHF

Classification Incorporating American College of Cardiology/American Heart Association Staging[27,28]

A: Normal ECG findings, normal heart size, normal LVEF, NYHA class I

B: Abnormal ECG findings, normal heart size, normal LVEF, NYHA class I

C: Abnormal ECG findings, increased heart size, decreased LVEF, NYHA class II-III

D: Abnormal ECG findings, increased heart size, decreased LVEF, NYHA class IV

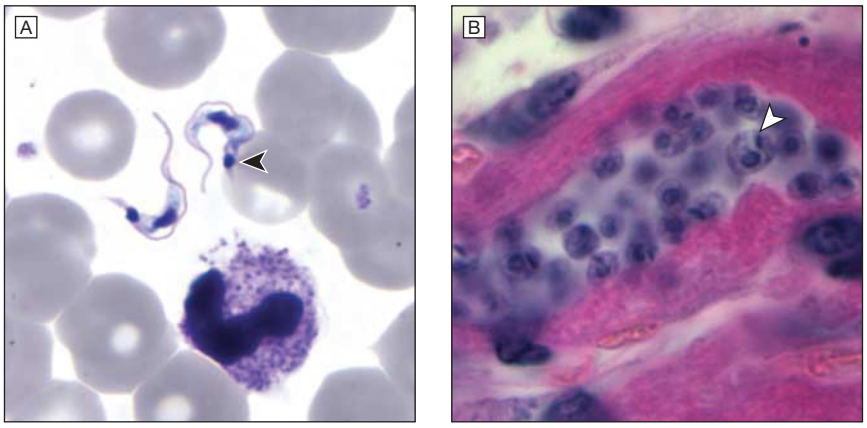
Abbreviations: CHF, congestive heart failure; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Chagas gastrointestinal tract disease results from damage to intramural neurons and predominantly affects the esophagus, colon, or both.[18,29,30] The esophageal effects comprise a spectrum ranging from asymptomatic motility disorders through mild achalasia to severe megaesophagus.[31] Manifestations include dysphagia, odynophagia, esophageal reflux, weight loss, aspiration, cough, and regurgitation. As in idiopathic achalasia, the risk of esophageal carcinoma is increased.[32,33] Colonic involvement leads to prolonged constipation, abdominal pain, and fecaloma. Patients with megacolon have an increased risk of volvulus and consequent bowel ischemia. Gastrointestinal tract involvement is less common than Chagas heart disease, is seen almost exclusively in patients infected in the Southern Cone (Argentina, Bolivia, Chile, Paraguay, southern Peru, Uruguay, and parts of Brazil), and is rare in northern South America, Central America, and Mexico. This geographical pattern is thought to be linked to differences in parasite strains.[34,35]

In approximately 1% to 10% of pregnancies in women with chronic *T cruzi* infection, the infant is born with congenital infection.[1,36,37] Most infected newborns are asymptomatic or have nonspecific findings such as low birth weight, prematurity, or low Apgar scores. Other signs include hepatosplenomegaly, anemia, and thrombocytopenia. Serious manifestations, including myocarditis, meningoencephalitis, and respiratory distress, are uncommon but carry a high risk of mortality.[37]

Trypanosoma cruzi infection in patients who become immunocompromised may reactivate, leading to increases in intracellular parasite replication and parasitemia detectable by microscopy. Reactivation occurs in a minority of patients

Figure 2. *Trypanosoma cruzi*



A, The trypomastigote forms of *Trypanosoma cruzi* in a peripheral blood smear from a patient with acute Chagas disease. Arrowhead indicates the kinetoplast (Giemsa stain, original magnification ×1000). B, Nest of *T cruzi* amastigotes within a cardiac myocyte in a patient with chronic Chagas disease. Arrowhead indicates the kinetoplast (hematoxylin-eosin, original magnification ×1000). Courtesy of the Division of Parasitic Diseases, US Centers for Disease Control and Prevention.

with chronic Chagas disease who are coinfected with human immunodeficiency virus or are receiving immunosuppressive drugs. Although the incidence in patients undergoing transplantation is not well defined, reactivation is more common in patients treated with highly immunosuppressive regimens.[38] Reactivated infection has features that differ from those of acute infection, and patients with drug-induced immunosuppression have a clinical picture distinct from that of those with AIDS. In recipients of solid organ or bone marrow transplants, reactivation is associated with subcutaneous parasite-containing nodules, panniculitis, and myocarditis; central nervous system involvement has rarely been reported.[39-42] By contrast, in patients with AIDS, the most common manifestations are meningoencephalitis and space-occupying central nervous system lesions that can be confused with toxoplasmosis.[43,44] Acute myocarditis, sometimes superimposed on preexisting cardiomyopathy due to chronic Chagas disease, can lead to rapid-onset congestive heart failure.[43,44]

Diagnostic Considerations

In the acute phase, the level of parasitemia is high, and motile trypomastigotes are often detected by microscopy of fresh preparations of anticoagulated blood or buffy coat (FIGURE 2).[1] The parasitemia decreases within 90 days of infection, even without treatment,[45] and is undetectable by microscopy in the chronic phase. Nevertheless, low-level parasitemias account for transmission from chronically infected individuals through blood transfusions, organ transplants, mother-to-infant transmission, or via the vector. Diagnosis of chronic Chagas disease relies on serologic methods, most commonly enzyme-linked immunosorbent assay and immunofluorescent antibody test. No single assay has sufficient sensitivity and specificity to be relied on alone; 2 tests based on different antigens or techniques are used in parallel to increase the accuracy of the diagnosis.[46,47] When results are discordant, a third assay may be used to confirm or refute the diagnosis, or repeat sampling may be required.

Identification of the parasite by microscopy, hemoculture, or polymerase chain reaction (PCR)-based methods provides definitive diagnosis of Chagas disease. However, the sensitivity of these methods is limited by the level of parasitemia, and a negative result does not exclude the diagnosis. PCR-based methods have high sensitivity in acute *T cruzi* infection, but their performance in chronic Chagas disease is variable and currently they are primarily research tools.[48] Because positive PCR results can occur in chronic infection in the absence of reactivation, laboratory monitoring for reactivated infection relies primarily on microscopic examination of fresh blood or buffy coat.

Programs to identify congenital infection rely on serologic diagnosis of infected mothers, followed by microscopic and PCR-based examination of cord blood, peripheral blood specimens, or both from their infants during the first 1 to 2 months of life.[36,49] If results of parasitological testing are negative or if testing is not performed early in life, the infant should be tested by enzyme-linked immunosorbent assay and immunofluorescent antibody test at ages 9 to 12 months, after the level of transferred maternal antibody has decreased.[50] All other children of infected mothers should also be tested.

Prognosis

The most important determinant of prognosis for *T cruzi*–infected persons is the likelihood of progression to heart disease. Most reviews estimate that 20% to 30% of infected persons will develop clinically apparent disease during their lifetimes, but estimates vary across published studies.[1,2,47,51] This variability reflects, in part, methodological differences such as study population, definitions of progression, and length and completeness of follow-up. Animal models suggest that *T cruzi* strain is an important determinant of clinical manifestations and severity[52]; other possible factors include the severity of the acute infection and age at which it occurred, host immune response, and human genetic factors.[2,35,53,54] Community-based studies demonstrate that survival of individuals whose disease remains in the indeterminate form is equivalent to that of the general population.[23,55,56] Echocardiography, radionuclide angiography, or autonomic testing may reveal minor abnormalities in as many as one-third of *T cruzi*–infected individuals

with normal ECG and chest radiography results,[57-59] but these findings have not been shown to indicate a worse prognosis.

Ventricular conduction defects precede onset of symptoms by years to decades.[23] During 6.7 years of follow-up in one community-based study, right bundle-branch block alone was associated with a 7-fold increase, and right bundle-branch block with at least 1 ventricular extrasystole on resting ECG with a 12-fold increase, in the risk of mortality compared with seropositive persons having normal ECG findings.[23] Later manifestations associated with poor prognosis include ventricular tachycardia or complex ventricular arrhythmias, increased left ventricular systolic diameter, and segmental or global left ventricular wall motion abnormalities.[15,59-62] A rigorous analysis identified congestive heart failure (New York Heart Association class III or IV), cardiomegaly, left ventricular systolic dysfunction on echocardiography, nonsustained ventricular tachycardia on 24-hour ambulatory monitoring, low QRS voltage, and male sex as the strongest predictors of mortality.[63] This study and others confirm that congestive heart failure and left ventricular ejection fraction less than 30% identify a group of patients with less than 30% survival at 2 to 4 years.[15,55,56,64] Patients with Chagas cardiomyopathy have sudden death due to ventricular arrhythmias or complete heart block, or die from intractable congestive heart failure or embolic phenomena.[56,63,65] The presence of an apical aneurysm is associated with a high risk of stroke.[66]

In selected patients with Chagas heart disease, empirical use of amiodarone or angiotensin-converting enzyme inhibitors, or implantation of a pacemaker or intracardiac defibrillator, may improve survival.[15,16,67] However, few controlled clinical trials have been conducted to evaluate the efficacy of specific pharmacological treatment or devices in Chagas cardiomyopathy. Experience in Brazil demonstrates that survival after heart transplantation for Chagas cardiomyopathy is equal to or better than that among patients receiving transplants for idiopathic or ischemic dilated cardiomyopathy; careful management of immunosuppressive therapy is essential.[38,68]

Longitudinal data to address the prognosis of Chagas gastrointestinal tract disease are sparse. Once disease is clinically apparent, progression is usually slow.[18,69,70] There are no data to suggest that antitrypanosomal therapy alters the course of the disease. Management focuses on symptom amelioration through dietary, medical, and surgical interventions.[18]

Evaluation of the Patient Newly Diagnosed With Chagas Disease

The initial evaluation consists of the medical history, including evidence of potential *T cruzi* exposure in endemic areas via blood transfusion or other routes; complete physical examination; and resting 12-lead ECG with a 30-second lead II rhythm strip (FIGURE 3).[23,71,72] The history should include a thorough review of systems, with an emphasis on symptoms suggestive of cardiac arrhythmias, early congestive heart failure, and gastrointestinal tract disease. Infected persons should be counseled not to donate blood. Diagnostic screening should be offered for children of seropositive women, family members of patients, and other individuals with a history of potential exposure to the parasite in endemic settings.

For practical purposes, a seropositive patient with no evidence of cardiac or gastrointestinal tract alterations evident on this evaluation is considered to have the indeterminate form, even if chest radiography and barium examination of the colon and esophagus are not performed. Because the prognosis of asymptomatic patients with normal ECG findings is good, the predominant view of the authors is that further initial evaluation is unnecessary and that subsequent follow-up should rely on annual history, physical examination, and ECG findings (Figure 3).

For patients with symptoms, signs, or abnormal ECG findings, further evaluation should be tailored to the clinical picture. Patients with symptoms or ECG changes consistent with Chagas heart disease[23,71,73,74] should undergo a comprehensive cardiac evaluation, including ambulatory 24-hour ECG monitoring to detect arrhythmias; exercise testing to identify exercise-induced arrhythmias and assess functional capacity and chronotropic response; and 2-dimensional echocardiography to assess biventricular function, wall motion, and structure. For asymptomatic patients with nonspecific ECG changes (eg, rsR′ not meeting criteria for right bundle-branch block or a minor increase in PR interval), the need for further evaluation should be judged on an individual basis.

Certain signs and symptoms raise immediate concern. Syncope, indicators of ventricular dysfunction, nonsustained or sustained ventricular tachycardia on resting ECG or ambulatory monitoring, severe sinus node dysfunction, and high-degree heart block are major predictors of sudden death.[67] These findings should trigger an intensive search for arrhythmias and conduction system abnormalities, proceeding to electrophysiologic studies if indicated by the results of noninvasive testing. Chest pain warrants evaluation for ischemia and noncardiac causes, such as esophagitis.[24,75,76] In patients with chest pain, cardiac scintigraphy scans may reveal perfusion defects thought to reflect microvascular ischemia or fibrosis, but angiography usually shows normal coronary arteries.[24]

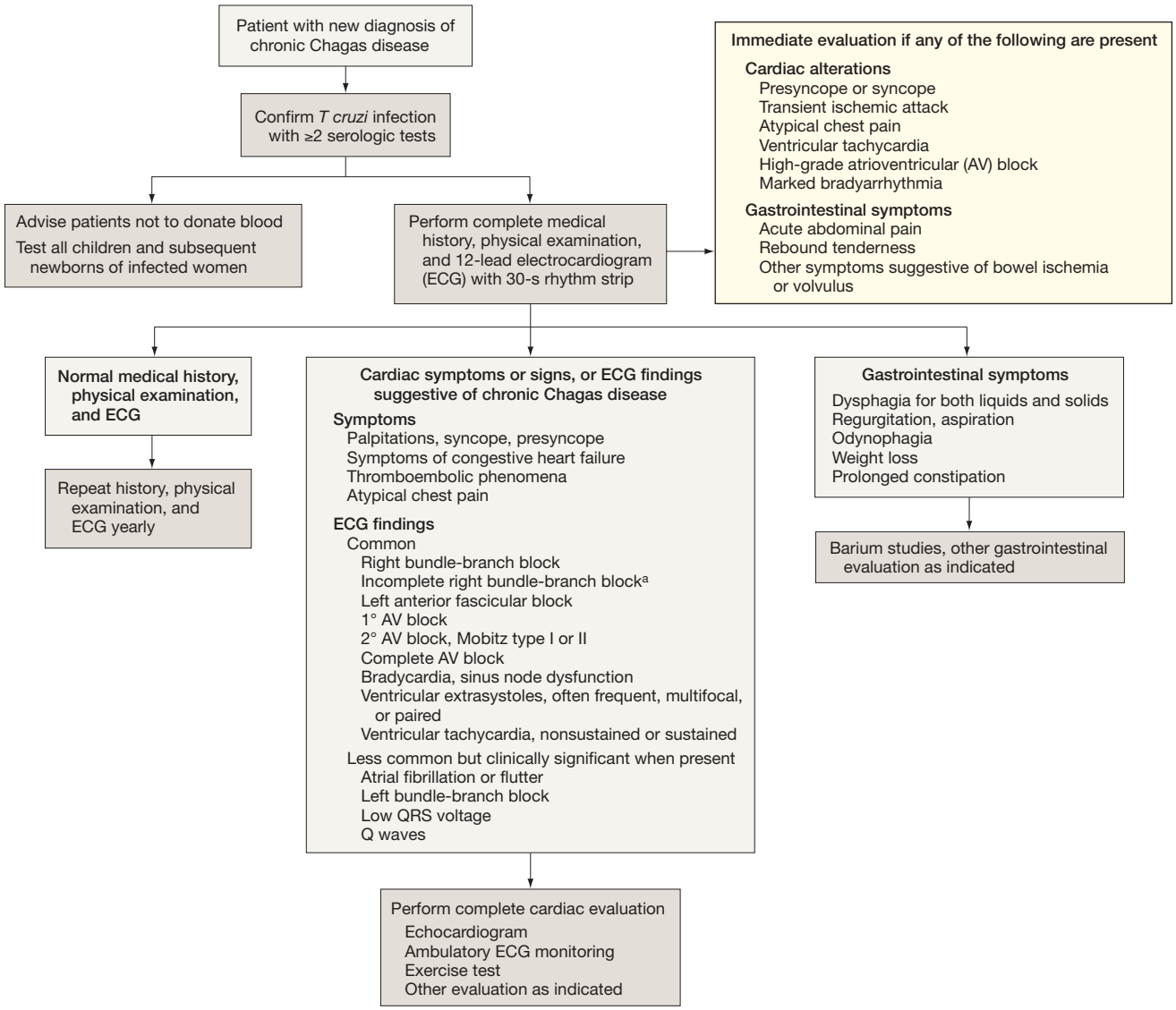
In patients without gastrointestinal tract symptoms, no barium studies are recommended. Patients with symptoms suggestive of esophageal or colonic involvement should undergo a barium swallow or enema, respectively. Following barium swallow, radiographs should be taken at 10 seconds and at 5 and 10 minutes.[77] Esophageal manometry may detect more subtle changes and may be indicated if results of the barium study are inconclusive.[78,79] Endoscopy is not indicated for the diagnosis of megaesophagus; however, patients with impaired esophageal motility are at increased risk of reflux esophagitis and esophageal carcinoma, and screening for these conditions may be indicated,

especially if a change in symptoms has occurred. Patients with Chagas gastrointestinal tract disease should be evaluated for heart disease following the algorithm outlined above.

Antitrypanosomal Drug Therapy

Benznidazole and nifurtimox are the only drugs with proven efficacy against Chagas disease.[2,80] Because benznidazole is better tolerated, this drug is viewed by most experts as the first-line treatment. Nevertheless, individual tolerance varies; if one drug must be discontinued, the other can be used as an alternative. Neither drug is approved in the United States; both can be obtained from the CDC and used under investigational protocols. Adults should be treated with benznidazole (5-7 mg/kg per day) in 2 divided doses for 60 days or with nifurtimox (8-10 mg/kg per day) in 3 divided doses for 90 days. Consultations about diagnostic testing, management, drug requests, and dosage regimens for special circumstances (eg, pediatric or immunocompromised patients) should be addressed to the CDC Division of Parasitic Diseases Public Inquiries line (770-488-7775; e-mail: ncidpdbpi@cdc.gov); the CDC Drug Service (404-639-3670); or, for emergencies after business hours, on weekends, and on federal holidays, the CDC Emergency Operations Center (770-488-7100).

Figure 3. Baseline Evaluation of the Patient Newly Diagnosed With Chronic *Trypanosoma cruzi* Infection



[a] QRS interval 0.10 to 0.11 seconds in adults. Criteria based on the *Minnesota Code Manual of Electrocardiographic Findings*,[74] with modifications from Maguire et al.[71] Different criteria may be required for ECGs in children.

Benznidazole (Radanil, Rochagan, Roche 7-1051), introduced in 1971, is a nitroimidazole derivative active against both the trypomastigote and amastigote forms. The drug is rapidly absorbed from the gastrointestinal tract; the average biological half-life is 12 hours. Elimination is predominantly renal; 22% of excretion is fecal. Children have fewer adverse effects than adults and tolerate higher doses. Dermatologic adverse effects occur in approximately 30% of patients and consist of rashes due to photosensitization, rarely progressing to exfoliative dermatitis. The dermatitis is usually mild to moderate and manageable with topical or low-dose systemic corticosteroids. However, the drug should be discontinued immediately in case of severe or exfoliative dermatitis or of dermatitis associated with fever and lymphadenopathy. Approximately 30% of patients experience a dose-dependent peripheral neuropathy. It occurs most commonly late in the treatment course and should trigger cessation of treatment; it is nearly always reversible but may take months to resolve. Bone marrow suppression is rare and should prompt immediate treatment interruption. Additional reported adverse effects include anorexia and weight loss, nausea and/or vomiting, insomnia, and dysgeusia. Laboratory testing (complete blood cell count and levels of hepatic enzymes, bilirubin, serum creatinine, and blood urea nitrogen) should be performed before beginning treatment; the complete blood cell count should be repeated every 2 to 3 weeks during the treatment course. Patients should be monitored for dermatitis beginning 9 to 10 days after initiation of treatment. Concurrent alcohol use can lead to disulfiram-like effects (abdominal cramps, nausea, vomiting, flushing, headache) and should be avoided.

Nifurtimox (Lampit, Bayer 2502), introduced in 1965, is a nitrofuran compound, also with activity against trypomastigotes and amastigotes.[80] The drug is rapidly absorbed from the gastrointestinal tract and extensively metabolized in the liver, where nitroreduction occurs through cytochrome P450 reductase. Elimination of metabolites is predominantly renal. In humans, plasma levels peak at 1 hour after a single oral dose and have an elimination half-life of 3 hours. Like benznidazole, nifurtimox is better tolerated by children,[51] and dosage recommendations differ by age.

Adverse effects are frequent but usually resolve when treatment is stopped. Gastrointestinal tract complaints occur in 30% to 70% of patients and include anorexia leading to weight loss, nausea, vomiting, and abdominal discomfort. Symptoms of central nervous system toxicity include irritability, insomnia, disorientation, and, less often, tremors. More serious but less common adverse effects include paresthesias, polyneuropathy, and peripheral neuritis. The peripheral neuropathy is dose-dependent, appears late in the treatment course, and should prompt interruption. Additional adverse effects include dizziness or vertigo, nervous excitation, mood changes, and myalgias. Laboratory testing (complete blood cell count and levels of hepatic enzymes, bilirubin, serum creatinine, and blood urea nitrogen) should be performed before beginning treatment, 4 to 6 weeks into the course, and at the end of treatment. Patients should be weighed and monitored for symptoms and signs of peripheral neuropathy every 2 weeks, especially during the second and third months of treatment. Concurrent alcohol use increases the risk of adverse effects and should be avoided.

Benznidazole and nifurtimox are both mutagenic[81,82] and have been reported to increase risk of lymphomas in experimental animals.[83,84] Although a higher incidence of neoplasms was reported in a small series of *T cruzi*–infected heart transplant recipients,[85] no increase in incidence of human lymphoma has been reported among the larger population of treated patients in countries where the 2 drugs have been in use for decades.[86] Nevertheless, definitive data on this issue are lacking.

Efficacy of Drug Treatment for Chagas Disease

Despite the public health importance of Chagas disease, few rigorous clinical trials have been conducted (TABLE 1).[87-90] The complex natural history of the infection and inadequate tools to assess cure have made it difficult to define appropriate end points and follow-up intervals. The published randomized, placebo-controlled trials assessed primarily parasite-related outcomes, antibody-related outcomes, or both rather than clinical outcomes.

Treatment of Acute and Congenital Infection

Based on several early trials and subsequent clinical experience in acute and early congenital Chagas disease, both drugs are known to reduce symptom severity and to shorten the clinical course and duration of detectable parasitemia.[2,45,86,91] Parasitological cure is thought to occur in 60% to 85% of patients in the acute phase and in more than 90% of congenitally infected infants treated in the first year of life.[45,80,91,92] Geographic variability in efficacy has been reported for acute[93] and chronic[94] infection and in animal models.[95,96] Treatment of infected infants should begin as soon as the diagnosis is made; the drugs are well tolerated in infancy.[45,97] Neither drug is available in a pediatric formulation; for infants and young children, the tablets should be prepared in a compounding pharmacy to provide the appropriate dose.

Treatment in the Chronic Phase

In the 1990s, 2 randomized, double-blinded, placebo-controlled trials of benznidazole for children aged 6 to 12 years with asymptomatic *T cruzi* infection demonstrated approximately 60% efficacy, as assessed by conversion from positive to negative serology results 3 to 4 years posttreatment (Table 1).[87,88] In 1 trial, treated children also showed a marked reduction in positive xenodiagnoses compared with the placebo group.[88] Benznidazole was well tolerated in these pediatric trials (Table 1). Together with growing clinical experience across Latin America, these studies prompted recommendations for early diagnosis and antitrypanosomal therapy for all infected children.[20,47] In

a recently published, nonrandomized, nonblinded trial, benznidazole treatment appeared to slow the development and progression of Chagas cardiomyopathy in adults.[90] Based on these and other data, a number of experts now recommend treatment of adults with chronic *T cruzi* infection in the absence of advanced Chagas cardiomyopathy.[90,98] A multicenter, randomized, double-blinded, placebo-controlled trial of benznidazole for patients with mild to moderate Chagas cardiomyopathy is currently under way.[99] Data from this study should help clarify treatment decisions for this group of patients.

Reactivated *T cruzi* Infection

Data from series of patients who underwent transplantation with reactivated infection showed that standard doses of benznidazole given for 30 to 180 days led to resolution of signs and symptoms and reduced intensity of parasitemia.[39-42] A standard 60-day benznidazole regimen decreased parasitemia and resulted in clinical improvement in a small series of patients coinfected with human immunodeficiency virus and *T cruzi*.[43] The optimal duration of therapy in immunocompromised patients and the usefulness of secondary prophylaxis have not been established.

Indications for Antitrypanosomal Therapy

Based on the literature reviewed above, recommendations for antitrypanosomal therapy vary by phase and form of Chagas disease and by patient age and are graded based on Infectious Diseases Society of America quality-of-evidence standards.[100] Drug therapy is recommended in all cases of acute and congenital infection, reactivated infection, and in children 18 years or younger with chronic *T cruzi* infection (TABLE 2).[45,49,87,88,101] For adults aged 19 to 50 years without advanced Chagas cardiomyopathy, antitrypanosomal drug treatment should generally be offered.[47,90,101,102] For those older than 50 years, the risk of drug toxicity may be higher than in younger adults,[45] and treatment is considered optional. The rationale for treatment in adults rests on data that are suggestive, but not yet conclusive, that treatment may prevent or slow progression of cardiomyopathy.[90] Individualized treatment decisions for adults should take into account the current lack of certainty of benefit, prolonged course, and frequent adverse effects. Because drug treatment might be expected to reduce the probability of congenital transmission, stronger consideration may be warranted for reproductive-aged women; nevertheless, data are lacking on this issue.

Similarly, antitrypanosomal treatment should be given stronger consideration in situations in which future immunosuppression is anticipated, for example, among previously untreated

Table 1. Prospective Controlled Trials of Benznidazole or Nifurtimox for Chronic Chagas Disease in the Published Literature

Source	Chagas Form	Study Design	Age, y	Length of Treatment, d	Comparison Groups	Sample Size, No.	Primary Outcome of Interest, %	Major Adverse Events or Adverse Effects >5%
de Andrade et al,[87] 1996[a]	Indeterminate (n = 120) Early Chagas heart disease (n = 9)[b]	Randomized, double-blinded	7-12	60			Negative seroconversion at 36 mo by AT-ELISA	Maculopapular rash and pruritus
					Benznidazole, 7.5 mg/kg per d	64	58	12.5
					Placebo	65	5	3.1
Sosa Estani et al,[88] 1998	Indeterminate	Randomized, double-blinded	6-12	60			Negative seroconversion at 48 mo by F29-ELISA	Intestinal colic
					Benznidazole, 5 mg/kg per d	55	62	NR
					Placebo	51	0	NR
							Xenodiagnosis-positive at 48 mo	
					Benznidazole, 5 mg/kg per d	55	5	NR
					Placebo	51	51	NR
Coura et al,[89] 1997[c]	Indeterminate with ≥2 of 3 pretreatment xeno-diagnoses positive[d]	Randomized but apparently not double-blinded	Adults[d]	30	Benznidazole, 5 mg/kg per d	26	Posttreatment xeno-diagnosis positive 1.8	NR
					Nifurtimox, 5 mg/kg per d	27	9.6	NR
					Placebo	24	34.3	NR
Viotti et al,[90] 2006[d]	Indeterminate and nonsevere determinate	Alternate assignment to benznidazole or no treatment; nonrandomized, unblinded	Mean, 39.4	30			Progression	Severe allergic dermatitis prompting discontinuation
					Benznidazole, 5 mg/kg per d	283	4.2	13.0
					No treatment	283	14.1	NR
					Benznidazole, 5 mg/kg per d	283	Mortality 1.1	NR
					No treatment	283	4.2	NR

Abbreviations: AT-ELISA, Antigen trypomastigote chemoluminescent enzyme-linked immunosorbent assay; CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio (mortality adjusted for ejection fraction); F29-ELISA, flagellar calcium binding protein F29-antigen–based enzyme-linked immunosorbent assay; IFA, indirect immunofluorescence assay; IHA, indirect hemagglutination; NR, not reported.

[a] Efficacy, 55.8% (95% confidence interval, 40.8%-67.0%) by intention-to-treat analysis based on AT-ELISA results.

[b] All children were asymptomatic but 9 had right bundle-branch block on ECG; no difference in distribution in treatment vs placebo groups.

[c] Neither age nor clinical findings reported in article; presumed to have the indeterminate form.

[d] Chagas cardiac disease Kuschnir grades I or II; those with grade III, defined by presence of heart failure, were excluded. Distribution at study entry: 63.6% Kuschnir 0, 26.1% grade I, 10.2% grade II. See Box for definition of Kuschnir grades. Median follow-up, 9.8 years.

T cruzi–infected patients awaiting organ transplantation, or patients coinfected with human immunodeficency virus. However, many experts recommend close posttransplantation monitoring for reactivation through periodic microscopic examination of the buffy coat and clinical evaluations for signs and symptoms such as fever and skin lesions, with treatment only if reactivation is demonstrated. Reactivation risk varies considerably, depending primarily on the degree of immunosuppression.[41,42]

For patients with advanced Chagas cardiomyopathy, antiparasitic treatment is not recommended, because existing pathology will not be affected; the focus is on supportive therapy. For patients with Chagas gastrointestinal tract disease, treatment decisions should be based on the potential to decrease risk of development or progression of cardiomyopathy; the same factors, such as age and the possibility of congenital transmission, should be considered as for other patients without advanced heart disease. In patients with megaesophagus, drug absorption may be impaired; treatment should be delayed until after corrective surgery. Benznidazole and nifurtimox are contraindicated in pregnancy and in patients with severe renal or hepatic dysfunction.

Documentation of Response After Treatment

For monitoring response to treatment, hemoculture and direct examination of blood or the buffy coat have high sensitivity in acute, early congenital, or reactivated *T cruzi* infection. In the chronic phase, there is no assay of proven value for documentation of response. The 2 key placebo-controlled trials each used a different experimental serologic assay, neither of which is widely available.[87,88] Negative seroconversion by conventional assays occurs after successful treatment but takes years to decades.[102] PCR-based techniques are useful in monitoring for treatment failure in persons with acute *T cruzi* infection, but their variable sensitivity limits their usefulness in those with chronic Chagas disease.

COMMENT

Because of newly instituted blood bank screening, increased community awareness, and demographic changes, United States–based clinicians are likely to encounter more patients with Chagas disease in the future. Baseline evaluation should include complete history, physical examination, and resting ECG with a 30-second lead II rhythm strip. Persons infected with *T cruzi* should be counseled not to donate blood, and screening should be offered for family members with a similar exposure history and for children of infected women. For patients with negative baseline evaluation results, follow-up should consist of yearly history, physical examination, and ECG. Antitrypanosomal treatment should always be offered for *T cruzi*–infected children aged up to 18 years and for patients with acute or reactivated disease and should generally be offered to patients aged 19 to 50 years without advanced heart disease. For patients older than 50 years without advanced cardiomyopathy, antiparasitic treatment is considered optional. Currently available drugs require a prolonged course, pose a significant risk of adverse effects, and require careful monitoring.

Table 2. Recommendations for Antitrypanosomal Drug Treatment According to Chagas Disease Phase and Form, Patient Age, and Clinical Status

Antitrypanosomal Drug Treatment by Chagas Disease Phase, Form, and Demographic Group	Strength of Recommendation and Quality of Supporting Evidence[a]
Should always be offered	
Acute *Trypanosoma cruzi* infection	AII
Early congenital *T cruzi* infection	AII
Children aged ≤12 y with chronic *T cruzi* infection	AI
Children aged 13-18 y with chronic *T cruzi* infection	AIII
Reactivated *T cruzi* infection in patient with HIV/AIDS or other immunosuppression	AII
Should generally be offered	
Reproductive-age women	BIII
Adults aged 19-50 y with indeterminate form, or mild to moderate cardiomyopathy (Kuschnir grades 0, I, or II)	BII
Impending immunosuppression[b]	BII
Optional	
Adults aged >50 y without advanced cardiomyopathy (Kuschnir grades 0, I, or II)	CIII
Patients with Chagas gastrointestinal tract disease but without advanced cardiomyopathy[c]	CIII
Should generally not be offered	
Advanced chagasic cardiomyopathy with congestive heart failure (Kuschnir grade III)	DIII
Megaesophagus with significant impairment of swallowing	DIII
Should never be offered	
During pregnancy	EIII
Severe renal or hepatic insufficiency	EIII

Abbreviation: HIV, human immunodeficiency virus.

[a] Infectious Diseases Society of America quality of evidence standards for treatment recommendations.[100] Strength of recommendation graded A to E. A: Both strong evidence for efficacy and substantial clinical benefit support recommendation for use; should always be offered. B: Moderate evidence for efficacy, or strong evidence for efficacy but only limited benefit, support recommendation for use. Should generally be offered. C: Evidence for efficacy is insufficient to support a recommendation for or against use; or evidence for efficacy might not outweigh adverse consequences or cost of treatment under consideration. Optional. D: Moderate evidence for lack of efficacy or for adverse outcome supports recommendation against use. Should generally not be offered. E: Good evidence for lack of efficacy or for adverse outcome supports recommendation against use. Should never be offered. Quality of evidence supporting the recommendation graded as I to III. I: Evidence from at least 1 properly designed, randomized clinical trial. II: Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than 1 center), or from multiple time-series studies; or dramatic results from uncontrolled experiments. III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

[b] For example, previously untreated patients with HIV infection or awaiting organ transplant.

[c] There are no data to suggest that treatment affects progression of gastrointestinal tract disease. Decisions should be based on the potential to decrease risk of development or progression of heart disease.

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Study concept and design: Bern, Montgomery, Herwaldt, Marin-Neto, Moore.
Acquisition of data: Bern, Montgomery, Herwaldt, Rassi, Marin-Neto, Dantas, Maguire, Morillo, Moore.
Analysis and interpretation of data: Bern, Montgomery, Herwaldt, Rassi, Marin-Neto, Dantas, Maguire, Acquatella, Kirchhoff, Gilman, Reyes, Salvatella, Moore.
Drafting of the manuscript: Bern, Montgomery, Moore.
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