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Addressing the Challenges of Chagas Disease:

An Emerging Health Concern in the United States

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Abstract

Chagas disease is an emerging health concern in the United States. US health care providers have an unparalleled opportunity to respond to the challenges this infection poses and to provide state-of-the-art care for patients with Chagas disease. Most of the approximately 300,000 persons with *Trypanosoma cruzi* infection living in the United States have chronic, asymptomatic infection acquired in endemic regions in Latin America. Congenital infection is often asymptomatic and, even when symptomatic, has no features that distinguish it from other congenitally transmitted infections. Health care providers and the public have limited awareness of this infection. Recognizing risk groups and performing targeted diagnostic testing for at-risk infants, children, and adults are a health priority because early treatment can effect cure and avert the life-threatening cardiac manifestations of Chagas disease. Two medications for treatment, benznidazole and nifurtimox, are available through the Centers for Disease Control and Prevention. Although challenges exist, informed health care providers can greatly reduce the effects of Chagas disease in the United States.

Keywords

Trypanosoma cruzi ; Chagas disease; neglected parasitic infection; cardiomyopathy; congenital infection

Chagas disease, caused by the protozoan parasite *Trypanosoma cruzi*, is 1 of 5 parasitic diseases designated as neglected parasitic infections by the US Centers for Disease Control and Prevention (CDC). These diseases are targeted as priorities for public health action, based on the number of people infected, the severity of the illnesses, and the availability of modalities for their treatment and prevention.[1] Chagas disease, as well as the other neglected parasitic infections such as neurocysticercosis, toxocariasis, toxoplasmosis, and trichomoniasis, are targeted in part to enhance physician awareness of these emerging

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infections. The objectives of this article are to summarize the burden of Chagas disease in the United States, to present the clinical manifestations of Chagas disease in children and adults, to provide guidance regarding the diagnosis and treatment of Chagas disease, and to discuss challenges to reducing the US burden of Chagas disease.

ESTIMATE OF THE BURDEN OF CHAGAS DISEASE IN THE UNITED STATES

An estimated 300,000 persons in the United States have Chagas disease.[2] Most are unaware that they are infected but are at a risk for developing life-threatening cardiac manifestations or debilitating gastrointestinal complications of Chagas disease. The countries of origin for approximately 85% of these *T. cruzi*–infected persons are Mexico, El Salvador, Guatemala, or Honduras. Persons originally from the South American countries of Argentina, Ecuador, Colombia, Brazil, and Bolivia account for an additional 10% of the US Chagas disease burden.[2]

A number of states in the southern United States have *T. cruzi* infection in animal populations.[3–6] The vector of *T. cruzi*, the triatomine bug, or an infected reservoir mammalian species, or both, has been documented in at least 28 states. However, domestic transmission seems uncommon, and almost all the US *T. cruzi* disease burden is composed of immigrants from endemic regions in Latin America. As of 2016, several states, including Arizona, Arkansas, Tennessee, and Texas, require reporting of cases, but a national reporting system is not in place. On the basis of a conservative calculation of progression of infection, at least 30,000 to 45,000 persons in the United States have undiagnosed Chagas cardiomyopathy. In addition, an estimated 40,000 infected women of childbearing age, who usually are unaware of their disease, live in the United States and have given birth to at least 2000 *T. cruzi*–infected newborns.[7] Transmission rates from infected mothers to their infants can range from 1% to 10%.[8,9] On the basis of the number of births to Latin American–born women, *T. cruzi* prevalence in their home countries, and a conservative estimate of 1% to 5% vertical transmission, approximately 63 to 315 infected infants are born each year in the United States.[2,8]

Widespread serologic screening of blood donors for *T. cruzi*, implemented in 2007, increased the awareness of Chagas disease in the United States and revealed that the population with Chagas disease represents an unmet medical need, requiring effort to identify and treat affected persons.[10] In the past decade, AABB (formerly known as the American Association of Blood Banks) has collected reports of approximately 2200 blood donors confirmed as positive for *T. cruzi* infection.[11]

TRANSMISSION OF CHAGAS DISEASE

Chagas disease is usually a vector-borne infection. The most common mode of transmission is through exposure to blood-sucking triatomine insects, commonly known as kissing bugs, that carry *T. cruzi* in their intestinal tracts (Table 1). Triatomines defecate when they bite, and feces of infected insects containing *T. cruzi* trypomastigotes enter the human body through a bite wound, intact mucous membranes, or conjunctivae.[12] Triatomines are night feeders that typically live in cracks of mud walls and thatched roofs of rural houses.

Most infected individuals have experienced repeated and prolonged exposure to the vector. Autochthonous, or locally acquired, transmission occurs in the United States, but only a small number of cases have been documented.[13] Vector-borne transmission also can occur when food or drink is contaminated by infected triatomines or their fecal material. Disease transmitted through contaminated foods or fruit juices is rare and has been reported only in areas endemic for Chagas disease and not from the United States.[14]

Chagas disease can be transmitted through exposure to blood from an infected person. Blood transfusion and organ transplantation are potential modes of transmission.[15] Screening of the US blood supply as the standard of care has rendered acquisition by this route rare. Widespread organ donor screening has reduced the risk of adverse outcomes with transplantation of organs from infected donors. Transmission via laboratory accident is possible but rare. Reports of congenital transmission in the United States have occurred in infants born to mothers with previously unappreciated chronic infection acquired in Latin America.[16,17] Breast milk–associated transmission has not been reported.

CLINICAL FEATURES

Acute infection typically either is asymptomatic or presents as a mild and self-limited influenzalike illness that often does not receive medical attention or is not recognized as Chagas disease. Children more often manifest symptoms than adults. Some persons have a red, indurated nodule at the site of inoculation called a “chagoma.” Eyelid edema, at times with a violaceous hue and conjunctivitis, known as Romaña sign can occur if the conjunctiva is the portal of entry. Myocarditis and/or meningoencephalitis are rare manifestations of acute infection.[18] The acute phase of infection lasts 4 to 8 weeks, and the infection then enters a chronic phase that, without treatment, persists for life (Table 2). Sixty to 80% of persons with chronic infection never manifest signs or symptoms of Chagas disease and have the form of infection designated “indeterminate.” These individuals have a normal physical examination and a normal electrocardiogram (ECG). Reactivation of the indeterminate form of chronic infection can occur in the setting of immune suppression. In 20% to 30% of those with chronic infection, the disease progresses for years to decades to the determinate form with end-organ involvement of the heart, gastrointestinal tract, or both.[18]

Early cardiac disease usually manifests as conduction system abnormalities and wall-motion abnormalities of the left ventricle. Ongoing damage can lead to complete heart block, ventricular tachycardia, or severe bradycardia from sinus node dysfunction. Sudden death can occur as a consequence of rupture of apical aneurysms resulting from damage to the left ventricle, dilated cardiomyopathy and heart failure, or ventricular arrhythmias.[20] The most common and consistent independent predictor of death is impaired left ventricular function.[21] Gastrointestinal tract manifestations include megaesophagus, which usually presents as achalasia and/or megacolon, with bloating and constipation that can be debilitating.

Approximately 10% to 40% of congenitally infected infants have signs suggesting infection at birth.[8,22–24] Congenitally infected infants can present with prematurity,

hepatosplenomegaly, jaundice, anemia, and thrombocytopenia, which might suggest congenital infection, but none of the clinical features are specific to Chagas disease. Other potentially life-threatening, although less common, manifestations of congenital Chagas disease include hydrops fetalis, hepatitis, pneumonitis, cardiac failure, and meningoencephalitis. Even severe diseases can go undiagnosed because of the lack of pathognomonic clinical features and because the diagnosis is not suspected. Most healthy-appearing congenitally infected infants do well in infancy, but 20% to 30% of children with untreated Chagas disease develop irreversible and often fatal heart disease after years or decades of silent infection.[7]

DIAGNOSIS

The diagnosis of chronic Chagas disease is established by serologic testing. However, no single serologic test is sufficiently sensitive and specific to confirm the diagnosis. For this reason, the standard approach is to perform at least 2 tests that use different techniques and different antigen preparations to detect antibodies to *T. cruzi* antigens. As a practical approach, the first step in the diagnostic process is to test for *T. cruzi* antibodies through a commercial laboratory. Most commercial laboratories use assays that are enzyme-linked immunosorbent assay based. Patients who test positive at a commercial laboratory should be further tested for confirmation of the diagnosis at a reference laboratory, such as the Parasitic Diseases Branch Laboratory of the CDC. Although there may be charges for specimen shipping, testing at CDC is performed at no charge to the patient. The state health department should be contacted regarding any request for testing at CDC, and in many states, including those in which Chagas disease is a reportable infection, specimens must be routed to CDC through the state public health laboratory.

The diagnosis of congenital Chagas disease can be established conclusively in newborn infants by the detection of trypomastigotes on a Giemsa-stained blood smear or by polymerase chain reaction on whole blood collected during the first 3 months after birth. Molecular testing is available at the Parasitic Diseases Branch of CDC. If the diagnosis is not established by polymerase chain reaction or detection of the parasite in a blood smear, serologic testing should be deferred until the infant is 9 months old so that antibody reflects that produced by the infant rather than that passively acquired from the mother.

Blood donor tests are screening tests. As of 2017, there are 2 blood donor screening tests approved by the US Food and Drug Administration, the ORTHO *T. cruzi* enzyme-linked immunosorbent assay Test System (Ortho-Clinical Diagnostics, Inc, Rochester, NY) and a chemiluminescent immunoassay (Abbott Prism Chagas test; Abbott Diagnostics, Abbott Park, Ill). Blood banks perform an additional, more specific test on human serum or plasma specimens found to be positive for antibodies to *T. cruzi*, the Abbott enzyme strip assay Chagas test, a recombinant antigen immunoblot assay, before informing the donor. The second test is approved only for blood donor screening, and confirmatory testing still is required to establish the diagnosis. Donors screening positive are notified by mail by the blood collection agency and advised to contact a health care provider for further evaluation.

IDENTIFICATION OF PERSONS AT RISK

Chagas disease must be considered a possibility to establish the diagnosis. Persons who have immigrated to the United States from locales endemic for *T. cruzi* infection comprise the primary at-risk group (Table 3).[19] Obtaining an accurate history is paramount in informing the decision to perform diagnostic testing in such persons, who usually have long-standing asymptomatic disease. Risk is enhanced if there has been a potential for prolonged exposure to triatomine bugs, for example, through residence in rural settings or in adobe or thatched-roofed dwellings in endemic regions.

Fewer than 30 cases of vector-borne *T. cruzi* infection acquired in the United States have been identified.[4,13] Domestically acquired infection has been described in individuals who lived in a rural area where the vector or an infected mammalian reservoir is found and who may have participated in outdoor activities such as hunting, camping, fishing, or gardening or nocturnal outdoor activities in such areas. Determination of US foci of vector-borne transmission is needed to inform the scope of targeted domestic testing.

Women in the childbearing years with unappreciated Chagas disease are of particular concern because the infection risk involves both mother and her children. Prevalence data are needed to identify US populations in which targeted screening of pregnant women should be routinely performed. A study of 4000 women delivering at 1 Houston hospital, at which 85% of women were non-US born, most from Chagas-endemic regions, found that 1 of every 400 mothers screened had chronic, previously unrecognized Chagas disease.[25]

Infants born to women identified as having Chagas disease should undergo testing as soon as possible after birth. Infants born to seropositive mothers should also have serologic testing after 9 months old, when detected IgG represents the infant's response rather than maternal antibody.[26] Detection of Chagas disease in pregnant women or newborns provides the opportunity for identifying additional cases in relatives, including siblings, because infection can be transmitted in other pregnancies. Case clusters have been defined, although not in US-based reports. Infection was confirmed in 18% of children born previously to maternal index cases in 1 family study from Chile.[27]

Adults with idiopathic cardiomyopathy who have lived in locales endemic for *T. cruzi* should undergo Chagas disease serologic screening. A large study from the Los Angeles area revealed a 19% prevalence of chronic Chagas disease among Latin American immigrants considered to have idiopathic cardiomyopathy.[28] The main cardiac screening test for early detection of myocardial involvement is the ECG. Chronic Chagas cardiomyopathy usually has characteristic ECG findings of either the right bundle branch block, left anterior fascicular block, or both. These findings precede decreased left ventricular ejection fraction (<50%) and/or presence of regional wall motion abnormality detectable by echocardiogram. Cardiac magnetic resonance imaging may detect myocardial involvement not apparent on ECG or echocardiogram that manifests as delayed myocardial enhancement, usually with associated abnormal wall motion, after intravenous contrast medium administration.[29]

INDICATIONS FOR TREATMENT OF CHAGAS DISEASE

Indications for the treatment of Chagas disease are shown in Table 4. Treatment of acute infection and congenital infection within the first few weeks of life is highly effective and prevents long-term complications from heart and intestinal diseases; cure rates are 80% to 100% and >90%, respectively.[16,19] The American Academy of Pediatrics recommends treatment of all cases of acute or congenital Chagas disease, as well as *T. cruzi* infection, in children younger than 18 years, who are considered to have early chronic infection.[26] Antitrypanosomal drug efficacy is approximately 60% for children younger than 12 years with chronic infection.[19] Treatment for adults without cardiac disease may prevent the development of cardiomyopathy, but data are lacking regarding treatment effectiveness rates in adults. Treatment is indicated for chronically infected patients who have undergone organ transplantation and in those with human immunodeficiency virus *T. cruzi* coinfection and who developed reactivation, which can be associated with return to acute infection levels of parasitemia.[19]

The results of a large, randomized, placebo-controlled trial assessing the effect of antiparasitic treatment on cardiac outcomes in adults with Chagas cardiomyopathy have recently been published. The Benznidazole Evaluation for Interrupting Trypanosomiasis trial enrolled almost 3000 patients with Chagas cardiomyopathy and, after 5 years, found no significant effect in the primary composite outcome of death, new heart failure, implantation of a cardioverter/defibrillator or pacemaker, or other extreme event between those who received benznidazole versus placebo.[32] Trypanocidal treatment did significantly reduce molecular testing detection of parasite in circulating blood. Despite these disappointing results for adults with established cardiomyopathy, there is sound rationale for providing treatment for patients with little or no evidence of cardiac involvement because parasite persistence is key to triggering this complication of the disease.[30] Most experts recommend treatment for patients with chronic *T. cruzi* infection with the exception of those older than 50 to 55 years and those with advanced cardiomyopathy.[19,31]

TREATMENT OPTIONS AND MANAGEMENT

The 2 medications used to treat *T. cruzi* infection, and currently the only drugs with proven efficacy, are nifurtimox and benznidazole. Neither is approved by the Food and Drug Administration, but both are available from CDC under investigational protocols. Health care providers can seek information regarding antitrypanosomal treatment through CDC's Parasitic Diseases Public Inquiries (404-718-4745 or by email at parasites@cdc.gov) or through the CDC Drug Service (404-639-3670). For emergencies outside regular business hours, providers can call the CDC Emergency Operations Center (770-488-7100). Infection must be confirmed before the release of drug under CDC protocols.

Nifurtimox is a nitrofuran that inhibits pyruvic acid synthesis and disrupts *T. cruzi* carbohydrate metabolism. Benznidazole is a nitroimidazole derivative that seems to inhibit ribonucleic acid synthesis and protein synthesis in *T. cruzi* (Table 5).[33] Benznidazole is considered first-line treatment based on the accumulated clinical experience and a better adverse effect profile.[19] Both drugs are administered orally with a dose range based on

age. The fewer number of administrations daily and shorter total course of treatment both favor the use of benznidazole. Contraindications for treatment with both drugs include severe hepatic or renal disease. Treatment is also contraindicated during pregnancy. Safety for infants exposed to drug through breastfeeding has not been evaluated so withholding treatment while breastfeeding is recommended. Exposure to drug through breastfeeding could enhance toxicity in infants receiving treatment or prolong exposure to drug in those who have completed treatment. Although drug is provided under CDC protocols at no charge to the patient, protocols for administration require several clinic visits, as well as blood test monitoring, and the costs for these are not provided through the protocol.

Adverse effects are common for both drugs. Most of these are reversible after discontinuing treatment, but resolution can take months. The adverse effects tend to be more frequent and more severe as patient age increases. Neonates, infants, and children usually tolerate the medications well. The most common adverse effect category for nifurtimox is gastrointestinal, with findings of anorexia and weight loss, nausea, vomiting, and abdominal discomfort predominating. Headache, dizziness, and vertigo are also common. Dose-dependent peripheral neuropathy can occur, and findings of paresthesias, polyneuropathy, or peripheral neuritis necessitate discontinuation of treatment. In 1 US cohort study, all 53 adult patients experienced adverse events during nifurtimox administration.[34] Patients experienced a mean of 8.2 adverse events, most commonly anorexia (79.2%), nausea (75.5%), headache (60.4%), or amnesia (58.5%). Most adverse events were mild (93.8%), and most patients (79.2%) were able to complete the 90-day treatment course.

The most common adverse effect category for benznidazole is dermatologic. Hypersensitivity or “allergic” dermatitis is common, occurring in approximately 40% of patients as a photosensitivity rash that is often of mild to moderate severity and can be managed with topical or low-dose systemic corticosteroids.[35] The rash can progress to or can manifest as a severe or exfoliative dermatitis, necessitating immediate discontinuation of treatment. Patients should be monitored for dermatologic adverse events beginning approximately 10 days after initiation of treatment. Other common adverse effects of benznidazole include a dose-dependent peripheral neuropathy that requires cessation of treatment, anorexia and weight loss, and insomnia.[1] In 1 US cohort study, all 30 adult patients had adverse events during benznidazole administration, most commonly rash (53%), headache (50%), anorexia (50%), and neuropathy (47%).[36] Forty percent had severe, but not life-threatening, adverse events most often manifesting as rash or angioedema; however, 70% were able to complete the 60-day treatment course. By contrast, adverse events attributed to benznidazole administration were noted in only 41% of a group of 107 children. Adverse events were observed less commonly in infants and toddlers than older children (18% vs 53%, $P < 0.001$).[37]

CHALLENGES TO OPTIMIZING CARE

Health care provider awareness of the possibility of *T. cruzi* infection in at-risk patients is critical to reducing the US Chagas disease burden. Failure to consider this diagnosis leads to missed opportunities to offer potentially lifesaving treatment. However, most US providers are not familiar with Chagas disease. A survey conducted among health care

providers in 5 medical specialties, including primary care, infectious diseases, cardiology, obstetrics and gynecology, and transplantation, who might encounter these patients, revealed a lack of awareness and knowledge regarding Chagas disease across all physician groups.[38] A questionnaire developed by the American College of Obstetricians and Gynecologists found that obstetrician-gynecologists rarely considered the possibility of Chagas disease.[39] A survey of members of the Pediatric Infectious Diseases Society regarding knowledge and awareness of congenital Chagas disease revealed that 75% rarely or never considered congenital Chagas disease as a diagnostic possibility in infants born to parents from Latin America.[40]

Gaps in current knowledge present challenges that should be viewed as opportunities to improve US patient outcomes from Chagas disease. Specifically, population-based studies are needed to better define the epidemiology of the disease in the United States, to identify strategies to target screening of high-risk pregnant women, to characterize Latino populations at risk for cardiomyopathy, and to define the extent and health impacts of vector-borne transmission within the United States.[41,42] Diagnostic tests with better specificity and sensitivity and validated rapid screening tests are needed. Safer and more effective drugs for treatment are needed. Among the candidate drugs being tested, the triazole antifungal posaconazole, well tolerated in humans, showed promising trypanocidal activity in a murine model of infection.[43] The failure of posaconazole to show efficacy for the treatment of chronic Chagas disease highlights the need for development of new drugs that are safe, effective, and readily available.[44] Finally, barriers exist to patients accessing treatment of Chagas disease in the United States, some of which are health systems related.[45] Al though overcoming such challenges will be a process, health care providers' commitment will lead to our identifying patients with Chagas disease and to societal awareness of *T. cruzi* infection as a health care threat, which will shift momentum and resources to optimizing care for those afflicted.

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TABLE 1.

Modes of Transmission of Chagas Disease*

Mode	Comment
Vector bome	Most common mode of transmission in endemic regions
Contaminated food or water	Reported from endemic regions only
Blood transfusion	Risk minimized through screening of the US blood supply
Organ transplantation	Many US organ procurement organizations perform targeted screening of at-risk donors
Laboratory accident	Rare mode of transmission
Congenital	Maternal-to-infant transmission rates range from 1% to 10%

*See Centers for Disease Control and Prevention[1] and Bern et al.[12]

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TABLE 2.

Clinical Features of Chagas Disease*

Phase of Disease	Features
Acute infection	Mild, flulike illness lasting 4–8 weeks with nonspecific symptoms; rarely, myocarditis or meningoencephalitis
Congenital infection	Symptomatic in 10%−40% with nonspecific findings that can include prematurity, hepatosplenomegaly, jaundice, anemia, and thrombocytopenia and, rarely, myocarditis, meningoencephalitis, or respiratory distress
Chronic infection (indeterminate phase) Chronic infection (determinate phase)	No signs or symptoms of disease; ECG has no findings suggestive of Chagas disease
Chagas cardiomyopathy	ECG abnormalities suggesting Chagas disease; arrhythmias, left ventricular dysfunction, congestive heart failure
Chagas gastrointestinal disease	Dysfunction associated with dilatation of the colon and/or esophagus
Reactivation during immunosuppression	Myocarditis, CNS abscesses

*Adapted from Bern.[19]

CNS indicates central nervous system.

TABLE 3.

Identification of Persons at Risk for Chagas Disease*

Risk Group	Comment
Residence in Chagas-endemic region	Risk enhanced by potential prolonged exposure to triatomines
US residence in locales with vector or mammalian species infected with *T. cruzi*	Fewer than 30 locally infected persons identified; risk thought to be related to outdoor activities
Infant born to a mother with Chagas disease	Perform testing as soon as possible after birth
All children of a mother with Chagas disease	Perform testing because congenital transmission is a risk with every pregnancy
Adult with idiopathic cardiomyopathy	Perform diagnostic testing for those who have resided in Chagas-endemic regions

*Adapted from Bern.[19]

TABLE 4.

Indications for Treatment of Chagas Disease*

Indication	Comment
Acute disease	Indicated for all cases; high cure rate
Congenital disease in infants	Indicated for all cases; high cure rate
Children younger than 18 y	Recommended for all cases; efficacy, ~60%
Women in the childbearing years	Recommended for the patient and to prevent congenital transmission
Pregnant women	Treatment indicated after delivery and breastfeeding cessation
Reactivation from immunosuppression	Recommended; decreases parasitemia and prolongs survival
All persons younger than 50–55 y	Efficacy not known; may prevent the development of cardiomyopathy
Adults with cardiomyopathy	Reduces parasite molecular detection; most experts recommend treatment for patients with early, but not for those with severe, cardiomyopathy

*See Bern,[19], Maguire,[30] and Viotti et al.[31]

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TABLE 5.

Medications for Treatment of Chagas Disease

	Nifurtimox	Benznidazole
Drug class	Nitrofuran	Nitroimidazole derivative
Access to drug	Release by CDC	Release by CDC
Shortages occur	No	Yes
Dose range, mg/kg per day *	8–20	5–7.5
No. daily doses	3–4	2
Route of administration	Oral	Oral
Elimination	Renal	Renal †
Usual duration of treatment, d	90	60
Cost to patient ‡	$0	$0
Most common adverse effect category	Gastrointestinal	Dermatologic
Cure rate for acute or early congenital disease	80%–90%	80%–90%

* Dosage regimens are age based.

† Drug is metabolized in the liver; metabolites are eliminated by the kidney.

‡ Under CDC protocols, drug is provided at no charge to recipients, but patients are responsible for the cost of monitoring testing.

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