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In the Clinic® Chagas Disease

Natasha S. Hochberg, MD, MPH,

Boston University School of Medicine, Boston University School of Public Health, and Boston Medical Center, Boston, Massachusetts

Susan P. Montgomery, DVM, MPH

Parasitic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

Chagas disease, which is caused by infection with the parasite *Trypanosoma cruzi*, is a leading neglected tropical disease in the United States. An estimated 240 000 to 350 000 persons in the United States are infected, primarily immigrants from Mexico, Central America, and South America, where the disease is endemic. The parasite is transmitted by the triatomine bug but can also be passed through blood transfusion, via organ transplant, or congenitally. Approximately 30% of infected persons later develop cardiac and/or gastrointestinal complications. Health care providers should consider screening at-risk patients with serologic testing. Early diagnosis and treatment with benznidazole or nifurtimox can help prevent complications.

Chagas disease, also known as American trypanosomiasis, is a leading cause of parasitic infection in the United States, with an estimated 240 000 to 350 000 cases (1, 2). In Latin America, an estimated 5.7 million people were infected in 2010 (3). About 1.2 million persons are affected by Chagas cardiomyopathy, and up to 12 000 deaths are estimated to be caused by Chagas disease each year (4, 5), mostly due to severe cardiac complications (6–9).

Risk Factors and Causes

How is Chagas disease transmitted?

Chagas disease is caused by infection with *Trypanosoma cruzi*. This hemoflagellate protozoan parasite was discovered in 1909 by Carlos Chagas, for whom the disease is named (10). There are 6 distinct lineages of *T cruzi* classified into discrete typing units (TcI to TcVI) and a potential seventh bat-associated genotype; these vary in their geographic distribution, host preference, and clinical manifestations (11, 12).

Triatomine bugs are the primary vector (4, 6). They are also known as kissing bugs, cone-nosed bugs, and blood suckers and have many names in endemic countries, such as vinchuca, chinche, or barbeiros. Providers should familiarize themselves with these local

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names to facilitate communication about potential exposure with patients. An example of a triatomine, *Triatoma sanguisuga*, is shown in Figure 1 (13). Triatomine bugs vary in size and appearance, but they are generally dark in color with light abdominal stripes, and adults are typically 1.3 to 3.8 cm long. Providers can ask about potential exposures, including if the patient has noticed bugs similar to this inside their home, if the patient lives in a rustic rural home made from mud, or if the patient's home has a thatched roof or walls or a roof with noticeable cracks. The vectors generally become active at night, feeding on human and animal blood by biting an exposed area of skin or mucous membranes (such as the lips or eyes). The bug defecates near the bite, and feces of infected bugs allows for passage of the parasite through breaks in the skin or conjunctiva. Some species are particularly known for rapidly defecating during or after feeding, thereby increasing the likelihood of transmission.

Vector-borne transmission occurs only in the mainland parts of Mexico, Central America, and South America. There are rare reports of local transmission in the United States, mostly based on investigations of blood donors with positive screening results (14). Distribution of infected persons is expanding to nonendemic regions, including Europe, due to population movement, and there are many reported cases in Spain among Bolivian migrants (15). Even if migrants are from a nonendemic country (such as Haiti), providers should consider the migration route of individual patients, as they may have spent time in endemic countries en route to their destination. The countries with the highest estimated prevalence include Bolivia, Argentina, Paraguay, Ecuador, El Salvador, and Guatemala (3). A map of Chagas disease vector transmission can be found at the Pan American Health Organization (PAHO) website (16).

Less commonly, transmission can occur via blood transfusion. Risk for transmission varies by blood component, with estimates ranging from 10% to 25% for whole blood or platelet transfusion (17, 18). Screening of the U.S. blood supply became widespread starting in 2007 and was nationwide by 2012 (17) after the U.S. Food and Drug Administration (FDA) issued final guidance on recommended donor screening (19). Blood centers reported screening results from 2007 to 2019, with 2462 donors having positive results on FDA-approved tests (20).

Vertical transmission may occur from a mother to a fetus. A systematic review of data on congenital transmission found that it occurred in 4.7% (95% CI, 3.9% to 5.6%) of infants born to infected pregnant women (21). Another systematic review found that higher maternal parasitic loads were associated with greater risk for vertical transmission (22). One study conducted at a single hospital suggested that cesarean section protects against congenital transmission, but this association may reflect socioeconomic factors and requires further study (23). The risk for transmission through breastfeeding has not been well evaluated (24).

Transmission may also occur via solid organ or bone marrow transplant. Donor-derived infection rates are highest for transplant of infected hearts (up to 75%), followed by livers and kidneys (0% to 19%) (25). Transmission has also been reported due to laboratory accident after unintentional inoculation with a needle contaminated with *T cruzi* (26).

Sporadic outbreaks have occurred due to oral transmission via uncooked food or water contaminated with infected triatomine vectors. Ten outbreaks of orally transmitted acute Chagas disease with 249 cases and 10 deaths were reported in Venezuela between 2007 and 2014 (27), and 776 cases of orally transmitted acute Chagas disease were reported in Brazil between 2000 and 2010 (3, 28).

What are the signs and symptoms of acute Chagas disease?

Most acute infections are asymptomatic or present with nonspecific manifestations, such as fever, lymphadenopathy, and hepatosplenomegaly (Table 1). Regardless of the route of transmission, severe manifestations include myocarditis and encephalitis; severity of disease is likely related to parasite burden. Most acute infections go unrecognized and are rarely diagnosed (4, 6, 8).

If there are symptoms, onset is typically 7 to 14 days after infection via vector-borne transmission. A firm swelling (chagoma) associated with local inflammation may develop at the site of parasite entry into the body (29) (Figure 2). The chagoma may persist for weeks. When inoculation occurs through the conjunctiva or a break in the skin close to the eye, the resulting chagoma is known as the Romaña sign, which is defined as unilateral swelling of the palpebrae and periocular tissue (30). Severe acute disease is rare and is more likely to occur in young children and older adults.

Congenitally acquired acute infections also are generally clinically silent. In the approximately 10% to 40% of infected newborns with illness, manifestations include low birthweight and prematurity with low Apgar scores. Hepatomegaly with or without splenomegaly is commonly reported (31, 32). Two cases of congenital infection were diagnosed in the United States in 2010 and 2015; both infants were born to immigrant mothers and had hydrops fetalis, a severe manifestation of congenital infection (33, 34).

In documented outbreaks of food-borne Chagas disease, symptomatic acute infections typically had faster onset and a more severe clinical course attributed to the amount of infectious parasite ingested (28, 35).

What are the different presentations of chronic Chagas disease?

If untreated, *T cruzi* infection is lifelong. Most patients present after acute infection has transitioned to chronic infection and are asymptomatic, in what is considered the indeterminate form of chronic Chagas disease (Table 1).

Chronic infections are asymptomatic for years to decades, and most remain asymptomatic through the remainder of the untreated patient's life (6). Provider awareness is critical for timely diagnosis and treatment of patients with chronic indeterminate Chagas disease, with the goal of preventing progression to cardiac and/or gastrointestinal disease. Diagnosis and treatment also are important to prevent possible transmission through blood donation; via organ donation; or, for women, congenitally to unborn children.

In approximately 30% of chronically infected patients, Chagas cardiomyopathy develops after years to decades (36). Conduction system abnormalities (for example, right bundle

branch block, left anterior fascicular block, or ventricular premature beats) are the earliest clinical manifestations; echocardiography may reveal subtle wall motion abnormalities. These changes may be present in the absence of symptoms, but symptoms develop as the dilated cardiomyopathy typically progresses through New York Heart Association functional classes I to IV. Chagas cardiomyopathy can cause stroke, heart failure, thromboembolic events, and death; heart failure, stroke, and sudden death are frequently reported as causes of death among patients with Chagas disease (36). Chronic Chagas disease should be considered in patients originally from endemic areas of continental Latin America who present with nonischemic cardiomyopathy.

Less frequently, chronic infections can present with gastrointestinal manifestations (37). As with cardiac disease, gastrointestinal symptoms develop years to decades after infection in approximately 10% of chronically infected patients. Patients can have both gastrointestinal and cardiac disease due to *T cruzi* infection, although this is rare. Symptoms of gastrointestinal Chagas disease result from parasite-caused damage to esophageal and/or colonic mural neurons and resultant motility disruption. Patients may report chest and/or abdominal pain, difficulty swallowing, or constipation. In advanced stages, megaesophagus and/or megacolon develop. Manifestations include dysphagia, odynophagia, regurgitation, aspiration, and weight loss for esophageal involvement and severe constipation, fecaloma, colonic torsion, and bowel ischemia for colonic involvement. Providers should consider chronic Chagas disease in patients originally from endemic areas who present with megaesophagus or megacolon. If they are diagnosed with Chagas disease, cardiac evaluation should also be performed.

Which adults in the United States are at risk for acute and chronic Chagas disease?

In the United States, the majority of infected persons are of Latin American origin, have acquired infection in their home countries, and have chronic Chagas disease. Due to migration of infected persons, prevalence is also increasing in other nonendemic regions and countries, including Europe, Canada, Japan, and Australia. In Spain, an estimated 47 000 to 67 000 Latin American immigrants are seropositive for *T cruzi* infection, with the majority originating from Bolivia, Ecuador, Argentina, and Paraguay (38). The actual incidence and prevalence in the United States are unclear because diagnostic testing is rarely performed and there are no population-level studies. Based on the number of immigrants from endemic countries and the prevalence of Chagas disease in those countries, an estimated 240 000 to 350 000 persons are seropositive for *T cruzi* infection in the United States (1).

Risk factors for infection include a prolonged stay in endemic areas, particularly in rural areas with poor housing (4). Cases of acute infection after short-term travel are extremely rare, with an estimate of 0.8 case per 1000 travel days reported among 79 previously uninfected travelers who traveled to their endemic countries of origin, primarily to visit friends and relatives (39). There is 1 report of acute Chagas disease in a traveler returning to the United States from Costa Rica (29). A family history of Chagas disease suggests increased risk; one study found a prevalence of 7.4% among persons with a family history of Chagas disease (40). To date, at least 100 cases of locally acquired infection have been

documented in the United States, with modes of transmission including triatomine vectors, blood transfusion, and organ transplant (1, 41, 42).

The diagnosis should also be considered in persons with other potential sources of infection, including exposure to a triatomine, having an infected mother, and exposure to blood contaminated with the parasite in a laboratory or health care setting. Transfusion-associated infection is extremely rare in the United States due to routine screening of the blood supply. Infection associated with organ transplant has been reported but is uncommon, possibly due to increasing implementation of organ donor screening.

What are strategies for prevention of acute Chagas disease?

Screening and preventive measures for Chagas disease include primary prevention (measures to prevent infection in naive hosts). Preventive measures center around vector avoidance in endemic countries. Strategies include applying insecticides in and around houses, improving home construction to reduce triatomine infestation, using bed nets at night to reduce exposure, and preparing and storing food properly to prevent contamination with infected vectors (43).

Measures for primary prevention also include preventing infection in newborns as well as blood, organ, or bone marrow recipients. Recommendations issued by a group of U.S. experts in 2021 strongly suggested screening women of childbearing age who have lived in endemic countries to prevent neonatal transmission, based on moderate-quality evidence (44). A World Health Organization (WHO) technical group further recommended screening girls (before fertile age) and women (especially pregnant women) to identify those who are at risk for transmitting infection to the fetus, including those who live in, those who were born in, and those who previously lived in disease-endemic areas (45) (Box: Considerations for Who Should Be Screened and Tested for Chagas Disease in the United States).

The WHO recommends screening blood donors as well as organ and tissue donors in endemic areas (43), and the FDA also recommends screening blood donors (19). Experts recommend screening of potential transplant donors who were born in endemic regions and recommends testing and, if indicated, treatment of recipients of organs from infected donors (46).

For laboratory personnel who handle blood from *T cruzi*–infected patients, *T cruzi* cultures, or *T cruzi*–infected triatomines, particularly in endemic countries, some experts recommend testing them yearly for infection and providing technical training and personal protective equipment to avoid exposure. If exposure occurs, local disinfection, testing, and (if indicated) antiparasitic treatment are recommended (47). No vaccine is currently available, but several candidates that protect against disease but not infection are in development (48).

What is the role of screening in prevention of chronic Chagas disease?

Screening for Chagas disease also allows for secondary prevention (preventing progression in chronically infected persons). Detection of new or longer-standing infections through screening allows for provision of antiparasitic therapy that may prevent development of Chagas cardiomyopathy and allows for initiation of Chagas-specific symptomatic treatment.

Recommendations issued by a group of U.S. experts in 2021 suggested screening persons who were born or who lived for a prolonged period (>6 months) in endemic countries (strong recommendation based on low-quality evidence), first-degree relatives of persons diagnosed with Chagas disease (strong recommendation based on low-quality evidence), and those with documented exposure to triatomines during travel or in states with known transmission-capable triatomines (conditional recommendation based on low-quality evidence) (44). The WHO also recommends screening organ and tissue recipients who are at risk for reactivation and neonates and children born to infected, untreated mothers (43). The WHO recommendation to screen girls (before fertile age) and women (especially pregnant women) also serves as secondary prevention to identify chronic infection and prevent progression to clinically apparent disease (45).

In the United States, the guidelines on opportunistic infections from the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Infectious Diseases Society of America (IDSA) include a recommendation to screen any HIV-infected person with epidemiologic risk factors for *T cruzi* infection (49). Screening of blood donors can also be used for secondary prevention because donors with reactive screening results are directed to consult their health care provider.

Diagnosis

How is acute Chagas disease diagnosed?

Patient history and clinical suspicion are critical to diagnosis of acute Chagas disease. History of exposure to triatomine vectors in endemic regions, either directly or through contamination of food or drink, is suggestive (4, 6). Congenital Chagas disease should be considered in infants born to mothers with confirmed infection (21).

Diagnosis of acute Chagas disease is made by testing for *T cruzi* trypomastigotes in peripheral blood. Testing should be timed for after the incubation period, when detectable parasitemia would be expected. Microscopic examination of Giemsa-stained blood smears or fresh buffy coat preparations to identify trypomastigotes can be performed (2). Molecular testing using polymerase chain reaction (PCR) detects parasite DNA and is more sensitive, although availability is limited. The differential diagnosis for acute Chagas disease includes other causes of nonspecific febrile syndromes. The Romaña sign is a less common sign of acute Chagas disease, and other causes of periorbital or preseptal cellulitis should be considered, including bacterial sinus infections and viral infections causing swelling of the eyelids or conjunctivitis. *T cruzi*–specific antibody develops within the first few weeks of infection and becomes detectable within months. Most available serologic tests are specific for IgG, meaning that standard serologic testing is not useful for diagnosis of acute Chagas disease in the United States (2).

In congenitally infected infants, Chagas disease is diagnosed by detection of trypomastigotes or parasite DNA in cord blood or newborn blood; detection of *T cruzi*–specific antibody in newborn blood can confirm maternal infection but is not useful for newborn diagnosis (32). Because the sensitivity of detection can be low due to inconsistent and waning parasitemia levels in the infected newborn, in babies whose PCR results are negative at

birth and/or within 2 months of birth, their status should be confirmed by serologic testing at age 9 to 12 months (after maternal antibody is gone). For symptomatic newborns, the differential diagnosis for acute Chagas disease includes infection with other pathogens, such as *Toxoplasma gondii*, cytomegalovirus, herpes simplex virus, rubella, or syphilis.

How is chronic Chagas disease diagnosed?

Because management of Chagas heart disease differs somewhat from management of other causes of cardiomyopathy and there is increased risk for stroke, early recognition is important (36, 50). Patient history and clinical suspicion are critical to diagnosing chronic Chagas disease. History of birth or residence in endemic regions or maternal origin in those regions should prompt testing for Chagas disease. During the chronic phase, diagnosis is made by detection of *T cruzi*–specific antibodies (2, 4). Chronic infections cannot be reliably diagnosed by microscopic examination or molecular (PCR) testing of peripheral blood because the parasite is not consistently found in the blood. In the United States, many patients with asymptomatic Chagas disease are first flagged through blood donor screening for *T cruzi*–specific antibodies. Currently, 3 tests are FDA-approved for blood donor screening for Chagas disease. These tests are not sufficient or appropriate for patient diagnosis, and the blood collection agency notification regarding a donor's reactive testing results advises consulting a health care provider for further diagnostic evaluation.

The standard for diagnosis of chronic Chagas disease is positive results on 2 or more different serologic tests that each use a different antigen preparation and, preferably, different formats (for example, enzyme-linked immunosorbent assay [ELISA] and immunoblot). No single test has adequate sensitivity and specificity to diagnose Chagas disease, and test performance tends to vary among endemic geographic areas (2).

In a study of 500 seropositive and 300 seronegative plasma samples from blood donors, 4 assays were assessed: InBios Chagas Detect Plus rapid test (sensitivity, 97.4% to 99.3%; specificity, 87.5% to 92.3%), Hemagen Chagas' Kit ELISA (sensitivity, 88.0% to 92.0%; specificity, 99.0% to 100.0%), Ortho T cruzi ELISA (sensitivity, 92.4% to 96.5%; specificity, 98.8% to 100.0%), and Wiener Chagatest Recombinante v3.0 ELISA (sensitivity, 94.0% to 97.1%; specificity, 96.7% to 99.3%) (51).

In the United States, serologic testing for Chagas disease is offered by several commercial diagnostic laboratories, although none of those laboratories currently use more than 1 test. To help confirm Chagas disease, CDC offers confirmatory serologic testing, with the Wiener Chagatest Recombinante v3.0 ELISA and a laboratory-developed test (trypomastigote excreted–secreted antigen immunoblot) used in parallel. If the CDC results are discordant, a second specimen is requested for repeated testing, and if the results are discordant again, a third test (a laboratory-developed immunofluorescent antibody test) is used.

What are the clinical manifestations and symptoms of chronic Chagas disease in immunocompromised patients (reactivation)?

Patients with chronic Chagas disease are at risk for reactivation of their infection if they have immunosuppression. Reactivation risk is important for chronically infected heart transplant recipients, with estimated rates ranging from 27% to as high as 90% depending on the

study (25). Reactivation of chronic Chagas disease can occur in hematopoietic stem cell transplant recipients, patients living with HIV who have CD4 T-lymphocyte cell counts below 0.200×10^9 cells/L (49), and patients receiving immunosuppressive chemotherapy for treatment of cancer or autoimmune conditions. Reactivation is characterized by parasitemia and manifestations that include cutaneous nodules, myocarditis, or meningoencephalitis. Meningoencephalitis or brain abscesses, similar to those caused by *Toxoplasma gondii*, are more common in people living with HIV than patients with immunosuppression due to other causes (49). Reactivation is diagnosed by detection of trypomastigotes in peripheral blood, either through morphologic identification in blood smears or wet preparations of microhematocrit buffy coat layers, or through molecular testing for parasite DNA. Because low levels of *T cruzi* DNA may be intermittently present in the blood in immunocompetent patients, laboratory diagnosis of reactivation necessitates identifying increased amounts of DNA over time. This is typically accomplished by PCR testing of serial specimens (52).

Treatment

What is the role of primary care providers in the management of Chagas disease?

Primary care providers play an essential role in screening patients for Chagas disease. Referral to specialists may be necessary to assist in evaluating and treating Chagas disease and its complications (as outlined in a later section). Primary care providers also play a key role in monitoring patients after treatment (with serial electrocardiograms, echocardiograms, and assessment of symptoms) as well as testing of family members.

Who should be treated?

Antitrypanosomal therapy should be provided for all cases of acute infection (IDSA grade A, level II), early congenital infection (IDSA grade A, level II), and chronic infection in children aged 18 years or younger (IDSA grade A, level I for children aged ≤12 years; IDSA grade A, level III for children aged 13 to 18 years) (2, 53). Because there is no real test of cure and because PCR results may not be positive in persons with low circulating levels of parasites, understanding treatment efficacy is difficult. Studies on the effectiveness of treatment (based on parasitologic cure) estimate a cure rate of 60% to 99% in patients with acute Chagas disease and congenitally infected infants treated within a year of birth (54–56). Treatment should also be provided for reactivated Chagas disease in patients with HIV/AIDS or other immunosuppression (IDSA grade A, level II) and should generally be offered to patients with impending immunosuppression (IDSA grade B, level II) according to a 2007 systematic review and meeting of experts (53).

Treatment of women of childbearing age with chronic Chagas disease should generally be offered (IDSA grade B, level III) or should always be offered if future pregnancies are planned (strong recommendation based on moderate-quality evidence) (2, 53).

Treatment of adults with chronic infection requires further study. In a 2007 systematic review, expert recommendations stated that treatment is considered optional for adults older than 50 years without advanced cardiomyopathy (IDSA grade C, level III) and for patients with gastrointestinal disease but without advanced cardiomyopathy (IDSA grade C, level

III) (53). Treatment should generally be offered to adults aged 19 to 50 years who are in the chronic indeterminate stage or have mild to moderate cardiomyopathy (IDSA grade B, level II) as per expert recommendations (53). More recent recommendations suggest the importance of considering potential risks, benefits, uncertainties, and patient preference but state that treatment may be offered to adults with normal electrocardiograms and cardiac function and those with early signs of cardiomyopathy (based on discretionary and weak evidence) (2).

In adults with chronic indeterminate (asymptomatic) Chagas disease, antitrypanosomal therapy may improve parasite clearance and slow the development of cardiomyopathy, but data are limited primarily to observational studies (53, 57–59).

In a trial of chronically infected adults, after a median follow-up of almost 10 years, fewer treated patients had disease progression or developed electrocardiographic abnormalities (57).

A meta-analysis of 17 studies of benznidazole compared with placebo or no treatment for chronically infected patients in the indeterminate phase or with visceral involvement showed odds ratios for seroreversion of 38.3 (CI, 10.7 to 137) in children and 17.1 (CI, 2.3 to 129.1) in adults (58).

In a study of 2854 patients with Chagas cardiomyopathy who received placebo or benznidazole and were followed for a mean of 5.4 years, benznidazole was associated with increased likelihood of parasite clearance (conversion to negative PCR results of 66.2% vs. 33.5%) but did not reduce mortality or cardiac deterioration (59).

Some experts argue that in light of the small number needed to treat to prevent 1 case of cardiomyopathy, treatment should be advised for adults in the indeterminate stage (60). Because of the weakness of the evidence, further studies are needed to determine whether treatment is beneficial in the setting of early cardiac disease.

Avoiding treatment of patients with advanced cardiomyopathy and heart failure (IDSA grade D, level III) and patients with megaesophagus and significant impairment of swallowing (IDSA grade D, level III) is recommended. Those with severe renal or hepatic insufficiency also should not be treated (IDSA grade E, level III) (53).

What pharmacologic treatment options are available for Chagas disease?

Two medications are currently available for treatment of Chagas disease (Table 2). Benznidazole is FDA-approved for the treatment of Chagas disease in pediatric patients aged 2 to 12 years (61), and nifurtimox is FDA-approved for treatment of pediatric patients (weighing ≥2.5 kg) from birth until they reach age 18 years. Use of benznidazole or nifurtimox to treat a patient outside the FDA-approved age ranges is based on clinical diagnosis and a decision by the treating physician under the practice of medicine (62). Although posaconazole may have some antitrypanosomal activity, it has not shown clinical effectiveness to date (63).

Benznidazole is the first-line drug option for treatment of *T cruzi* infection and is available in the United States (6, 8, 9, 62). The dosage regimen for patients aged 2 to less than 12 years is 5 to 8 mg/kg of body weight per day (53). This is also the recommended dose for patients younger than 2 years and those aged 12 years or older. For all patients, treatment is given orally in 2 divided doses for 60 days (62). Some studies suggest that treatment duration could be shortened, but additional data are needed (57, 64). Adverse effects are reported less often in infants and young children than in adolescents or adults (65). Common adverse effects include dermatitis in 29% to 50%; the rash or photosensitization usually appears in the first few weeks of treatment and is more common in females than males (66). Peripheral neuropathy occurs in 0% to 30%, generally later in the treatment course; it is reversible but may last for months and should prompt immediate discontinuation of benznidazole. Anorexia and weight loss (5% to 40%), nausea or vomiting (0% to 5%), insomnia, and bone marrow suppression (<1%) may also occur, and patients should undergo regular clinical and laboratory monitoring while receiving treatment (2). Overall, 7% to 30% of patients may require treatment discontinuation due to adverse effects.

The FDA-approved dosage for nifurtimox in children from birth until age 18 years varies by patient weight. The dose is 10 to 20 mg/kg per day for those weighing at least 2.5 kg but less than 40 kg and 8 to 10 mg/kg per day for those weighing 40 kg or more. Nifurtimox is taken orally with food 3 times daily for 60 days (a decrease from the previous recommendation of 90 days) (6, 62). As with benznidazole, adverse effects are less common in young children than in adolescents or adults (67). Adverse effects (in ≥5%) include anorexia, nausea, vomiting, abdominal pain, headache, dizziness or vertigo, and polyneuropathy. With nifurtimox, 6% to 75% of patients may require treatment discontinuation due to adverse effects (4, 67).

Alcohol increases the risk for and severity of adverse effects, and consumption is contraindicated during treatment with benznidazole or nifurtimox. Full lists of warnings and precautions can be found on the FDA labels (61, 68).

A sensitive and practical test of cure is lacking to assess treatment response (8, 9). Treatment failure, particularly among immunosuppressed patients (for example, posttransplant patients or those with HIV), may be confirmed by positive PCR results (69), but a negative PCR result does not necessarily indicate cure (49). Drug candidate trials have used PCR as an indicator of treatment failure, but such testing requires rigorous standardization, and results may vary by location and the parasite's discrete typing unit (70). Hemoculture and examination of buffy coat or blood can be used to assess treatment response in cases of reactivation or acute and early congenital infection. For patients with chronic disease who are not immunocompromised, repeating serologic testing at least once every year is recommended, but the reversion to a negative result may take decades in chronically infected patients (71). All patients with chronic Chagas disease should be monitored annually with 12-lead electrocardiography (53), or biannually in the setting of reduced ejection fraction or major changes (36). The American Heart Association (AHA) recommends repeating echocardiography every 1 to 2 years for patients with reduced ejection fraction and every 3 to 5 years for those with preserved ejection fraction (36). Additional repeated cardiac evaluations (for example, 24-hour Holter monitoring and exercise stress testing) should be

considered for those with clinical status changes or other manifestations, as outlined by the 2019 AHA guidelines (36).

What are special considerations for managing immunosuppressed patients?

In HIV-infected persons with Chagas disease, most cases of *T cruzi* reactivation have occurred in patients not taking antiretroviral therapy (ART). Optimization of ART might help prevent *T cruzi* reactivation (CDC/NIH/IDSA grade B-III) (49). In patients with evidence of reactivation, starting or optimizing ART is recommended once the patient's Chagas disease is clinically stable (CDC grade A-III) (49).

What are special considerations for managing pregnant patients?

Treatment is not recommended during pregnancy because the teratogenic risks of benznidazole and nifurtimox are not well understood (53, 61, 68). However, treatment should be considered if it would be life-saving for the mother. Benznidazole treatment should be deferred until after breastfeeding has stopped, and infants exposed to nifurtimox through breastfeeding should be monitored for adverse effects.

When should primary care providers consider referring patients to a specialist for treatment?

Patients infected with *T cruzi* should be referred to appropriate specialists, including infectious disease specialists, cardiologists, and gastroenterologists, to address disease complications.

Infectious disease specialists—Depending on the primary care provider's comfort level, knowledge, and time available during the visit to address Chagas disease, they may be able to manage the disease without referral to an infectious disease specialist. Referral can be helpful in confirming the diagnosis, evaluating potential end-organ complications, considering whom to treat, and monitoring patients during and after treatment. It is anticipated that most primary care providers will want to refer patients to infectious disease specialists until they become comfortable treating *T cruzi*–infected patients.

Cardiologists—Referral to a cardiologist depends on the provider's comfort with treating heart failure and their need for help in managing complications of chronic Chagas heart disease in accordance with standard guidelines. Treatment for heart failure associated with Chagas disease is based on extrapolation of data from other causes of heart failure (53, 72) and usually includes 1 or more categories of medications, including β-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, digoxin, and anticoagulants. Patients should be carefully monitored for bradyarrhythmia if β-blockers or digoxin are given (6). Notably, patients with Chagas heart disease are at higher risk for atrial fibrillation and cardiac thrombus; anticoagulation is recommended for those with atrial fibrillation, a previous thromboembolic event, or a cardiac thrombus detected by echocardiography and may be indicated in those with apical aneurysms. Further details are available in the AHA guidelines (36). Pacemakers and implantable cardioverter-defibrillators may be used in patients with advanced chronic cardiac Chagas disease to

prevent arrhythmias and sudden cardiac death, particularly for secondary prevention (73). Heart transplant may be required in patients with refractory heart failure (6).

Gastroenterologists—Depending on the provider's comfort with treating symptoms and the need for a surgical procedure, referral to a gastroenterologist or surgeon may be indicated. Esophageal symptoms may be mitigated by drugs that relax the sphincter, although the relief may be short-lived (37). Surgical options include pneumatic balloon dilatation (often performed via endoscopy) and laparoscopic myotomy (Heller technique), both of which may help in partial recovery of esophageal peristalsis. Additional surgical procedures, including esophagectomy, have been performed in advanced cases. Endoscopic botulin toxin injection in the sphincter region can be considered for those who have high surgical risk or serious concomitant diseases. Early stages of colonic involvement may respond to high-fiber diets and laxatives or enemas, but surgical resection may be needed for late stages of megaesophagus and megacolon. Referral to a specialized center for surgical management is recommended (37). Rates of symptom recurrence vary by type of surgical procedure (74).

What counseling or services should be offered to family members?

Family members of persons with Chagas disease are more likely than the general population to have the disease. Screening should be offered to all persons who shared a household in an endemic country with a patient with Chagas disease and to children of infected mothers (4, 44, 75).

Practice Improvement

What do professional organizations recommend for prevention, screening, diagnosis, and management of Chagas disease?

The 2019 PAHO guidelines for the diagnosis and treatment of Chagas disease and the 2015 Brazilian Society Chagas Disease both address the topic (76, 77). Although formal guidelines on screening and diagnosis have not been issued by U.S. professional organizations (such as IDSA or the American Society of Tropical Medicine and Hygiene), a set of recommendations from U.S. experts was published in 2021 (44) that agrees with the basic concepts outlined in the PAHO guidelines, including the use of 2 different serologic tests for diagnosis of chronic Chagas disease. Recommendations for treatment of chronic Chagas disease are not uniform; the PAHO guidelines suggest trypanocidal therapy for adult patients with chronic *T cruzi* infection and no specific organ damage (conditional recommendation, low-quality evidence), whereas the Brazilian guidelines suggest this should be determined on a case-by-case basis.

Guidelines from the WHO exist for blood donor counseling and selection (78, 79), and there are international and U.S. guidelines on organ transplantation (46, 80). Several Brazilian and U.S. guidelines address the role of echocardiography and other cardiac testing for Chagas disease (36, 50, 81, 82).

What are the reporting requirements?

In the United States, Chagas disease is reportable in certain states (83). Providers should check their state health department website or the Council of State and Territorial Epidemiologists website (84, 85). As of 2022, Chagas disease was explicitly reportable in 7 states (Arizona, Arkansas, Louisiana, Mississippi, Tennessee, Texas, and Utah) and implicitly reportable in several others (84, 85).

What resources are available for providers?

Questions about treatment should be directed to CDC's Parasitic Diseases Inquiries (404–718-4745; e-mail, parasites@cdc.gov). For emergencies (including disease in a newborn or an immunocompromised person or acute Chagas disease with severe manifestations) outside regular business hours, providers should call CDC's Emergency Operations Center (770–488-7100) and ask for the person on call for parasitic diseases.

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Considerations for Who Should Be Screened and Tested for Chagas Disease in the United States*

Perform Screening

- Persons who were born or who lived for >6 mo in endemic areas (Mexico, Central America, South America), especially women of childbearing age and HIV-infected persons
- First-degree relatives of persons diagnosed with Chagas disease, especially neonates and children born to infected, untreated mothers
- Blood donors who have lived in endemic countries
- Organ and tissue donors and recipients who have lived in endemic countries
- Recipients of organs transplanted from infected donors
- Laboratory personnel who handle blood from infected patients, *T cruzi* cultures, or triatomines

Consider Screening

- Those with documented exposure to triatomines during travel or in states with known transmission-capable triatomines

Clinical Conditions That Warrant Diagnostic Testing in Persons From Endemic Countries

- Electrocardiographic or echocardiographic abnormalities that suggest infection (see Table 1)
- Evidence of thromboembolic phenomenon
- Symptoms or signs of gastrointestinal disease (see Table 1)

*From reference 45.

CLINICAL BOTTOM LINE

Risk Factors and Causes...

Chagas disease is endemic in the mainland parts of Mexico, Central America, and South America, and approximately 240 000 to 350 000 persons living in the United States are infected. Providers should consider screening persons who were born or who lived for a prolonged period (>6 months) in endemic countries and first-degree relatives of persons diagnosed with Chagas disease. Infection can occur congenitally or after blood transfusion (although this is rare due to routine screening in the United States) or organ transplant.

CLINICAL BOTTOM LINE

Diagnosis...

Diagnosis of Chagas disease varies by phase of infection. Acute Chagas disease is diagnosed by detection of the parasite either morphologically (identification in blood smears, buffy coat preparations, or tissues) or molecularly using PCR to detect *T cruzi* DNA. Chronic Chagas disease is diagnosed by detection of *T cruzi*–specific antibodies based on positive results on 2 or more different serologic tests. During chronic infection in immunocompetent patients, the parasite is often not detectable in the blood, but reactivation can occur when chronically infected patients become immunosuppressed. Reactivation is diagnosed by detection of parasites in the blood, either morphologically or by identifying increasing levels of parasite DNA.

CLINICAL BOTTOM LINE

Treatment...

Treatment should be offered to patients with acute infection, patients with congenital disease, immunosuppressed patients or transplant recipients with reactivation, and children younger than 18 years with chronic infection. Treatment should generally be offered to nonpregnant women of childbearing age and adults aged 19 to 50 years who are in the chronic indeterminate stage or have mild to moderate cardiomyopathy; treatment of other patients with Chagas disease can be considered. Treatment for Chagas disease consists of either benznidazole or nifurtimox; however, these are currently FDA-approved only for children, and treatment of adults is under the practice of medicine. The decision to treat should generally be made in conjunction with an infectious disease specialist who can help monitor for the frequent adverse reactions. Cardiologists and gastroenterologists also can assist in the evaluation and treatment of complications.

Figure 1. Triatoma sanguisuga.
Courtesy of James Gathany and the Centers for Disease Control and Prevention.

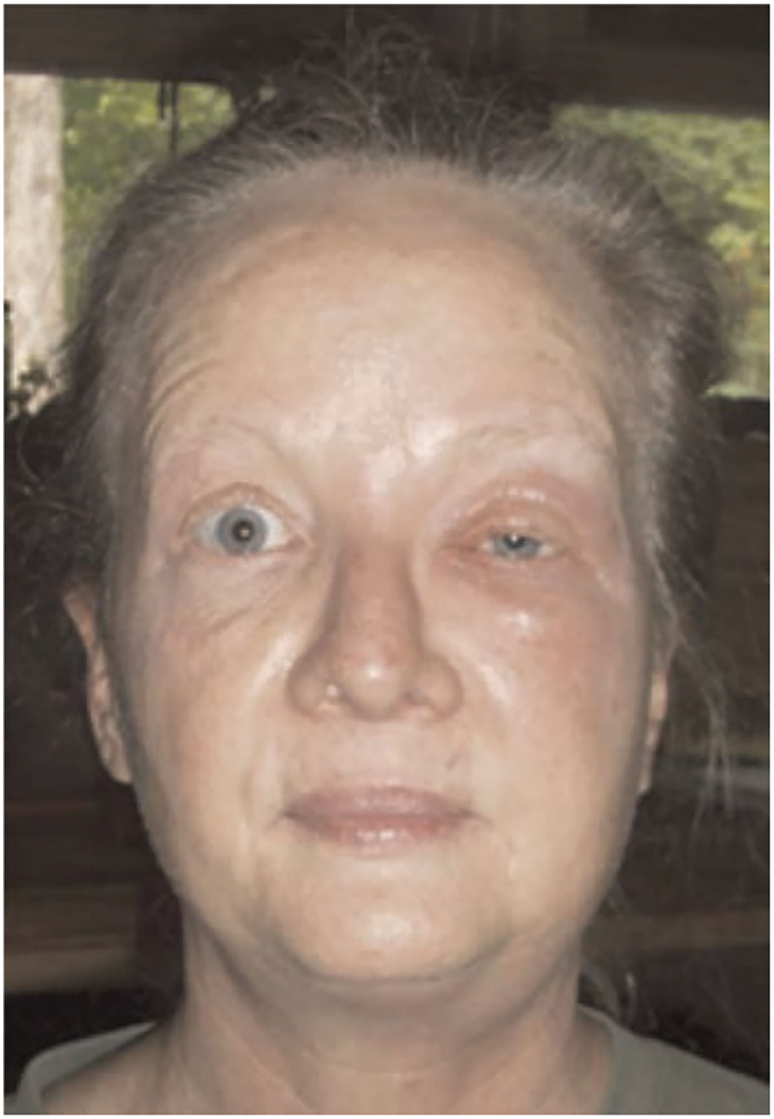

Figure 2. Image of a traveler returning from an endemic country with the Romaña sign, a manifestation of acute Chagas disease.

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Table 1.

Symptoms and Signs of Different Manifestations of Chagas Disease

Stage	Symptoms and Signs on Physical Examination	Potential Radiographic and Cardiac Findings
Acute	Often asymptomatic with normal physical examination findings May have chagoma, fever, lymphadenopathy, or hepatosplenomegaly Myocarditis or encephalitis (rare)	Evidence of myocarditis on electrocardiogram and echocardiogram (rare)
Congenital	Often asymptomatic with normal physical examination findings May have low birthweight, prematurity, low Apgar scores, hepatomegaly, or splenomegaly Hydrops fetalis (rare)	–
Indeterminate	Asymptomatic (no signs on physical examination)	Normal
Chronic (cardiac)	Symptoms include palpitations, lightheadedness, chest pain, symptoms of heart failure (e.g., peripheral edema, orthopnea) Physical examination may show irregular cardiac rhythm, signs of heart failure or stroke	Electrocardiogram: Conduction system abnormalities, including right bundle branch block, left anterior fascicular block, bifascicular block, first-degree atrioventricular block, ventricular premature beats, atrial fibrillation, bradyarrhythmia, tachyarrhythmia (e.g., atrial fibrillation, ventricular tachycardia) Echocardiogram: Regional wall motion abnormalities, dilated cardiomyopathy, reduced ejection fraction, apical aneurysm
Chronic (gastrointestinal)	Symptoms include abdominal pain, dysphagia, odynophagia, regurgitation, and constipation Signs include weight loss Symptoms of colonic torsion (rare)	Barium swallow, barium edema, chest/ abdominal CT scan: Megaesophagus or megacolon
Reactivation (patients with HIV)	Symptoms and signs of meningoencephalitis	May have central nervous system lesions on imaging (CT, MRI)
Reactivation (transplant recipients, immunosuppressed patients)	Cutaneous nodules, myocarditis, meningoencephalitis	Echocardiogram may show myocarditis

CT = computed tomography; MRI = magnetic resonance imaging.

Table 2.

Indications, Dosing, and Adverse Effects for Medications Used to Treat Chagas Disease

Medication	Indications by Age and Acute/Chronic Status	Pregnancy and Breastfeeding Considerations	FDA Status	Dosage	Adverse Effects
Benznidazole	Approved for patients aged 2–12 y Recommended for all acute and chronic infections in children aged ≤18 y, including congenital infections Recommended for patients aged 19–50 y in chronic indeterminate stage or with mild to moderate cardiomyopathy Consider for patients aged >50 y without advanced cardiomyopathy Avoid treating patients with advanced cardiomyopathy and heart failure	Pregnant patients should not be treated Consider deferral of treatment until after breastfeeding has stopped	Approved for pediatric patients aged 2–12 y Treatment for older children and adults is based on the decision of the treating physician	5–8 mg/kg of body weight per day Administered in 2 divided doses, taken orally for 60 d	Dermatitis, peripheral neuropathy, anorexia, bone marrow suppression, nausea, vomiting
Nifurtimox	Approved for patients from birth to age 18 y Recommended for all acute, congenital, and chronic pediatric cases Recommended for patients aged 19–50 y in chronic indeterminate stage or with mild to moderate cardiomyopathy Consider for patients aged >50 y without advanced cardiomyopathy Avoid treating patients with advanced cardiomyopathy and heart failure	Pregnant patients should not be treated Treatment should be deferred until after breastfeeding has stopped	Approved for pediatric patients weighing ≥2.5 kg from birth to age <18 y Not approved for adults; treatment for adults is based on the decision of the treating physician	Taken orally with food 3 times daily for 60 d For patients from birth to age <18 y: For those weighing ≥2.5 to <41 kg: 10–20 mg/kg per day For those weighing ≥41 kg: 8–10 mg/kg per day	Anorexia, nausea, vomiting, abdominal pain, headache, dizziness, neuropathy

FDA = U.S. Food and Drug Administration.