Chagas disease in solid organ and heart transplantation

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Purpose of review
The diagnosis and management of acute and chronic infections with the microorganism *Trypanosoma cruzi*, which causes Chagas disease, is important in solid organ transplantation in both endemic and nonendemic countries. In this review, we examine recently published data on the topic of Chagas disease in solid organ transplantation, with an emphasis on data relevant to heart transplantation.

Recent findings
Most people with chronic *T. cruzi* infection have the intermediate form of disease, but approximately 2% of infected persons will progress to Chagas cardiomyopathy per year. The risk of *T. cruzi* transmission with liver or kidney transplantation appears to be substantially less than that with heart transplantation. For patients with Chagas cardiomyopathy undergoing heart transplant, a structured clinical and laboratory monitoring protocol is necessary to monitor for *T. cruzi* reactivation. Recent data indicate that laboratory monitoring of peripheral blood with polymerase chain reaction testing can identify reactivation prior to the occurrence of symptoms and allograft injury.

Summary
Transplant clinicians should exercise vigilance in surveillance for Chagas disease in both organ donors and recipients. Although Chagas disease may seem uncommon, it is pervasive in endemic and several nonendemic countries, including the United States and Spain.

Keywords
Chagas cardiomyopathy, Chagas disease, donor selection, heart transplantation, organ donor *Trypanosoma cruzi*

INTRODUCTION

Chagas disease continues to be a major public health issue in South, Central, and North America with 7.7 million persons infected in 18 countries [1]. Although the number of new infections has decreased in Latin America, the prevalence of disease remains high because of the chronic nature of infection with the causative organism *Trypanosoma cruzi* [2]. The diagnosis and management of Chagas disease in solid organ transplantation is extremely important in Latin America because of the high prevalence of chronic *T. cruzi* infection in organ donors and the high transmissibility of *T. cruzi* infection through solid organ transplantation [3,4▪▪]. Particular vigilance is required in endemic countries that perform heart transplantation, which in 2010 were Brazil, Argentina, Colombia, Chile, Mexico, Uruguay, Peru, Paraguay, and Ecuador [5]. Outside Latin America, immigration from endemic countries has led to a substantial population of chronically infected persons in nonendemic countries (Fig. 1) [1,6]. In Chagas disease nonendemic countries, failure to identify Chagas disease before heart transplantation and inexperience with the specialized management that is required for these patients has led to several cases of fatal Chagas disease reactivation (CDR) after heart transplantation [7,8▪▪]. In this review, we will examine recently published data on the topic of Chagas disease in solid organ transplantation, which provide new insights into important issues in the diagnosis and management of Chagas disease in organ donors and recipients.

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KEY POINTS

- Persons who were born in, or lived in, a Chagas disease endemic country and who are presenting with a dilated (nonischemic) cardiomyopathy should be tested for *T. cruzi* infection using serological methods.
- Organ donors with a similar risk profile should be tested for chronic *T. cruzi* infection, as there is a substantial risk of transmission of *T. cruzi* infection with transplantation, with infection occurring in 13–22% of liver or kidney transplant recipients, and 75–100% of heart transplant recipients as such use of heart allografts from potential donors that are seropositive for *T. cruzi* infection is not recommended.
- The risk of *T. cruzi* transmission with liver or kidney transplantation appears to be less than that with heart transplantation, but patients receiving transplants from *T. cruzi*-infected donors require clinical and laboratory monitoring after transplant.
- The incidence of Chagas disease reactivation after heart transplantation for Chagas cardiomyopathy is between 21 and 45%, and because of this risk, heart transplantation for Chagas cardiomyopathy should be performed in the setting of a structured clinical and laboratory monitoring protocol for *T. cruzi* reactivation.

CHRONIC *TRYPANOSOMA CRUZI* INFECTION AND THE DEVELOPMENT OF CHAGAS CARDIOMYOPATHY

Identification of patients with chronic *T. cruzi* infection is of paramount importance because the manifestation of advanced cardiac Chagas disease, Chagas cardiomyopathy, has a markedly worse prognosis as compared with other causes of cardiomyopathy [9,10]. The prevalence of *T. cruzi* infection in endemic countries varies from a low of 0.1% in Costa Rica to a high of 8% in Bolivia, as determined by testing of blood donated to blood banks [2].

Political and economic turmoil in Latin America in the late 20th century and early 21st century led to immigration of a large number of persons from Latin America to the United States, Spain, Canada, and other countries of Europe [6,11]. Using *T. cruzi* prevalence data, Bern and Montgomery [12] estimated that there were 300 000 persons with chronic *T. cruzi* infection living in the United States in 2005 [13▪▪]. Testing of the blood supply in the United States has shown a prevalence about 10 times lower than this of 1 : 13 000 overall, or 1 : 200 persons born in Central or South America [14]. A similar method yielded an estimate of 36 567 –122 232 persons living in Spain with chronic *T. cruzi* infection [15].

In both endemic and nonendemic countries, as the severity of cardiac disease worsens, the prevalence of Chagas disease in susceptible patients increases. Chagas cardiomyopathy is the indication for heart transplantation in 35% of patients in Brazil and 13% of patients in Argentina [3,16]. In the United States, testing of patients with dilated (nonischemic) cardiomyopathy who were born and lived for more than 1 year in a Chagas disease endemic country showed a seroprevalence of 13% in New York and 19% in Los Angeles [17▪,18]. In a cohort of

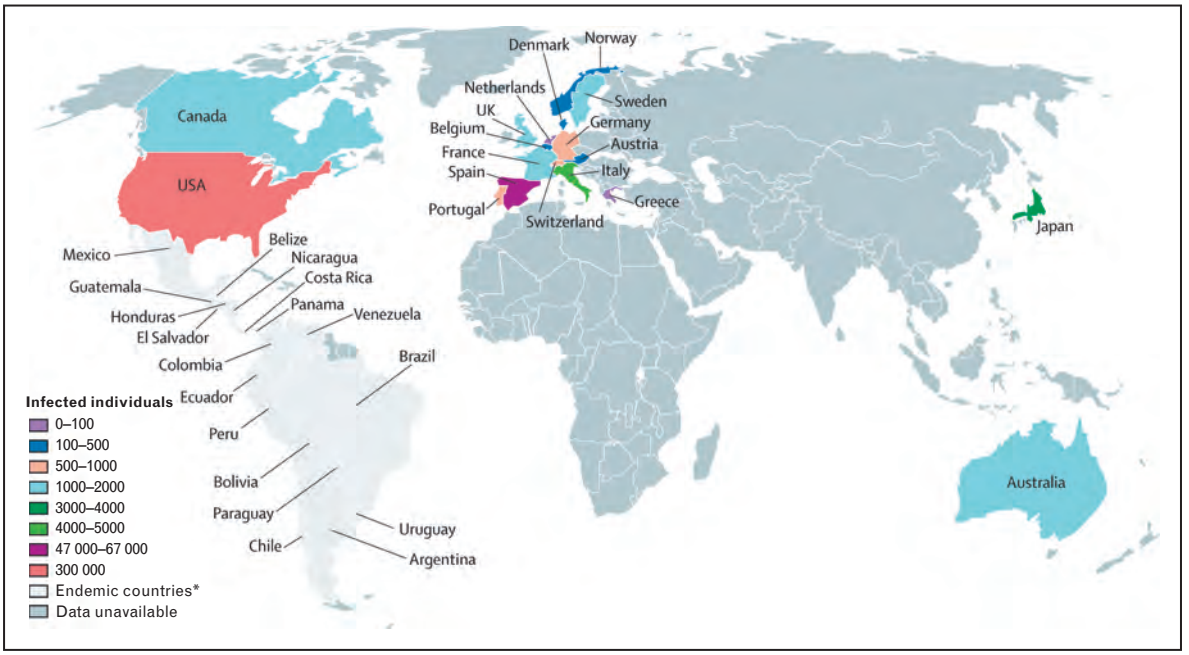

FIGURE 1. Estimated number of persons with chronic *Trypanosoma cruzi* infection living in nonendemic countries. Reproduced with permission from [1].

patients with dilated cardiomyopathy who were born in a Chagas disease endemic country and who presented to our center for heart transplantation, we found that 11 out of 20 patients (55%) were seropositive for Chagas disease [8▪▪]. Given this high prevalence, we recommend that all patients with dilated cardiomyopathy who were born or lived in an endemic country should be tested for *T. cruzi* infection using two serological assays with different formats and antigen preparations, in accordance with World Health Organization guidelines [19]. Our practice has been to send patient samples to the Centers for Disease Control and Prevention (CDC) for testing.

Most persons with chronic *T. cruzi* infection have the intermediate form of disease during which they have no clinical manifestations but do have a detectable serologic response [1]. Older studies indicated that between 20 and 30% of persons with intermediate disease progress to chronic cardiac Chagas disease [20]. Cardiac Chagas disease initially manifests as asymptomatic conduction blocks and normal systolic function, but can progress over time to recurrent ventricular tachycardia and end-stage heart failure [1]. Recently, epidemiologic data from Brazil have shed light on the incidence rate for development of cardiomyopathy [21▪]. Over a 10.5-year follow-up period, 24% of initially asymptomatic *T. cruzi* seropositive persons developed Chagas cardiomyopathy, for an incidence rate of 1.85% per year. However, some caution is necessary in interpreting this result, as this study was performed in Brazil and patients who acquire *T. cruzi* infection in Colombia and Argentina have a 20-fold higher parasite load compared with those acquiring *T. cruzi* infection in Brazil [22,23]. In animal models, a higher number of *T. cruzi* organisms in the initial inoculum are associated with more inflammation and lower survival [24].

TRYPANOSOMA CRUZI INFECTION IN ORGAN DONORS AND DONOR-TRANSMITTED INFECTION

The management of organ donors with *T. cruzi* infection has become an important issue in both endemic and nonendemic countries. The heart is an important reservoir of *T. cruzi* organisms in chronically *T. cruzi*-infected patients; heart transplantation from an infected donor will lead to transmission of *T. cruzi* infection in most cases. In the presence of the immunosuppression required for heart transplantation, the likelihood of CDR is significant. Indeed, donor-transmitted *T. cruzi* occurred in two heart transplant recipients in Southern California in 2005 and 2006 and resulted in the death of both recipients [25]. As such, use of heart allografts from potential donors that are seropositive for *T. cruzi* infection is not recommended [26].

For noncardiac allografts, recent literature has shown that acceptable outcomes can be achieved using donors that are seropositive for *T. cruzi* infection without posttransplant prophylactic antitrypanosomal therapy. McCormack *et al.* [27] reported that two out of nine recipients (22%) of liver allografts intentionally accepted from *T. cruzi*-infected donors developed *T. cruzi* infection, without clinical symptoms, over a median follow-up of 15 months. Monitoring of *T. cruzi* infection was performed via Strout's method, and the two patients with *T. cruzi* infection were treated and both survived. Similarly, Cicora *et al.* [28▪] recently reported that six recipients of kidney allografts intentionally accepted from *T. cruzi*-infected donors did not develop signs or symptoms of Chagas disease over a median follow-up of 36 months.

There is also a significant experience with solid organ transplantation using *T. cruzi*-infected donors in the United States, but unlike the series reported above, the use of a *T. cruzi* positive donor was unintentional in all cases. Huprikar *et al.* [4▪▪] recently reported the CDC experience with transplantation of organs from 14 *T. cruzi* seropositive donors to 32 recipients between 2001 and 2011. In this series, four seropositive donors were used for heart transplantation, which resulted in three cases of CDR (transmission of Chagas disease in 75%). In contrast, two out of 10 (20%) recipients of liver allografts and two out of 15 (13%) recipients of kidney allografts developed *T. cruzi* infection. *T. cruzi* infection either manifested clinically or was detected via PCR monitoring. These findings agree with previous recommendations that liver and kidney allografts from *T. cruzi* seropositive donors can be considered for use, when transplantation is performed along with a monitoring protocol for *T. cruzi* infection [26].

Universal testing of all potential organ donors is performed in the endemic countries Argentina and Brazil [3,29]. In the United States, as of 2009, only four organ procurement organizations were performing universal testing of donors for *T. cruzi* infection, and another three were performing risk-based testing [30]. Given that Hispanic/Latino persons are now the most populous minority ethnic group in the United States, a small but significant number of donors, especially in states with a high Hispanic/Latino population, such as California, Texas, Florida, and Arizona, can be expected to be seropositive for *T. cruzi* (Fig. 2) [31,32]. In support of this, a 2006 study showed that one of 404 donors in Southern California were seropositive for *T. cruzi* [33]. We agree with recommendations that targeted testing be performed on all organ donors in the

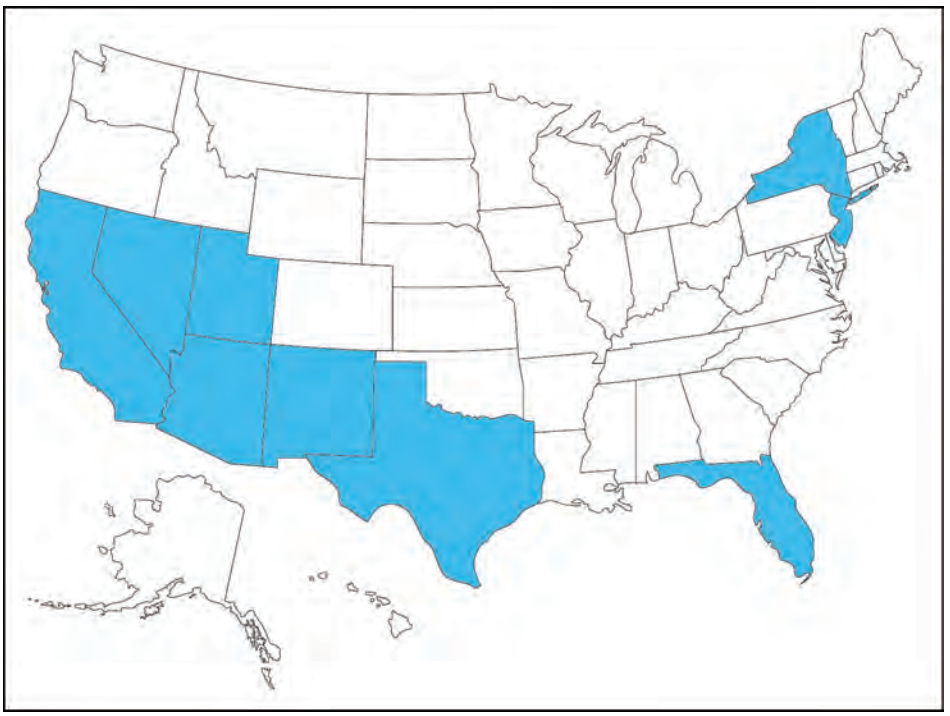

FIGURE 2. States with a greater than the national average Hispanic/Latino population. In this map of the United States, states are colored blue if their population of Hispanic/Latino people is greater than the national mean (16.3%). Reproduced with permission from United States 2010 Census Data [32].

United States [26]. On the basis of the epidemiologic factors associated with *T. cruzi* seropositivity in blood donors, birth in an endemic country, more than 3 months of residence in an endemic country, as well as Hispanic/Latino ethnicity are strongly markers for *T. cruzi* seropositivity [14].

Spain is a Chagas disease nonendemic country with a large population of immigrants from endemic countries, and consequently the management of organ donors and recipients with chronic *T. cruzi* infection is an important issue [34]. Spain has developed consensus guidelines regarding the management of organ donation and infection that includes recommendations on management of Chagas disease [35]. These guidelines are similar to the recommendations put forth for the United States transplant community by the Chagas in Transplant Working Group [26]. Both of these guidelines are summarized in Table 1.

HEART TRANSPLANTATION FOR CHAGAS CARDIOMYOPATHY

Given the potential for CDR with immunosuppression, Chagas cardiomyopathy was initially considered a relative contraindication to heart transplantation [36], but subsequent studies have shown that the survival after heart transplantation for Chagas cardiomyopathy is not different than heart transplantation performed for other indications [37]. Nevertheless, CDR can cause both cardiac and noncardiac manifestations. Cardiac manifestations include new conduction blocks potentially requiring pacemaker placement, valvular regurgitation, and most seriously, allograft dysfunction that can progress to cardiogenic shock and death [8▪▪,37]. Importantly, the myocarditis of an acute CDR can easily be mistaken for allograft rejection [38], which if treated with intensified immunosuppression can lead to more severe *T. cruzi* infection. Noncardiac manifestations of CDR include skin lesions, fever, and encephalitis [39,40].

Brazil has the most experience with heart transplantation for Chagas disease in the world, most recently publishing a series of 107 patients who underwent heart transplantation between 1985 and 2010 [41]. Argentina has the next largest experience, reporting 16 heart transplants for Chagas disease between 1998 and 2010 [3]. We have recently published our experience with heart transplantation for 11 cases of Chagas cardiomyopathy at our center in the United States [8▪▪]. In this section, we discuss the specialized laboratory testing and clinical monitoring for CDR that must be implemented to ensure good long-term outcomes for patients who undergo heart transplantation for Chagas cardiomyopathy.

Table 1. Recommendations from guidelines on the diagnosis and management of Chagas disease in organ transplantation

Recommendation	Guidelines	
	United States	Spain
Screening should be performed in donors and recipients who were born or have resided in CD endemic areas through serological testing.	+++	+++
Serological testing for TC infection should be performed using the Ortho EIA or the Abbott Prism Chagas test systems.	+++	
Transplantation of any organ from donors with acute TC infection is contraindicated.	+++	+++
Transplantation of the heart from donors with chronic TC infection is contraindicated.	+++	+++
Transplantation of organs other than the heart (liver or kidneys) from donors with chronic TC infection can be considered.	+++	+++
If transplantation is performed using organs from a donor chronically infected with TC, close monitoring of the recipient using TC PCR and microscopy of blood specimens is recommended.	+++	+++

CD, Chagas disease; EIA, enzyme-linked immunosorbent assay; TC, *Trypanosoma cruzi*.
Adapted from [26] and [34].

Monitoring of heart transplant recipients for Chagas cardiomyopathy begins with a comprehensive pathologic evaluation of the explanted heart. At our center, this includes gross pathologic evaluation and histopathology to make an assessment of the presence of *T. cruzi* intracellular amastigotes; the degree of fibrosis, necrosis, and myocytolysis; and the degree and location of cellular infiltration [42]. In our experience, all patients with Chagas cardiomyopathy have had myocarditis in the explanted heart. We identified *T. cruzi* amastigotes in two out of 12 (17%) cases [42]. We have also routinely sent paraffin blocks of explanted cardiac tissue to the Infectious Disease Pathology Branch at the CDC for *T. cruzi* immunohistochemistry and *T. cruzi* PCR testing.

Benvenuti *et al.* [43▪▪] recently published a study of 34 cardiectomy specimens from patients who underwent heart transplantation for Chagas cardiomyopathy. Interestingly, they found that multiple parameters of *T. cruzi* organism burden including the degree of myocarditis, the presence of *T. cruzi* organisms by microscopy or immunohistochemistry, and PCR of *T. cruzi* DNA did not differ between 18 patients with CDR and 16 patients without CDR. Not surprisingly, high-grade myocarditis was more common when *T. cruzi* organisms were identified. More research is needed to determine the parasitic and host factors that lead to parasite persistence in Chagas cardiomyopathy and CDR after heart transplantation.

Given the potential for increased morbidity and mortality from CDR, we developed a systematic management program for patients undergoing heart transplantation for Chagas cardiomyopathy at our center [8▪▪]. Our protocol is detailed in Table 2 and is composed of both clinical and laboratory monitoring. Clinical monitoring for CDR comprised: first, serial visits with evaluation for symptoms/signs

Table 2. Clinical and laboratory monitoring protocol for *T. cruzi*/Chagas disease reactivation after heart transplantation

Before heart transplantation	
Screen all patients with dilated cardiomyopathy who were born in or lived in a Chagas disease endemic country for TC infection	
Perform serological testing using two serological assays with different formats and TC antigen preparations	
After heart transplantation	
Examine cardiac explant by microscopy for presence of TC amastigotes and myocarditis	
Examine paraffin blocks of explanted tissue by IHC for TC and tissue PCR for TC	
Perform serial clinical evaluation for signs/symptoms of allograft dysfunction and arrhythmia (including ECG and 2D echocardiogram)	
Perform serial laboratory evaluation using microscopy of blood buffy coat with attention to TC organisms, EMB with attention to presence of TC amastigotes, and whole blood PCR testing for TC at CDC per schedule:	
Posttransplant month 1 and 2	Weekly
Posttransplant month 3– 6	Every 2 weeks
Posttransplant month 6–12	Monthly
Posttransplant month 13–24	Every 3 months
Posttransplant month 25 and greater	Every 6 months

2D, two-dimensional; EIA, enzyme-linked immunosorbent assay; EMB, endomyocardial biopsy; IFA, immunofluorescence assay; IHC, immunohistochemistry; TC, *Trypanosoma cruzi*.
Adapted with permission [8▪▪].

of allograft dysfunction, fever, new skin lesions or arrhythmia; second, ECG with evaluation for new conduction blocks; and third, echocardiography to assess for new left ventricular dysfunction. Laboratory monitoring for CDR comprised: first, microscopy of a buffy coat blood sample for *T. cruzi*; second, endomyocardial biopsy (EMB) to assess for the presence of amastigotes; and third, whole blood testing by PCR for *T. cruzi* at the Reference Diagnostic Laboratory of the Division of Parasitic Diseases and Malaria at CDC.

The goal of clinical monitoring is to identify any CDR causing symptoms or allograft injury and promptly initiate treatment with an antitrypanosomal agent [44]. The goal of laboratory monitoring is to identify any subclinical CDR before symptoms and injury to the cardiac allograft and noncardiac tissues can occur. Traditionally, laboratory monitoring has utilized parasitological methods and histological examination of serial EMB samples for *T. cruzi* amastigotes. Over the last 10 years, multiple studies have shown the value of PCR testing on peripheral blood to detect subclinical CDR before allograft dysfunction and symptoms develop [45,46]. In our centers' experience using whole blood PCR testing performed by the CDC, in three cases of laboratory-confirmed reactivation (*T. cruzi* parasitemia detected on serial samples), no clinical symptoms were apparent at the time of detection and no further *T. cruzi*-related complications occurred after treatment [47]. It is important to note that PCR testing is performed by the Reference Diagnostic Laboratory of the Division of Parasitic Diseases and Malaria at CDC, and all decisions regarding treatment were made after consultation with their staff.

The reactivation rate of Chagas disease after heart transplantation for Chagas cardiomyopathy is variable, with an incidence of 21–39% reported in Brazil [37,41,48]. Campos *et al.* [48] identified the number of rejection episodes, development of neoplasia, and use of mycophenolate mofetil as independent determinants of CDR. In our series of 11 patients undergoing heart transplantation for Chagas cardiomyopathy, we identified CDR (two clinical reactivations and three laboratory-confirmed reactivations) in five or 11 patients (45%) [8▪▪]. In the United States, benznidazole is the recommended first-line treatment for CDR, as its side-effects are generally considered more tolerable that the other antitrypanosomal agent nifurtimox [44]. Of note, both of these agents are not approved by the United States Food and Drug Administration, and thus must be obtained through the CDC. Finally, recent investigations in animals have shown that several existing therapeutic agents, including posaconazole and allopurinol have antitrypanosomal activity [49,50], although a recent clinical trial showed a higher rate of treatment failure in patients treated with posaconazole as compared with benznidazole [51].

Given the high rate of CDR after heart transplantation for Chagas cardiomyopathy, some centers have instituted a 'prophylactic' treatment strategy in which all heart transplant recipients are automatically treated with antitrypanosomal therapy. For example, Spain employs a prophylactic treatment strategy [35]. The United States guidelines do not recommend a prophylactic treatment strategy, and in our experience with PCR-based laboratory monitoring, subclinical *T. cruzi* reactivation can be detected before allograft dysfunction develops [8▪▪,26]. Both antitrypanosomal agents have significant side-effects and do not lead to cure of chronic *T. cruzi* infection [44], so chronic monitoring for CDR remains important even after therapy.

CONCLUSION

Because of its high prevalence in persons born or having lived in Chagas disease endemic countries and its high transmissibility with organ transplantation, chronic *T. cruzi* infection remains an extremely important issue in solid organ transplantation. Persons who were born in, or lived in, a Chagas disease endemic country and who are presenting with a dilated (nonischemic) cardiomyopathy should be tested for *T. cruzi* infection. Likewise, organ donors with a similar profile should also be tested. The risk of *T. cruzi* transmission with liver or kidney transplantation appears to be substantially less than that with heart transplantation. Recent data show that donors with Chagas disease can be accepted for liver and kidney transplantation without detrimental effects on outcomes with proper monitoring. For patients with Chagas cardiomyopathy undergoing heart transplantation, a structured clinical and laboratory monitoring protocol is necessary to monitor for *T. cruzi* reactivation. Recent data indicate that laboratory monitoring of peripheral blood with polymerase chain reaction testing can identify reactivation prior to the occurrence of symptoms and allograft injury.

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Conflicts of interest

There are no conflicts of interest.

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