

REVIEW ARTICLE

Heart Transplantation for Chagas Cardiomyopathy

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Abstract

Heart transplantation (HT) is an established treatment for patients with advanced heart failure (HF). Chagas disease (CD), caused by the *Trypanosoma cruzi* (*T. cruzi*) is an important cause of HF in Latin America. Considering CD is a chronic infectious disease, the use of immunosuppressive therapy after HT can reactivate *T. cruzi* infection and compromise outcomes. Early diagnosis and treatment of this complication is extremely important, which requires knowledge, experience, and a high degree of suspicion by transplant physicians. Furthermore, with the international immigration of people, CD is no longer exclusive to Latin America, since a large number of immigrants with *T. cruzi* infection are living in non-endemic countries. This phenomenon represents not only a new global epidemiological problem, but also a challenge for transplant teams. This review aims to discuss the peculiarities of HT in the context of CD, with a focus on reactivation of the infection, clinical manifestations, etiological treatment of *T. cruzi* and differential diagnosis with allograft rejection, among HT recipients.

Introduction

Heart transplantation (HT) is an established treatment for selected patients, with advanced heart failure (HF), with refractory to optimal medical treatment, and without contraindications that would compromise the outcomes.^{1,2}

The procedure in these patients has proven to be a treatment that is effective in decreasing mortality rates

Keywords

Trypanosoma cruzi; Chagas disease; Cardiomyopathy; Heart failure; Heart transplantation.

and improving patients' quality of life.³ At present, not only are the number of heart transplant candidates increasing, but they are also becoming much more complex.^{3,4} The great advances that have occurred in the field of transplants notwithstanding, there are still challenges to be faced:

- older age of both recipients and donors;
- the need for mechanical circulatory support (not available in several Centers);
- the growing use of combined organ transplants;
- high proportion of sensitized candidates;
- shortage of organ donors;
- uncommon etiologies of HF requiring HT;
- Chagas disease (CD) as a worldwide challenge and the complexity of *T. cruzi* infection reactivation.⁽⁵⁻⁷⁾

In the past, CD was considered a contraindication for heart transplantation due to the possibility of reactivation of *T. cruzi* infection as a consequence of immunosuppressive therapy to prevent allograft rejection.^{5,8} The first heart transplant due to CD was performed in Brazil in June 1985, by Dr Euryclides de Jesus Zerbini, in the city of São Paulo.⁸ Since then, CD has emerged as a complex indication for heart transplant, and even today it remains a challenge for transplant teams in endemic countries. As a result, CD has added more challenges to the field of transplantation.

Brazilian physicians were pioneers in performing HT in chagasic patients, gaining experience in this new area of transplants. From 1985 on, HT has become a well-established alternative for patients with end-stage Chagas heart disease.^{5,9,10} Despite the complexity of the reactivation of *T. cruzi* infection, which occurs frequently in HT recipients, its proper diagnosis allows for an adequate treatment and ensures a good prognosis.⁵

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Peculiarities of Chagas Disease in the Context of Heart Transplant

Since 1990, several intergovernmental initiatives coordinated by both the Pan American Health Organization (PAHO) and the World Health Organization (WHO) have been implemented in an attempt to eliminate domestic triatomines and to prevent transmission via blood transfusions in Latin America.¹¹ As a consequence, the number of new cases of infection was significantly reduced. However, an estimated 7,968,094 *T. cruzi* infected individuals worldwide, mostly in Latin America, have been reported.¹²

The increased flow of individuals from rural areas to large cities and the international migration of people has led to a globalization of the disease that is no longer exclusive to Latin America. A large number of immigrants with chronic *T. cruzi* infection are living in non-endemic countries, such as those in North America and the European Union, as well as in Australia and Japan. This fact causes concern for transplant teams and a challenging epidemiological problem.^{6,7}

Chagas disease is characterized by an acute phase after an initial infection followed by a chronic form. The acute phase, usually asymptomatic or accompanied by mild symptoms, progresses with high levels of *T. cruzi* in the blood, proliferation of amastigote forms in various tissues, and resolution in 4 to 8 weeks. The patients then evolve to the chronic form, with low parasitemia levels. The chronic form is also divided into indeterminate, an asymptomatic form that can persist for life, and a clinically symptomatic form occurring in 20% to 30% of all cases. The cardiac, digestive, or cardio-digestive clinical manifestations may appear even decades after the initial infection.¹³ The chronic cardiac form includes arrhythmias, conduction defects, HF, and sudden cardiac death. Heart failure due to Chagas etiology has a worse prognosis and a higher mortality rate when compared to other etiologies.¹⁴

Chagas disease is the third leading cause of HT in endemic countries, corresponding to 35% of all patients undergoing the procedure^{5,9,10}

The reactivation of chronic infection by *T. cruzi* may occur in conditions of immunosuppression, such as AIDS, cancer undergoing chemotherapy, or after the use of immunosuppressive drugs, such as in the context of organ transplants.¹³

Transplant professionals from endemic and non-endemic countries need to be aware of the risk of *T. cruzi*

transmission from infected donors to recipients as well as to the risk of reactivation of chronic infection in organ transplant recipients, receiving immunosuppressive therapy to avoid allograft rejection.^{5,13}

Recipient Selection and Listing Criteria

The indications and contraindications for HT in the setting of CD follow the classic HT guideline criteria for other HF etiologies.^{1-2,5} A patient with severe terminal HF refractory to optimal medical treatment and without formal contraindications, might benefit from the procedure and should be included on the waiting list for a heart transplant.^{1,2,5} Clinical treatment needs to be optimized for symptom relief and to improve survival, necessarily including the following drugs: an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker, or angiotensin receptor-neprilysin inhibitor added to a beta blocker (in maximum tolerated doses) and a mineralocorticoid antagonist if possible.¹⁵⁻¹⁷

Some peculiarities in the selection of HT potential donors and recipients in the context of CD should be observed.^{2,5}

Chagas patients usually have lower values of pulmonary arterial pressure, which can reduce right ventricular dysfunction, a frequent complication in the postoperative period of HT. Thus, cardiac manometry by right cardiac catheterization may not be always necessary before HT.^{2,5} Most of these patients come from poor rural areas. Social inequalities may influence results and survival rates after HT, but these issues are still not well understood. However, it seems that the patient's socioeconomic condition has no impact on outcomes after HT.¹⁸ The megaesophagus and megacolon may occur in CD as a cardio-digestive form and should be evaluated. Depending on the severity of digestive manifestation, these may constitute contraindications to the procedure.⁵

Chagas cardiomyopathy is a highly arrhythmogenic disease, and sudden cardiac death corresponds to 55%-65% of all deaths, frequently caused by malignant arrhythmias, such as tachycardia and ventricular fibrillation.¹⁸ Patients with malignant ventricular arrhythmias usually receive an implantable cardioverter-defibrillator (ICD). They may require multiple ICD therapies, more than 4 shocks per day, featuring an electrical storm. This group of patients might also benefit from a heart transplant.¹⁹

In Brazil, according to governmental regulation, serology for *T. cruzi* infection in all potential donors and recipients is mandatory, and a positive donor for heart

recipients is not accepted.¹³ Potential organ donors and recipients should always be screened for Chagas disease, in both endemic and non-endemic countries whose potential donor/recipient has a positive epidemiology.^{6,13}

Mechanical circulatory support has a potential benefit as a bridge for HT in chagasic patients. However, due to the high costs, this device is not available in the Public Health System (SUS in Portuguese) in Brazil, which funds more than 90% of heart transplants in the country.⁵

Immunosuppression Strategies

Induction therapy for HT, regardless of the etiology of HF, consists of intense immunosuppressive therapy during the transplant procedures or in its immediate postoperative period. It is recommended in high-risk patients in an attempt to reduce the risk of hyperacute rejection or delay the use of higher doses of calcineurin inhibitors, thus minimizing kidney damage.^{19,20} The most widely used inducing agents are polyclonal anti-thymocyte immunoglobulins (polyclonal antibody - thymoglobulin) and interleukin 2 receptor inhibitors, which have low immunogenicity, such as daclizumab and basiliximab²¹

Basic immunosuppressive therapy for the maintenance of heart transplant patients generally includes a calcineurin inhibitor agent (Cyclosporin A or tacrolimus). These agents must be associated with mycophenolate mofetil, mycophenolic acid, azathioprine, rapamycin, or everolimus. Prednisone is associated with this standard regimen and, in most patients, can be suspended six months after the transplant, in the absence of rejection.²¹ In the context of Chagas disease, induction and/or maintenance immunosuppressive therapy can reactivate *T. cruzi* infection.^{2,5,13}

There are no randomized control clinical studies comparing the various immunosuppressive regimens in HT chagasic patients. However, a greater number of reactivations have been described in recipients using mycophenolate mofetil.⁽²²⁾ Therefore, it is recommended that Chagas patients receive the lightest immunosuppressive therapy, as long as there is no rejection.⁵

Diagnosis and Treatment of Rejection

Graft rejection is an important cause of morbidity and mortality after heart transplant in general, although the incidence of treated rejection continued to decline. In the last decade, only 12.6% of HT recipients were treated for rejection between hospital discharge and one year after transplant.³

Rejection is classified into hyperacute, antibody-

mediated, and acute cellular rejection (ACR), the last representing the most prevalent form of rejection in an HT setting. Histologically, it is defined by inflammatory infiltrates, which are typically lymphocyte predominant, and associated myocyte injury. The International Society for Heart and Lung Transplantation (ISHLT) has revised (R) categories of ACR as follows: 0R (no rejection), 1R (mild), 2R (moderate), or 3R (severe).²³

Hyperacute rejection is mediated by preformed antibodies to the allograft in the recipients and manifests as a severe graft failure within minutes or a few hours after the HT procedure. It is now uncommon due to the advent of prospective cross-matching and more potent immunosuppressive therapy.²³

Antibody-mediated rejection is poorly defined and challenging, especially in HT performed for Chagas cardiomyopathy.^{5,23} The frequency of hyperacute rejection and antibody-mediated rejection after HT due to CD have not been reported.⁵

Although rejection is a major cause of death amongst chagasic recipients, occurring in 10%–14% of all patients, no difference in the incidence of rejection episodes (grade 2R or 3R) between HT recipients with or without Chagas disease has been reported in Brazil.^{3,9,10,20,24}

To date, there are no laboratory markers for rejection. Most patients are asymptomatic, and symptoms, when present, are vague and nonspecific. Thus, early detection of cardiac rejection relies on histological diagnosis through endomyocardial biopsy (EMB), the gold standard method for the diagnosis, and the monitoring of allograft rejection. Despite its invasiveness, EMB is associated with a very low morbidity and mortality when performed by experienced operators.²⁵ In most transplant centers, it is used for routine rejection surveillance, varying the frequency of biopsies in Center protocols.

A myocarditis secondary to reactivation of the *T. cruzi* infection in the transplanted heart can often occur, which makes the differential diagnosis between allograft rejection and reactivation of Chagas' disease a great challenge.⁵

Endomyocardial biopsy is considered the best method for the differential diagnosis between inflammation caused by immunological rejection and *T. cruzi* infection reactivation. The definition of one of these two conditions is still a challenge if parasites are not found at the biopsy fragments. Under routine histopathology staining techniques, if parasites are not seen, the inflammatory histopathological features found in either rejection (grade 2R or 3R) or reactivation are quite similar. Thus, the detection of an inflammatory mononuclear

infiltrate in the EMB slides is not enough to rule out the diagnosis of Chagas disease reactivation and poses a medical dilemma as the aggressive immunosuppressive treatment to abort rejection may facilitate Chagas disease reactivation.⁵

The findings of *T. cruzi* amastigote nests with inflammatory mononuclear infiltrates in the EMB fragments do not exclude concomitant allograft rejection, as the two conditions may occur concomitantly.

The therapy of rejection in transplant recipients with and without Chagas disease is similar. In general, a mild grade of rejection (ISHLT 1R), in the absence of clinical or hemodynamic compromise, generally do not require additional intervention. However, higher grades (\geq 2R) require an aggressive supplemental immunosuppression. The majority of cases with ACR respond properly to pulse corticosteroid therapy, although rescue therapy may be required for certain patients.^{5,21}

Rejection constitutes a risk factor for Chagas reactivation, as over 85% of all patients have at least one rejection episode before reactivation occurs.⁽⁵⁾

Moreover, up to 43% of all patients with findings of inflammatory infiltrate compatible with the diagnosis of 2R or 3R rejection, at EMB fragments, do not respond to immunosuppressive therapy, but they do show a good response to anti-trypanosomal drug treatment.⁵

Post Heart Transplant *T. Cruzi* Infection Reactivation

Clinical presentation

The instituted immunosuppressive therapy increases the risk of *T. cruzi* infection reactivation. The incidence after HT varies from 19.6% to 90% in Brazil.^{9,20,24} A recent publication from a United States case series shows a rate of CD reactivation of 61%, which is within the broad range reported here.⁽²⁶⁾

The Latin America Guideline for the Diagnosis and Treatment of Chagas Heart Disease has established several risk factors for reactivation, as follows:^{25,26}

- number of rejection episodes;
- intensity of Immunosuppression;
- use of mycophenolate mofetil;
- presence of malignancy;
- HIV infection and other immunosuppression status.⁵

Considering the potential morbidity and mortality, the diagnosis and appropriate management of Chagas disease reactivation in the context of organ transplants

is extremely important. Therefore, this procedure must be performed within a structured clinical and laboratory protocol to monitor the reactivation of the infection and its subsequent treatment.^{5,9,13} The diagnosis of reactivation is based on clinical signs and symptoms and/or the presence of parasites in blood, cerebrospinal fluid and other fluids, bone marrow, or tissues.^{5,9} After HT, the patient must be closely and regularly monitored. Clinical monitoring aims to identify the first signs of reactivation and promptly establish anti-*T. cruzi* treatment. Clinical reactivation has cardiac and extra-cardiac manifestations including: myocarditis, ventricular dysfunction, arrhythmias, new atrioventricular/intraventricular blocks on the ECG, new skin lesions (subcutaneous nodules, panniculitis), fever, bone marrow involvement or neurological manifestations. The central nervous system involvement is a rare and severe clinical manifestation. It manifests through meningoencephalitis, chagoma, brain abscess, or stroke, as well as through spacing-occupying lesions in the white matter of the brain.^{5,9,27} Figure 1 is an example of post-heart transplant Chagas reactivation.

The myocarditis of the reactivation can be mistakenly diagnosed as a graft rejection, receiving intensified immunosuppressive treatment, which will aggravate the reactivation of the infection.²⁸ The differential diagnosis between rejection and reactivation myocarditis is still a major challenge. In the presence of inflammatory infiltrate, amastigote nests and/or positive PCR for *T. cruzi* in the myocardium, it can be said that there is a reactivation, but it is impossible to safely exclude associated allograft rejection. Despite this complexity, the survival rates of chagasic patients undergoing HT do not differ from other etiologies.^{9,20}

Parasitological diagnosis of reactivation

The purpose of laboratory monitoring is to identify any subclinical signs of reactivation before cardiac and extra-cardiac symptoms, as well as allograft dysfunction.^{5,13} Serological tests are useful only in potential donors, in the diagnosis of chagasic cardiomyopathy in potential recipients, and in seronegative recipients who receive organs from seropositive donors.^{5,13} These tests play no role in the diagnosis of reactivation. Traditionally, laboratory monitoring has used parasitological methods (direct blood search of *T. cruzi* and blood cultures) and serial histological examinations of EMB, in search of *T. cruzi* amastigotes, in tests with low sensitivity.^{5,13} In recent years, several studies have demonstrated the value of the PCR test in peripheral blood and EMB fragments

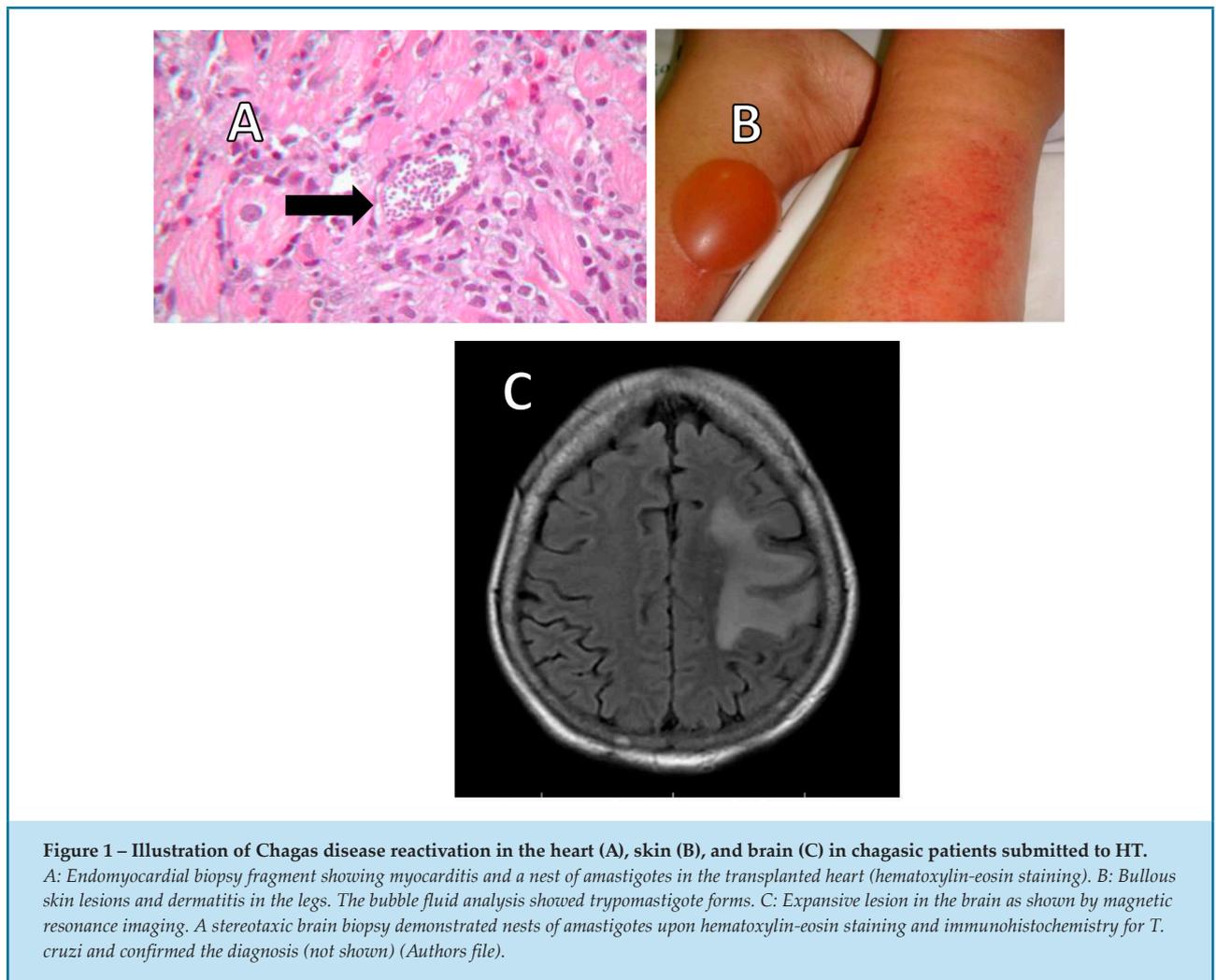


Figure 1 – Illustration of Chagas disease reactivation in the heart (A), skin (B), and brain (C) in chagasic patients submitted to HT.

*A: Endomyocardial biopsy fragment showing myocarditis and a nest of amastigotes in the transplanted heart (hematoxylin-eosin staining). B: Bullous skin lesions and dermatitis in the legs. The bubble fluid analysis showed trypomastigote forms. C: Expansive lesion in the brain as shown by magnetic resonance imaging. A stereotaxic brain biopsy demonstrated nests of amastigotes upon hematoxylin-eosin staining and immunohistochemistry for *T. cruzi* and confirmed the diagnosis (not shown) (Authors file).*

in detecting early reactivation, before the appearance of symptoms and/or cardiac allograft dysfunction.²⁹⁻³² Several studies have shown that PCR analysis is able to detect *T. cruzi* either in the blood or in EMB before clinical manifestations of reactivation by two or more months. Currently, PCR diagnosis is a precious tool to help physicians decide whether patients should begin treatment with anti-parasite drugs or changes in the immunosuppression protocol.²⁹⁻³²

It is very important to monitor HT recipients for early detection of *T. cruzi* reactivation, allowing etiological treatment before clinical manifestations appear. However, no specific definition about when and how the monitoring protocol should be applied is available. Some centers agree that Chagas recipients should be routinely monitored for *T. cruzi* reactivation as they are monitored for rejection and any time when clinical suspicion occurs. Variations in the protocol can occur depending on the transplant team's policy.^{5,17,26,33}

Thus, concerning the frequency of clinical visits, laboratory monitoring, and EMB, there is still no consensus in the literature. Table 1 is our suggestion for a clinical, laboratory, and histological monitoring protocol for chagasic patients undergoing HT and the etiological treatment, which is in line with main available guidelines.^{5,17,26,33} In countries where Chagas disease is not endemic, failure to identify patients with Chagas disease reactivation constitutes a major medical problem, as severe or fatal outcomes may supervene the incapacity to establish a proper diagnosis.^{33,34}

Etiological treatment of reactivation

Benznidazole and nifurtimox are the anti-trypanosomal drugs of choice and have proven to be effective when administered to patients in the acute phase of Chagas disease and in those showing *T. cruzi* infection reactivation.^{5,13} However, their efficacy upon the chronic phase has been a subject of debate.

Table 1 – Clinical and laboratory monitoring of *T.cruzi* infection reactivation after heart transplantation in Chagas disease and etiological treatment**Procedure****Before transplantation**

- Serological tests for Chagas disease for the donor
- Serological tests for Chagas disease for the potential recipient with some possibility of Chagas cardiomyopathy

After transplantation

- Periodic clinic visits with attention to signs/symptoms of reactivation, including ECG and Echocardiogram
- Routine blood *T.cruzi* test (smear, blood culture) for diagnosis of infection reactivation
- Routine blood test for *T.cruzi* by PCR if available
- Routine periodic endomyocardial biopsies, with *T.cruzi* search (histology, immunohistochemistry, and PCR analysis, when available)
- Search of *T.cruzi* in tissues (skin, bone marrow, among others) in a suspicion of *T.cruzi* infection

Frequency of procedures after transplantation

- First month: weekly
- Second month: every two weeks
- Third to sixth month: monthly
- Seventh to 12th month: every 3 months
- After 12 months: every six months

Etiological treatment of reactivation

- Benznidazole 5mg/Kg/day for 60 days

Adapted from references 2,5, and 26.

Thus, etiological treatment for Chagas disease is recommended for patients with acute infection, congenital infection, women of childbearing age for the prevention of vertical transmission, and reactivated infection in immunosuppressed patients. Other chronically infected people in the early chronic phase (especially children less than 15 years of age) may also benefit from treatment.¹³

Antiparasitic treatment is not recommended for patients in the chronic phase with advanced cardiomyopathy, as is the case of the heart transplant candidates, since there is no evidence of benefit. There is no evidence to support the prophylactic anti-*T.cruzi* treatment strategy for reactivation.¹³

In the heart transplant scenario, the presence of clinical manifestations of *T.cruzi* infection reactivation or identification of the parasite in the blood, cerebrospinal fluid, EMB fragments, or in other tissues constitute sufficient evidence to begin etiological treatment without delay. Benznidazole, a nitroimidazole derivative, is the first-line treatment drug of choice.^{5,13} Each tablet contains 100mg of the active substance. It is absorbed by the gastrointestinal tract and predominantly excreted by the kidneys, with a half-life of 12 hours. The recommended dose is 5mg/kg/day, for 60 days, with the daily dose being divided into two or three times.^{5,13} Its most important side effect is urticarial

dermatitis, which occurs in about 30% to 60% of all patients, commonly occurring early at the end of the first week of treatment, presenting a good therapeutic response with the use of antihistamines or small doses of corticosteroids. In a few cases, fever and adenomegaly may appear, in which case the medication should be discontinued. Other adverse effects include polyneuropathy, with pain and/or tingling in the lower limbs. Anorexia, significant leukopenia, and agranulocytosis are rare, and when present, the interruption of treatment is mandatory.¹³ Nifurtimox is not available in Brazil. These trypanosomicidal medications are contraindicated in pregnant women and in patients with either renal or hepatic impairment.¹³ A patient may have more than one reactivation episode after treatment. Therefore, it is necessary to maintain the monitoring of reactivation after anti-*T.cruzi* treatment.^{5,13}

Post Heart Transplant Complications and Survival

The clinical outcomes, morbidity, and mortality in HT recipients with and without Chagas disease are similar.⁹ ^{10,20}In both classes of patients, the major complications reported after transplant are almost the same: allograft dysfunction (20%); rejection (2R or 3R, 10%-14%); bleeding (10%); non *T.cruzi* infection (20%-30%); acute kidney failure

(up to 70%); cardiac allograft vasculopathy, which seems to be less frequent in chagasic recipients. Moreover, a reported higher incidence of malignancy has not been confirmed in all series.^{8-10,20,35}

In Brazil, the survival rate of Chagas patients undergoing HT is 76%, 71%, and 46% at six months, 5 and 10 years respectively, which is better when compared to the cohort of patients undergoing HT due to other etiologies.⁽⁹⁾ It has been postulated that the reason for the detected differences may well be due to particular chagasic patient characteristics, such as their young age, less comorbidities, and less previous cardiac surgery.^{8-10,20}

However, it should be emphasized that the only national registry compiling the results of HT in Brazil was carried out in 1999, more than 20 years ago^{5,9,10}

Conclusions

Heart transplantation is an established treatment for end-stage Chagas cardiomyopathy. The reactivation of *T.cruzi* infection occurs frequently in HT recipients, but a proper diagnosis allows for an adequate treatment and ensures a good prognosis. The survival rate of Chagas patients undergoing HT is better when compared to patients undergoing HT due to other etiologies.

Despite many advances in this complex field, there are still many unanswered questions and challenges. Chagas disease (American trypanosomiasis) is no longer exclusive of Latin American. The globalization of Chagas disease also requires attention and knowledge from transplant teams in non-endemic countries. Failure to diagnose Chagas disease in potential organ donors and recipients from endemic areas, as well as reactivation after transplant can evolve to fatal consequences.

With the incorporation of PCR techniques, the reactivation concept should be revised. The differential diagnosis

between rejection and reactivation remains a challenge and warrants further study. Multicenter studies comparing different immunosuppression protocols are desirable, as are a national registry to assess candidate selection, the management of immunosuppression to prevent and treat rejection episodes, the treatment of eventual *T. cruzi* reactivation, patient surveillance, and the evaluation of long-term results from the procedure.

Author Contributions

Conception and design of the research: Moreira MCV. Acquisition of data: Moreira MCV, Andrade GFMP. Analysis and interpretation of the data: Moreira MCV, Castilho FM, Cunha-Melo JR. Writing of the manuscript: Moreira MCV, Castilho FM, Andrade GFMP, Cunha-Melo JR. Critical revision of the manuscript for intellectual content: Moreira MCV, Cunha-Melo JR.

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