Chagas disease

José A Pérez-Molina, Israel Molina

Chagas disease is an anthropozoonosis from the American continent that has spread from its original boundaries through migration. It is caused by the protozoan Trypanosoma cruzi, which was identified in the first decade of the 20th century. Once acute infection resolves, patients can develop chronic disease, which in up to 30–40% of cases is characterised by cardiomyopathy, arrhythmias, megaviscera, and, more rarely, polyneuropathy and stroke. Even after more than a century, many challenges remain unresolved, since epidemiological control and diagnostic, therapeutic, and prognostic methods must be improved. In particular, the efficacy and tolerability profile of therapeutic agents is far from ideal. Furthermore, the population affected is older and more complex (eg, immunosuppressed patients and patients with cancer). Nevertheless, in recent years, our knowledge of Chagas disease has expanded, and the international networking needed to change the course of this deadly disease during the 21st century has begun.

Introduction

More than 100 years ago, Trypanosoma cruzi was identified as the causative agent of Chagas disease, yet the condition remains a major social and public health problem in Latin America and is regarded as a neglected tropical disease by WHO. According to WHO, and in common with other neglected tropical diseases, “Chagas disease is a proxy for poverty and disadvantage: it affects populations with low visibility and little political voice, causes stigma and discrimination, is relatively neglected by researchers, and has a considerable impact on morbidity and mortality”. In addition, stigma often precludes prompt detection and control of the disease since many patients do not want to know about the condition. In the seven southernmost American countries, the disease causes the loss of about 752,000 working days because of premature deaths and US$1.2 billion in productivity. The estimated annual global burden of disease is $627·46 million in health-care costs and 806,170 disability-adjusted life-years; 10% of this burden affects non-endemic countries. Migration and specific modes of transmission have led to Chagas disease spreading beyond its natural geographical boundaries and becoming a global issue. Furthermore, the typical patient profile has changed owing to increasing age and associated comorbidities.

Life cycle of T cruzi

T cruzi takes two forms in human beings. The trypomastigote, with a flagellum extending along the outer edge of an undulating membrane, does not divide in blood, but carries the infection throughout the body. The amastigote, which has no flagellum, multiplies within various types of cell, preferring those of mesenchymal origin (figure 1).

T cruzi is a heterogeneous species with high genetic and phenotypic diversity. It circulates between insect vectors and mammalian hosts, and has been classified into six near-clades (Tcl to TcVI) known as discrete typing units. This genetic diversity has been related to geographical distribution, pathogenesis, clinical features, and response to therapy. T cruzi is transmitted in endemic areas by various species of three genera of blood-sucking triatomine insects, also known as kissing bugs (Triatoma, Panstrongylus, Rhodnius). All three genera are widely distributed in Latin America, from Mexico to Argentina and Chile, and inhabit both forest and drier areas.

T cruzi can be transmitted through routes other than vectorial spread. These routes have a major role in non-endemic countries and a growing importance in endemic areas. It is estimated that the mother-to-child transmission rate is about 4·7% (range 3·9–5·6%) and that this rate could be higher in endemic countries than in non-endemic countries (5% vs 2·7%). The main biological determinant for congenital transmission is maternal parasitaemia, which could be as high as 31% when T cruzi is detectable by PCR, although transmission is also possible when PCR is negative. An association between some discrete typing units and lower rates of congenital transmission (eg, Tcl compared with TcV in Brazil) has also been suggested. On the other hand, an effective cellular immune response to T cruzi seems to have a relevant role in congenital infections. Sustained exposure to the vector is associated with decreased parasitaemia and congenital transmission, probably because frequent exposure to infected vectors induces a Th1 immune response that overcomes the less effective pregnancy-induced Th2 polarisation.

T cruzi can also be transmitted through blood and blood products; the estimated transmission rate per
Infected blood unit is 10–25%. Infection rates after solid organ transplantation from an infected donor seem to be lower for kidney recipients (0–19%) than for liver recipients (0–29%) and heart recipients (75–100%). Other less frequent modes of transmission include consumption of contaminated food and drink (oral transmission) and laboratory accidents.
Epidemiology

Chagas disease is endemic in 21 continental Latin American countries, from southern USA to the north of Argentina and Chile. It has traditionally been confined to poor, rural areas of Central and South America, where vectorial transmission is the main route of contagion. Residents of infested houses are continuously exposed to vector bites, and the incidence of infection by T cruzi is less than 0.1% to 4% per year in hyperendemic regions such as the Bolivian Chaco.26,27 Recent internal migration from rural to urban areas, congenital transmission, and blood donation have enabled the disease to spread to previously unaffected regions, mainly large urban areas, where urban disease cycles might be established in peripheral areas.28 The prevalence of T cruzi infection is highest in Bolivia (6.1 cases per 100 inhabitants), Argentina (3.6), Paraguay (2.1), Ecuador (1.4), El Salvador (1.3), and Guatemala (1.2).23 In the USA, enzootic cycles of T cruzi transmission are established in selected areas of some southern states, although only a few autochthonous infections have been reported.30,31

Since the early 1990s, the most effective measures for Chagas disease control in Latin America have been programmes for vector control and compulsory blood bank testing.30 Consequently, prevalence has decreased substantially (table 1), and vectorial transmission was interrupted in Uruguay in 1997, in Chile in 1999, and in most of Brazil in 2000 (figure 2).33,34 Nevertheless, the frequency of transmission has increased in regions such as the Amazon basin (oral transmission)35 and some areas of the Gran Chaco (because of resistance to pyrethroids by the vector).36

Chagas disease has crossed international borders and is now a global epidemic, to the extent that it can be transmitted in non-endemic regions. The pooled prevalence of infection in Latin American migrants living in Europe is estimated to be 4.2% (95% CI 2.2–6.7) with the highest prevalence among migrants from Bolivia (18.1%) and Paraguay (5.5%).6 In the USA, about 300 000 immigrants are estimated to be infected with T cruzi.7 However, the estimated index of underdiagnosis is around 95%,37 and health professionals’ expertise in this area is clearly insufficient.8

Clinical manifestations

The clinical course of Chagas disease usually comprises an acute phase and a chronic phase (table 2). Acute infection can occur at any age, though usually during the first years of life, and is asymptomatic in most cases. Acute phase symptoms include fever, inflammation at the inoculation site (inoculation chancre), unilateral palpebral oedema (Romana sign; when the conjunctiva is the portal of entry), lymphadenopathy, and hepatosplenomegaly. The acute phase lasts 4–8 weeks, and parasitaemia decreases substantially from 90 days onwards.38,39 Severe acute disease occurs in less than 1–5% of patients and includes manifestations such as acute myocarditis, pericardial effusion, and meningoencephalitis (risk of mortality 0.2–0.5%).40,41 Most congenitally infected newborn babies are asymptomatic or have mild symptoms, but a minority have severe life-threatening disease.42 Oral transmission through food or drink contaminated with triatomine faeces seems to cause more severe disease, with higher mortality than vector-borne disease.43,44

The acute phase usually resolves spontaneously after which time patients remain chronically infected if untreated. Most people never develop symptoms or visceral
involvement and thus are the largest group of patients affected. This so-called indeterminate form of Chagas disease has a good prognosis and is characterised by seropositivity for *T cruzi*, absence of clinical signs and symptoms of cardiac and digestive involvement, and normal chest radiography and electrocardiography.41 Increasingly more patients with indeterminate disease are diagnosed with subtle cardiac or digestive abnormalities, as diagnostic methods become more sensitive (eg, echocardiography, MRI, and oesophageal manometry). Nevertheless, whether such alterations are associated with poorer prognosis remains unclear.42

Roughly 30–40% of chronically infected patients can develop organ involvement 10–30 years after acute infection (mainly cardiomyopathy or megaviscera [megaesophagus, megacolon, or both]). This evidence originates from studies done in the 1980s,44,45,46 within a very different socioeconomic context, and they did not

### Table 2: Clinical features and diagnosis of Chagas disease

<table>
<thead>
<tr>
<th>Geographical distribution</th>
<th>Clinical signs and symptoms</th>
<th>Diagnosis</th>
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<td><strong>Acute forms including reactivation in immunosuppressed patients</strong></td>
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<tr>
<td>Vectorial</td>
<td>Endemic countries</td>
<td>Incubation period of 1–2 weeks. Signs of portal of entry: indurated cutaneous lesion (chagoma) or palpebral oedema (Romana sign). Most cases are mild disease (95–99%) and unrecognised. Persistent fever, fatigue, lymphadenopathy, hepatomegaly, splenomegaly, morbilliform rash, oedema. In rare cases, myocarditis or meningoencephalitis. Anaemia, lymphocytosis, raised AST and ALT concentrations. Risk of mortality 0.2–0.5%.</td>
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<tr>
<td>Congenital</td>
<td>Endemic and non-endemic countries</td>
<td>Incubation period: birth to several weeks. Most are asymptomatic or have mild disease. Prematurity, low birth weight, abortion, neonatal death. Fever, jaundice, oedema, hepatomegaly, splenomegaly, respiratory distress syndrome, myocarditis, meningoencephalitis. Anaemia and thrombocytopenia. Risk of mortality &lt;2%.</td>
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<tr>
<td>Oral</td>
<td>Restricted areas of endemic countries (Amazon basin) and local outbreaks</td>
<td>Incubation period 3–22 days. Fever, vomiting, periocular oedema, dyspnoea, fever, myalgia, prostration, cough, splenomegaly, hepatomegaly, chest pain, abdominal pain, digestive haemorrhage. Risk of mortality 1–35%.</td>
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<tr>
<td>Transfusion and transplant</td>
<td>Endemic and non-endemic countries</td>
<td>Incubation period 8–160 days. Persistent fever. Clinical characteristics similar to those of vectorial cases (excluding portal of entry signs). Risk of mortality is variable and depends on the severity of baseline disease.</td>
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<td>Reactivation in HIV-infected patients</td>
<td>Endemic and non-endemic countries</td>
<td>Behaves as other opportunistic infections. Reactivation with &lt;200 CD4 cells per μL (mostly with &lt;100). Affects CNS (75–90%) as single or multiple space-occupying lesions or as severe necrohaemorrhagic meningoencephalitis. Cardiac involvement (10–55%) myocarditis, pericardial effusion or worsening of previous cardiomyopathy. Risk of mortality 20%.</td>
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<tr>
<td>Reactivation in other immunosuppressed patients</td>
<td>Endemic and non-endemic countries</td>
<td>Reactivation after transplantation or in patients with haematological malignancies. Clinical characteristics similar to those of patients who undergo transfusion and those with pancytopenia and other skin disorders. Risk of mortality is variable and depends on the severity of baseline disease and prompt diagnosis.</td>
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<tr>
<td><strong>Chronic form</strong></td>
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<tr>
<td>Cardiac and gastrointestinal form</td>
<td>Endemic and non-endemic countries</td>
<td>Cardiac manifestations: fatigue, syncope, palpitations, dizziness, stroke. Late manifestations: chest pain (atypical), dyspnoea, oedema, left ventricular dysfunction, congestive heart failure. Alterations in 12-lead ECG, echocardiography, or other heart function tests. Gastrointestinal: dysphagia, regurgitation, severe constipation (dilated oesophagus or colon). Alterations in oesophageal manometry, barium swallow, or barium enema.</td>
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AST = aspartate aminotransferase. ALT = alanine aminotransferase. CSF = cerebrospinal fluid. ECG = electrocardiogram.
account for potential confounders such as frequent loss to follow-up, concomitant comorbidities, repeated exposure to vector bites, *T cruzi* discrete typing unit, and severity of the initial episode. Updated information on the long-term natural history of the disease, however, remains scarce. Results of recent studies have shown progression to cardiac involvement of around 1.4–5.0% per year.55–57

Cardiac involvement is the most frequent and severe type of organ involvement, occurs in 14–45% of chronically infected patients,68–70 and affects mainly the conduction system and myocardium. The most common initial signs are one or more of: left anterior fascicular block, right bundle branch block, and segmental left ventricular wall motion abnormalities. Late manifestations include sinus node dysfunction leading to severe bradyarrhythmia, high-degree atrioventricular blocks, non-sustained or sustained ventricular tachycardia, complex ventricular extra-systoles, progressive dilated cardiomyopathy with congestive heart failure, apical aneurysms (usually of the left ventricle), and emboli due to thrombus formation in the dilated left ventricle or aneurysm.58 Sudden death is the main cause of death in patients with Chagas heart disease, followed by refractory heart failure and thromboembolism.59–61 Chronic cardiac involvement due to *Chagas* disease should be differentiated from, but may be associated with, other causes of dilated cardiomyopathy.62 Impaired left ventricular function, New York Heart Association (NYHA) class III or IV, cardiomegaly, and non-sustained ventricular tachycardia indicate a poor prognosis in patients with chronic *Chagas* disease.62

Gastrointestinal involvement is less common (10–21%) and occurs more frequently in the Southern Cone of South America.63–65 Manifestations range from asymptomatic motility disorders to mild achalasia to severe megaeosophagus. Symptoms include dysphagia, odynophagia, oesophageal reflux, weight loss, aspiration, cough, and regurgitation. Patients with megaeosophagus may be at increased risk of oesophageal cancer, and upper gastrointestinal endoscopy might be indicated, especially in patients with new or progressive symptoms. Megacolon is characterised by persistent constipation and can lead to faecaloma, volvulus, and bowel ischaemia.64 The sigmoid and rectum are dilated in nearly all cases of megacolon, whereas dilatation of more proximal colonic segments is rare. An increased risk of colorectal cancer has been found in patients with megacolon. Small intestine and biliary involvement is very rare.65 Cardiac and gastrointestinal involvement seldom present together (5–20% of patients with myocardiopathy).

Chagas disease is also a major cause of cardioembolic stroke, which is up to twice as common in Chagas heart disease as in other forms of cardiomyopathy.66–68 The incidence of ischaemic stroke has been estimated as 2.7 events per 100 patients per year,69 and around a third of patients who experience ischaemic stroke may have asymptomatic *T cruzi* infection.52 Neuropathy, in the form of mild sensory polynaropathy, can present in up to 10% of patients although may not necessarily be associated with other visceral involvement.52

Pathogenesis

In the acute phase of the disease, organ damage is secondary to the direct action of the parasite and the acute inflammatory response. Nests of *T cruzi* amastigotes are found in tissues (mainly cardiac, skeletal, and smooth muscle) and elsewhere (CNS, gonads, and mononuclear phagocyte system).65–66 In this phase, highly efficient control of the parasite is the result of an intense inflammatory response with active antibody production and activation of the innate immune response (natural killer cells and macrophages) by Th1 proinflammatory cytokines such as tumour necrosis factor α and interferon γ.

The pathogenesis of chronic chagasic cardiomyopathy is not completely understood and, until recently, the consequences of the disease were considered to be autoimmune. Although several autoantigens that cross-react with *T cruzi* antigens andautoantibodies have been identified, the role of autoimmunity in pathogenesis is unknown.67 Recent evidence has shown that tissue damage is the principal role of *T cruzi* and the chronic inflammatory response that *T cruzi* elicits.68–70 There is a growing consensus that the balance between persistence of infection and host immune response is crucial for the establishment and progression of cardiomyopathy.69–71 During the chronic phase, inflammation is the main determinant of progression; the other potential contributory factors are virulence of the *T cruzi* strain and tissue tropism.69–71 An inflammatory environment predominates in the cardiac form, with the production of cytokines such as interferon γ and tumour necrosis factor α and other cytotoxic mechanisms involving CD8+ T cells, which lead to tissue damage and, ultimately, to severe cardiomyopathy; in the indeterminate clinical form, a regulatory immune response (characterised by production of interleukin 10 and interleukin 17) predominates.

Diagnosis

Parasitological diagnosis

Diagnosis of acute and congenital disease is made by direct microscopic visualisation of trypomastigotes in blood and, occasionally, other body fluids such as cerebrospinal fluid.89 In congenital infection, diagnosis can also be based on positive serology results beyond 8 months. Parasites can be observed through a simple fresh blood examination or in Giemsa-stained thin and thick blood smears (sensitivity 34–85%) (table 2). Concentration methods such as microhaematocrit and the Strout method raise the diagnostic yield to more than 95%.70 Indirect parasitological methods include PCR, which is more sensitive than blood culture and xenodiagnosis and has proven to be very useful in the
diagnosis of mother-to-child transmission, where it is more sensitive than concentration techniques.\textsuperscript{13,14,70}

Parasitaemia is low and intermittent in the chronic phase of the disease, thus making direct parasitological and PCR-based diagnostic methods unreliable. Diagnosis of chronic infection, therefore, relies on serological testing through detection of IgG antibodies against \textit{T cruzi} (figure 3).\textsuperscript{10,71} Serological techniques are based on whole parasite antigens and purified extracts (conventional tests) and on recombinant antigens and synthetic peptides (non-conventional tests). The most common tests are indirect fluorescent assay, indirect haemagglutination, and ELISA.\textsuperscript{72} Since no single standard reference test is available, diagnosis should be based on the presence of IgG against various \textit{T cruzi} antigens by use of at least two serological assays with different antigens.\textsuperscript{10} Serology results can be discordant and samples can yield persistent inconclusive results (3\% in a general clinical laboratory). A third assay is then indicated to clarify infection status. Techniques such as western blot can prove useful in these circumstances, especially in countries where \textit{Leishmania} spp are endemic.\textsuperscript{73} Given the high sensitivity and specificity of ELISA, a single test may be sufficient for screening, thus rendering serological confirmation necessary only in the event of a positive result.\textsuperscript{73} Rapid diagnostic tests (eg, immunochromatographic assays using recombinant proteins) are not sufficiently sensitive to be used as first-line serological diagnostic tools.\textsuperscript{74} Nevertheless, both these tests and the use of dried blood samples are a good option for patients who have difficulty accessing health-care facilities or whenever large-scale screening is needed.\textsuperscript{74–76}

For diagnosis of chronic \textit{T cruzi} infection, PCR has low and varying sensitivities that range from 50\% to 90\%.\textsuperscript{71} The factors contributing to that variability are blood volume, methodology, genes targeted, phase of infection, presence of immunosuppression, patient’s home country, and genetic diversity of \textit{T cruzi}.
\textsuperscript{71,77} However, PCR may be helpful when serology results are inconclusive, for monitoring early detection of treatment failure, and in the management of immunosuppressed patients.

**Diagnosis of visceral involvement**

Visceral complications must be assessed. Resting electrocardiography (ECG) should be performed during the initial examination even in asymptomatic patients. Cardiac ultrasonography should be used routinely, especially in patients with ECG disturbances, men over 30 years, and women over 45.\textsuperscript{78} Additional cardiac tests such as 24 h Holter monitoring, ergometry, and cardiac MRI should be considered in symptomatic patients. Several scales have been proposed to classify the severity of Chagas cardiomyopathy.\textsuperscript{46,81}

Barium swallow and enema are the most common diagnostic procedures used to assess gastrointestinal involvement in symptomatic patients. Since megacolon and megarectum can appear in almost 20\% of asymptomatic patients, colon enema may be considered at screening.\textsuperscript{80} Oesophageal manometry should be performed in patients who report related symptoms, even in the presence of a normal oesophagogram.\textsuperscript{81}

**Treatment**

Treatment with antitrypanosomal drugs is always recommended for acute and congenital Chagas disease, reactivated infections, and chronic disease in children younger than 18 years. Since persistence of parasitosis and concomitant chronic inflammation underlie chronic chagasic cardiomyopathy, parasiticidal treatment is generally offered to patients with chronic Chagas disease in the indeterminate phase and patients with...
mild-to-moderate disease (table 3). However, opinions differ about the impact of aetiologic treatment in this phase. Results of a systematic review and meta-analysis showed that treatment with benznidazole had little benefit, and that the observed effect could be marginal compared with placebo or no treatment in the chronic phase. In the BENEFIT trial, treatment with benznidazole did not significantly reduce cardiac clinical impairment in patients with moderate-to-severe cardiomyopathy.

On the other hand, treatment of women of childbearing age has proven effective in interrupting vertical transmission. Treatment should be individualised for patients older than 50 years and for patients with comorbidities.

Only two drugs, benznidazole and nifurtimox, are licensed for the treatment of Chagas disease. Both have been the mainstay of parasitidal treatment for almost 50 years, although their safety and efficacy profile is far from ideal. Furthermore, since the effectiveness of treatment seems to decrease with time from primary infection, early detection and intervention are crucial. Nifurtimox was the first drug used and is administered orally in three to four doses for 60–90 days (table 3).

Cure rates in the chronic indeterminate phase range from 86% in children younger than 14 years to 7–8% in adults. The frequency of adverse effects with nifurtimox is 43–97.5%; the most common are anorexia, nausea, vomiting, weight loss, neurological disorders (irritability, insomnia, disorientation, mood changes, paresthesias, and peripheral neuropathy), digestive manifestations such as nausea and vomiting, and, occasionally, fever and rash. Treatment is discontinued in 14–75.0% of cases.

Benznidazole is generally preferred over nifurtimox because of its better tolerability profile, tissue penetration, and, possibly, efficacy. It is administered orally in two or three doses usually for 60 days (table 3). Higher doses of up to 15 mg/kg are recommended in cases of meningencephalitis. According to some reports, 30 days of treatment can be useful for chronically infected adults. Benznidazole has considerable activity during the acute and early phases of T cruzi infection: serological cure is achieved in up to 100% of patients with congenital disease treated during the first year of life and in 76% of patients with acute disease. In the chronic phase, cure rates are much lower: 60–93% in children aged up to 13 years and 2–40% in adults with late chronic disease, although these values improve with longer follow-up. The most common adverse effects involve hypersensitivity, mainly in the form of skin rash (29–50%), digestive intolerance (5–15%), and general symptoms such as anorexia, asthenia, headache, and sleeping disorders (40%). Neuropathy and depression of bone marrow are considered rare. Treatment is discontinued in 9–29% of cases, even though these reactions are reversible and severe in less than 1% of cases.

Neither elevated serum drug levels nor high daily doses (>300 mg) have been associated with an increased frequency of adverse events.

The symptoms of mild toxic drug reactions can be treated with antihistamines, corticosteroids, or both, although antitypanosomal treatment should be
interrupted when toxicity is severe. Nifurtimox seems to be safe as a secondary treatment after interruption of benznidazole because of adverse effects. The addition of corticosteroids to prevent adverse effects does not appear to benefit patients taking nifurtimox, and discouraging results have been found in patients taking benznidazole.

**Novel therapeutic approaches**

Since the introduction of benznidazole and nifurtimox, only allopurinol and the triazoles (ergosterol biosynthesis inhibitors) have been studied in clinical trials, observational studies, and case reports. Monotherapy with ravaconazole or posaconazole has not proven to be efficacious for the treatment of chronic *Trypanosoma cruzi* infection, and the combination of posaconazole and benznidazole did not provide any further efficacy or safety advantages over benznidazole monotherapy. Recent evidence suggests that current benznidazole regimens can be optimised by administration of intermittent dosing schedules, or combination therapies.

An important obstacle for drug development is the poor translation of in-vivo data to human disease. Available animal models have limited predictive value for the preclinical evaluation of novel therapies, thus partly explaining the clinical failures observed with novel triazoles. Animal models that can predict more confidently the efficacy of new drug candidates in clinical trials must be standardised.

**Medical follow-up**

The clinical course of Chagas cardiomyopathy is difficult to predict. Some patients with ECG or echocardiographic evidence of disease remain asymptomatic for life, whereas others show a progressive course with severe arrhythmias or heart failure. Some patients die suddenly without previous symptoms. Nevertheless, for patients with more advanced disease (NYHA class III or IV, left ventricular dysfunction, cardiomegaly, or ventricular arrhythmias), the risk of mortality is clearly increased and can reach 85% at 10 years. Treatment with benznidazole does not seem to reduce the clinical impairment of patients with moderate-to-severe cardiomyopathy, since there is no evidence that antiparasitic treatment affects the progression of gastrointestinal involvement.

The current criterion for cure is reversion to negative results in conventional serological tests. In adult patients in the chronic phase, this might take 10–20 years. Although research in this area is very active, there are no reliable early surrogate laboratory markers for cure or for progression to cardiomyopathy, especially in patients in the indeterminate phase. Some of the markers studied include immunological molecules, host antigens, cytokine production, lymphocytic phenotype, metabolic molecules, and specific serological techniques. Although there are candidates that, alone or in combination, could satisfy some criteria for use in clinical practice, none has been validated for routine clinical use. Some of the difficulties faced in the validation of those surrogate markers for cure are the lack of a consensus definition for early therapeutic response, the likelihood of reinfection in endemic areas, the different biological behaviour between acute and chronic infection, the potential role of parasite genotype, and the need for long follow-up to establish cure with current methods needed for validating new methods.

**Treatment of chagasic cardiomyopathy and digestive involvement**

The haemodynamic and neurohormonal responses in Chagas cardiomyopathy are similar to those of other cardiomyopathies. Medical therapy should be started with the same regimens as in heart failure of other causes. However, since patients with Chagas disease frequently have low blood pressure and a high incidence of bradyarrhythmias, they might be unable to tolerate target doses of angiotensin-converting enzyme inhibitors and beta-adrenergic blockers. Amiodarone may improve survival in patients who are at high risk of sudden arrhythmic death syndrome and can be recommended as the treatment of choice for patients with sustained ventricular tachycardia and for those with non-sustained ventricular tachycardia with myocardial dysfunction. Implantation of a pacemaker is the recommended treatment for severe bradyarrhythmias and advanced conduction abnormalities. The roles of cardiac resynchronisation therapy and implantation of a cardioverter-defibrillator are not well established in Chagas heart disease, although these approaches could improve NYHA functional class, left ventricular ejection fraction, and survival.

There is no specific management for mild digestive symptoms such as dysphagia or constipation. For severe cases (megasyndrome), endoscopic or surgical management is essential.
Prevention
Prevention of infection requires control of vectorial transmission and screening of blood and organs for donation. Travellers should avoid sleeping in hovels or mud dwellings potentially infested with triatomines, use insect repellent and bednets, and avoid potentially contaminated fruit or cane juices such as those from street vendors. In the laboratory, personnel should use protective equipment suitable for risk group 2 organisms.121 No vaccine is available for prevention of transmission of T cruzi. To avert the serious consequences of chronic infection, early diagnosis is crucial in both endemic and non-endemic areas where screening should be offered to all Latin American migrants (excluding those from the Caribbean region), especially in women of childbearing age, who might have been exposed to the vector or contaminated blood products. Screening should likewise be offered to children whose mothers were born in endemic areas and to all family members of an index case.122 Especially for highly prevalent populations, the screening of Chagas disease turns out to be cost-effective.123

Pregnant and lactating women
Pregnant women potentially exposed to the parasite should be screened for T cruzi infection. For a woman with a new diagnosis, the appropriate protocol for assessment of visceral involvement and treatment after delivery should be followed. The infection itself does not justify caesarean section.124 Although there is no definite evidence of teratogenicity,125 treatment with benznidazole or nifurtimox is not recommended during pregnancy because of the lack of data on fetal safety. Parasitcidal treatment has been associated with chromosomal aberrations in children126,127 and binding of reactive metabolites to fetal proteins in rats.128 In cases of acute infection or reactivation, the risk–benefit ratio should be evaluated as with other potentially teratogenic drugs. If benznidazole is taken inadvertently, termination of pregnancy is not indicated. Chronic infection should be treated after delivery to decrease the risk of mother-to-child transmission in future pregnancies.129

Discontinuing or interrupting breastfeeding in mothers with chronic Chagas disease is not recommended. Data on the transmission of T cruzi through lactation in human beings are scarce, and available reports are subject to substantial limitations.130 If the mother has fissured or bleeding nipples, temporary discontinuation of breastfeeding may be recommended, although thermal treatment of expressed milk (pasteurisation or microwaving) before feeding the infant can be a safe alternative.131 Similarly, in cases of acute infection or reactivations, breastfeeding may pose a risk for the infant. To avoid any possibility of transmission, human milk banks should exclude mothers with Chagas disease as donors. Treatment with benznidazole or nifurtimox during lactation is commonly discouraged, mainly because parasitcidal treatment is not immediately necessary to the mother with chronic infection. Recent information has shown that benznidazole seems to be safe in this situation,132 as may be nifurtimox.133

Immunosuppressed patients
Organ and bone marrow recipients never exposed to T cruzi can be infected through graft tissue, bone marrow, or blood products. Acute infection has a prolonged incubation period (mean ~112 days) and severe and sometimes atypical clinical manifestations such as long-lasting fever, panniculitis, and meningoencephalitis.134,135 Diagnosis relies on the detection of circulating trypanomastigotes using parasitological or molecular tests (table 2). Treatment with benznidazole should be initiated as soon as possible to improve prognosis.136,137 Although screening for T cruzi is now part of transplant programmes, the shortage of suitable organs for donation has encouraged the use of organs from donors infected with the parasite. Though useful for some recipients, this practice is not risk free.138,139

Early diagnosis of chronic infection in immunosuppressed individuals is important and, ideally, should be confirmed before immunosuppressive treatment is administered. T cruzi can behave as an opportunistic parasite, where reactivation is the most life-threatening disorder.134,135 Reactivation can be confirmed with two approaches—namely, microscopy, which reveals trypanomastigotes in blood and other body fluids, and histology, which reveals inflammatory signs around tissue amastigotes. In general, positive findings in blood by PCR are not automatically indicative of reactivation, since they are also seen during the indeterminate chronic phase. The risk of reactivation varies according to the organ transplanted and the degree of immunosuppression: 20–50% in heart recipients,136 8–37% for kidney recipients137,138 19% for liver recipients,137 and around 27% for patients undergoing bone-marrow transplantation.139,140

In cancer, reactivations have been reported mainly in a few patients with haematological malignancies, whose cellular immunity is compromised, and usually result in fatal neurological complications.141 In patients co-infected with HIV and T cruzi, reactivation typically occurs in those who do not take antiretrovirals, with CD4 counts below 200 cells per μL or previous opportunistic infections.142 In patients with systemic autoimmune diseases, reactivation seems to be rare and has been associated with immunosuppressive drugs such as mycophenolate mofetil, azathioprine, and high-dose cyclosporin.143

Future challenges and opportunities
Prevention of new infections and end organ disease is a major challenge, which can be addressed by making diagnosis and treatment readily available, especially in children, young adults, and women of childbearing age. Thus, the frequency of secondary transmission would
decrease, and the effectiveness of current drugs, which are far from ideal, would be maximised. Such measures must be undertaken within a global strategy that includes improving the socioeconomic conditions of the less fortunate populations in endemic countries, maintaining programmes for vectorial control, and increasing awareness of the disease in non-endemic countries. This strategy should go hand in hand with measures to facilitate access to the health system and drugs for most vulnerable populations, thereby empowering the primary health level and favouring social participation. 141

Prospective cohort studies based on standardised methods are needed to establish the epidemiology of Chagas disease, both in endemic and non-endemic areas, while accounting for other competing risk factors for cardiovascular disease. The data obtained will ensure more accurate prognosis and identify individuals most at risk and able to undergo more proactive measures. Multidisciplinary groups comprising professionals caring for patients with Chagas disease (such as infectious disease specialists, cardiologists, gastroenterologists, surgeons, psychologists, and social workers) are increasingly needed in an ageing population with increasing comorbidities. Measures to ensure long-term follow-up, which is very often interrupted, should be implemented. These challenges are especially pertinent for migrants who have to face many barriers to accessing diagnosis and treatment (legal and bureaucratic challenges, illegal employment, lack of knowledge about the disease, and the health-care resources of the host country). Active searching for patients is often the only way to bring them into the health-care system. 142

Investigation of reliable prognostic factors for visceral involvement in asymptomatic patients is also a priority. The identification of low-risk patients would reduce unnecessary complementary tests and medical visits. Similarly, the lack of early surrogate markers of cure remains a major obstacle to clinical management (very long follow-up and many unnecessary tests) and increases concern during follow-up (uncertainty of cure). Furthermore, the lack of early markers of cure hinders the development of new treatments owing to the need for an unfeasibly long follow-up period to determine efficacy. Effective, better-tolerated, low-cost drugs are needed and can only be developed if data can be translated rapidly from the laboratory to clinical practice. To do that, we should improve the drug development process to identify new targets for drug action and the translation of data from the laboratory to clinical research. Better animal models are needed that reflect more accurately the conditions of chronic infection in human beings. More stable international collaborations, ideally public–private partnerships, should be established to face the great challenges for drug discovery and clinical research, and to ensure that Chagas disease is no longer regarded as a neglected tropical disease.

Contributors
JAP-M and IM performed the scientific literature search and reviewed the most relevant articles. JAP-M wrote the first draft of the manuscript and prepared the tables and figures. IM reviewed and edited the full report. Both authors have seen and approved the final text.

Declaration of interests
We declare no competing interests.

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Seminar


