Chagas Disease: Where to now?

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Highlights

This special issue includes expert reviews on the neglected cardiological syndrome – Chagas Disease (CD), also known as American trypanosomiasis. First described in 1909 this syndrome is endemic in several Latin American countries. This specially commissioned themed issue of the International Cardiovascular Forum Journal brings together notable experts who discuss a wide range of emerging topics in CD. These include the changing, and challenging, epidemiology of CD in migrants and visitors to the Europe and the USA. We also review what treatments exist for the primary infective aetiology, and how to manage Chagas cardiomyopathy when it has reached its end-stage heart failure form. We have expert reviews on advanced imaging techniques and their role in the assessment and care of Chagas’ patients and the opportunity to protect against sudden death in this enigmatic condition.

This special issue includes expert reviews on the neglected cardiological syndrome – Chagas Disease (CD). CD, otherwise known as American trypanosomiasis was described by Carlos Justiniano Ribeiro Chagas more than a century ago. It was an amazing achievement, and one that, had he survived longer, may well have earned him a Nobel Prize. He identified both the causative agent, Trypanosoma cruzi (T. cruzi), the transmission vector, the full clinical description of a highly complex disease, and he identified the potential reservoirs of the disease causing agent. This illness has been partially controlled by efforts in endemic countries, but with more widespread travel and migration in the 21st century, countries with little or no experience of this illness may become the targets of new outbreaks; a challenge to our ability to control infectious diseases in the modern era of global mobility. Much local knowledge and hard work needs to be supported and developed with the aim of complete eradication, whilst ensuring previously unaffected countries in the developed world are aware of the challenges in their incoming populations who derive from the endemic countries of central and south America.

The fact that CD can be transmitted through non-vector mechanisms, such as through blood transfusions, organ donations, accidental laboratory transmission or vertically from mother to child at birth releases new risks and needs also in Europe and the USA, which the timely review by Esther Cambronero-Cortinas describes in this themed issue. Dr. Cambronero-Cortinas describes how the prevalence of CD has decreased from 20 million in 1981 to 8–10 million in 2005, people at risk falling from 100 million to 28 million, new cases from 700,000/year in 1990 to 41,200/year in 2006, and mortality from 50,000 deaths per year to the current 12,500. These reductions can be ascribed to improved vector control campaigns and blood donation screening, hygiene and public health awareness.

There are marked differences, however, in prevalence between endemic countries, with the highest prevalence in the poorest areas of Bolivia, Paraguay, Argentina and Mexico. Europe, with its significant migrant populations, especially from Latin America, may have around 4 million people, especially in southern European countries such as Spain and Italy, at risk. The prevalence of CD among Bolivians in Europe for example is estimated to be between 6.8 to 25%. Of course the route of subsequent transmission is different in these immigrants. With congenital transmission rates estimated to be around 4.7% (range 3.9–5.6), significantly higher for mothers with detectable parasitaemia. It is, for example, estimated that each year between 63 to 115 newborns would be infected each year from these numbers. Obstetrician-gynecologists in non-endemic countries may need up-skilling in CD which has not been a significant part of their European curricula to date. T. cruzi screening may need to be introduced across at-risk European countries, especially as 94–96% of infected individuals in non-endemic areas probably remain undiagnosed. CD has become a worldwide public health concern and will remain so for the foreseeable future.

Dr. Rodríguez-Zanella and colleagues discuss the role of advanced imaging in CD from diagnosis to risk stratification. Imaging is critical for adequate diagnosis, staging and prognosis. Currently Echocardiography and Cardiac Magnetic Resonance are the mainstay, with emerging roles for more advanced techniques such as Speckle Tracking Echocardiography. Cynthia V. Rivero and Patricia S. Romano discuss objectively the role
for drugs that target the aetiologic infective agent.\textsuperscript{5} The authors describe the vector parasite aspects of CD and how each year 56,000 new cases of infection and 12,000 deaths linked to CD are seen in endemic areas.\textsuperscript{7} They describe the two phases of CD, the initial, acute phase with a high number of parasites circulating in the blood and mild nonspecific symptoms (fever, headache, enlarged lymph glands, pallor, muscle pain, swelling and others) and the chronic phase which develops in approximately one third of patients two or three decades after the acute infection. This phase is asymptomatic in around 70% of the patients. During the chronic phase, the parasites are hidden mainly in the heart and digestive muscles, with up to 30% of patients suffering cardiac disorders and 10% digestive (typically enlargement of the esophagus or colon) or neurological complications. They describe how the acute disease can be cured with trypanocidal treatments.\textsuperscript{6} Aetiologic treatment in the chronic phase, in contrast, remains controversial, whereas they argue specific antiparasite treatment is necessary for all chronic-phase Trypanosoma cruzi-infected individuals.\textsuperscript{9} There is an important body of evidence, they stress, that strongly suggests the involvement of parasitic presence in the disease progression toward cardiomyopathy. Only two approved anti-parasite drug treatments are available, Benznidazole (BZN) and Nifurtimox (NTX), after more than four decades of effort. More effort they plead is needed in this area, as they review all the major trials in this area, old and new. They conclude anti-parasitic treatment during the chronic phase of T. cruzi infection remains highly recommended, with Benznidazole (BZN) therapy in the early stages of chronic Chagas infection reducing the progression to cardiac complications, and cruzipain inhibitors showing potential for acute and chronic CD treatment. Lastly they feel the combination of BZN (at low doses) with other trypanocidal compounds may be a clever strategy whose results will be made clear in the next few years.

Dario Di Toro and Adrian Baranchuk review sudden death in CD.\textsuperscript{10} They describe how sudden death is a dramatic and not uncommon presentation of the disease and how some of these deaths could be preventable, with accurate identification of high-risk patients. ICD's because of cost, remain limited in the resource poor countries of the endemic region. The authors argue the true incidence of sudden death in CD remains unknown. According to unofficial statistics, around 50,000 deaths due to CD occur every year, 60% of which are sudden. As 16 to 18 million infected individuals live in Latin America, the annual rate of sudden death may be estimated in 0.17 to 0.19%.\textsuperscript{11} Sudden death in patients with CD occurs predominantly in males between 30 and 50 years of age, therefore having a disproportionate economic impact in poorer communities. Factors which may predict a higher risk in addition to male gender, include impaired functional capacity, syncope and certain ECG findings (RBBB, ST-segment elevation, AF, high heart rate, premature ventricular contractions, pathological Q waves, low QRS voltage, QT dispersion) as well as non-sustained Ventricular Tachycardia (NSVT) on ambulatory ECG monitoring. They describe how amiodarone remains widely used as an antiarrhythmic agent in patients with CD, with an increasing use of ICD implantation despite it being empirical, based on extrapolated recommendations for heart failure of other aetiologies. They also describe how cardiac resynchronization therapy (CRT) has become an established treatment for patients with moderate to severe heart failure due to CD in the presence of wide QRS complex, optimized heart failure treatment, and evidence of ventricular dyssynchrony.

Lastly, Reinaldo Bestetti, and Rosemary Daniel review the treatment of chronic heart failure secondary to CD.\textsuperscript{12} They describe how CHF affects about half patients with Chagas cardiomyopathy, with an annual mortality approaching 20%, higher than that observed in non-Chagas Disease heart failure. As no randomized trial has been conducted in patients with Chagas cardiomyopathy with CHF, treatment relies on evidence obtained in non-Chagas Disease heart failure. They review and recommend aldosterone receptor antagonists, angiotensin converting enzyme inhibitors and beta-blockers and in more advanced forms the additional need for diuretics, digoxin, and possibly angiotensin receptor blockers in patients intolerant to ACEI with heart transplantation being a valid option for patients with end-stage HF. They remind us there is specific evidence for the benefits of non-pharmacological including exercise training.

This is an excellent and fascinating issue that we strongly recommend to you the interested reader.

**Declarations of Interest**

The authors declare no conflicts of interest.

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The authors state that they abide by the requirements for ethical publishing in biomedical journals.\textsuperscript{13}

### REFERENCES

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