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HEART FAILURE (HJ EISEN, SECTION EDITOR)

Chagas Cardiomyopathy in Latin America Review

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Abstract

Purpose of Review Chagas cardiomyopathy is a major public health disease in Latin America and, due to migration, is becoming a worldwide health and economic burden. This review sought to present the clinical and epidemiological aspects of Chagas cardiomyopathy, as well as some specific features and principles of treatment. We also retrospectively assessed our institutional experience with mechanical circulatory support in refractory heart failure due to Chagas cardiomyopathy over a 10-year period.

Recent Findings The role of antiparasitic treatment in patients with heart failure due to Chagas cardiomyopathy is controversial. Heart transplantation, although formerly contraindicated, is currently established as an important therapeutic option. Also, the favorable characteristics of Chagas patients, such as younger age, little comorbidity, and no reoperations or severe pulmonary hypertension, could be an advantage for a mechanical circulatory support indication in advanced heart failure due to Chagas cardiomyopathy.

Summary Despite the absence of large evidence-based data, much has been accomplished since Carlos Chagas' discovery one century ago. Our institutional experience shows that mechanical circulatory support in Chagas patients is associated with more successful bridging to heart transplantation when compared to non-Chagas patients.

Keywords Chagas disease · Cardiomyopathy · Heart failure · Anatomopathology · Heart transplantation · Mechanical circulatory support

Introduction

Chagas disease is a chronic disease, first described in 1909 by the Brazilian physician Carlos Chagas, caused by the protozoan Trypanosoma cruzi (*T. cruzi*). [1, 2] The disease is prevalent in American tropical and subtropical regions. Chagas cardiomyopathy (CC) is one of the chronic manifestations of *T. cruzi* infection and is a major public health disease

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that is becoming a worldwide health and economic burden [3, 4]. In fact, the global budget of Chagas disease is similar to or exceeds those of other prominent diseases, such as rotavirus or cervical cancer, even in the USA where Chagas disease has not been traditionally endemic [5, 6].

T. cruzi is transmitted to humans mainly through the bite of an insect vector that belongs to the subfamily Triatominae, the "kissing bug." The main bug vectors adapted to living with humans are the Triatoma infestans (widespread in the Southern Cone countries of South America), the Rhodnius prolixus (in northern South America, specially Colombia and Venezuela), and the Triatoma dimidiate (countries of Central America) [7, 8]. Transmission may also occur through alimentation, blood transfusion, or congenitally, as well as through solid organ transplantation or laboratory accident [8–10].

The World Health Organization estimates that eight million people are infected with *T. cruzi* worldwide, mainly in Latin America [2, 11]. However, due to migration, *T. cruzi*–infected individuals have spread throughout the world, and it is estimated that 400,000 infected persons live in non-endemic countries, mainly in the USA and Europe [6, 12•, 13••].

Patients with Chagas disease remain infected for life. The incubation period lasts for 5–10 days and is followed by the acute phase of disease for 4–8 weeks [14]. The acute phase is asymptomatic or exhibits only mild symptoms and signs such as fever, anorexia, and a local swelling at the bite site of the Triatominae, called *chagoma*. The most recognized marker of acute Chagas disease is the *Romaña's* sign, a unilateral painless periorbital swelling after contamination with the bug feces [7]. In one study, the prevalence of chronic Chagas reached 18% of the street cleaners in Midwestern Brazil, but less than 1% recalled an acute infection stage [15].

The chronic phase can have four clinical forms: indeterminate, cardiac, gastrointestinal, and mixed (both cardiac and gastrointestinal involvement). It begins once parasitemia falls below detectable levels by microscopy [14]. Patients with the indeterminate form have serologic evidence of *T. cruzi* infection, but neither symptoms, nor physical signs. Patients with the indeterminate form of the disease have an excellent prognosis, and their survival rates are similar to healthy individuals [16]. Although most patients remain asymptomatic for the next 30 years, one third will develop cardiac and/or gastrointestinal involvement within 10–30 years [7, 8, 13••]. Megaesophagus and/or megacolon occur in about 15% of patients as a result of peristaltic dysfunction. Gastrointestinal involvement has been related to the geographical distribution of *T. cruzi* serotypes and appears to be more common in central regions of Brazil, less frequent in Bolivia, and practically non-existent in Central America, and Mexico [17].

Chagas Cardiomyopathy

CC is characterized by a chronic myocarditis that may affect all cardiac chambers, the conduction system, and the autonomic nervous system [16]. The pathogenesis of cardiac damage is not completely understood. The interaction of chronic infection, autoimmunity, denervation, and microvascular and endothelial dysfunction may have a role in the myocardial remodeling process, tissue scarring and, ultimately, chronic heart failure (HF) [13••]. Additionally, transmission forms, genetic polymorphisms, immunosuppression, and co-infection (e.g., human immunodeficiency virus or other viruses) have also been associated to the disease progression [4, 18, 19].

The chronic phase can be classified into stages of cardiac impairment according to international recommendations adapted to the CC **(**Fig. 1**)** [2, 20]. Stage A includes patients with the indeterminate form, without HF. Stage B includes patients with asymptomatic structural cardiopathy, and C patients with current or previous HF symptoms and ventricular dysfunction [NYHA functional class I, II, III, and IV]. Finally, stage D comprises patients with HF symptoms at rest, refractory to maximized clinical treatment (NYHA IV), requiring specialized and intensive interventions. Arrhythmia-related symptoms include palpitations, dizziness, lipothymia, and syncope. And since Chagas disease is associated with sympathetic and parasympathetic denervation, the occurrence of dysautonomia and vagal dysfunction can occur before the development of LV dysfunction and HF.

In 2006, a risk score was developed to predict death in CC [21]. Six independent prognostic factors were identified: New York Heart Association class III or IV, evidence of cardiomegaly on radiography, left ventricular systolic dysfunction on echocardiography, non-sustained ventricular tachycardia on 24-h Holter monitoring, low QRS voltage on electrocardiography, and male sex. The 10-year mortality rates for the high-risk groups were 84%.

Previous studies demonstrated that patients with CC have worse long-term outcomes than patients with other HF etiologies, including the ischemic [22–24]. The poor prognosis of CC might also be related to the progressive remodeling process, with significant more ventricular arrhythmias and thromboembolic disorders [20, 25, 26].

The most appropriate diagnostic strategy depends on the clinical stage of the infection. Because of the low parasitemia in the chronic phase of Chagas disease, parasitological tests are not used in the investigation of CC. The diagnosis of CC is based on positive *T. cruzi* serology, with at least two serological tests of different principles. The most frequently used are enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence (IIF), and indirect hemagglutination (IHA) [14, 27]. Molecular biology techniques, especially the polymerase chain reaction (PCR), have been proposed as useful tools for the diagnosis of *T. cruzi* infection [28].

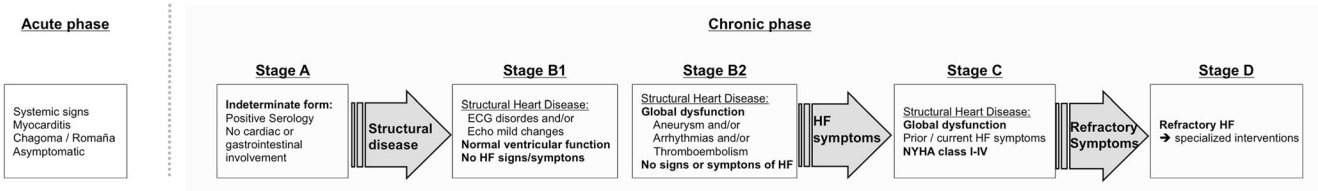

Fig. 1 Chagas cardiomyopathy and heart failure staging. Echo, echocardiography; HF, heart failure

Electrocardiographic abnormalities, such as atrioventricular or bundle-branch conduction delays, ventricular repolarization changes, and ectopies, are common. The most frequently found abnormality is the association of right bundle branch block with left anterior hemiblock [29–31]. Atrial fibrillation and polymorphic ventricular extrasystoles occur late and are common in the presence of ventricular dysfunction. Nonsustained ventricular tachycardia indicates a poor prognosis in patients with chronic CC [32]. The presence of pathological Q-waves does not correspond to segmental left ventricle (LV) wall motion abnormalities, but may reflect an advanced degree of heart disease [33].

Echocardiography allows assessing regional and global LV contractility, ventricular impairment, aneurysms, intracavitary thrombi, and diastolic function [2, 34]. The segments frequently involved are the apical and posterior walls, with hypokinesis and aneurysms being most common [35]. Chronic myocardial damage causes major alterations in diastolic function, and signs of increased LV filling pressures usually precede systolic dysfunction [36]. In fact, the combination of diastolic dysfunction and elevated brain natriuretic peptide (BNP) measurement adds important prognostic information to patients with Chagas disease [37]. Besides BNP, several other non-specific biomarkers have been reported in CC, such as N-terminal proBNP, troponin, creatine kinase–myocardial band, and matrix metalloproteinase 2 [38, 39].

Treatment should be directed according to the disease stage [40]. The major goal for the indeterminate stage is to stop the progression to the clinically determined form, in particular, preventing the manifestation of cardiac disease. Despite the absence of strong evidence-based data, the therapeutic approach for the symptomatic stage of CC should follow the standard recommendations for HF treatment, including neurohormonal modulation, anticoagulation, cardiac resynchronization therapy, and implantable cardioverter defibrillator [13••, 41–44]. Treatment with antitrypanosomal drugs is always recommended for acute and congenital Chagas disease, reactivated infections, and chronic disease in children younger than 18 years [45]. Currently available trypanocidal drugs, benznidazole and nifurtimox, carry a substantial risk of adverse effects, such as skin rash, digestive intolerance, anorexia, asthenia, headache, sleeping disorders, neuropathy, and myelosuppression and need careful monitoring. In acutely infected individuals, trypanocidal therapy should be performed as soon as possible, except during pregnancy or in patients with kidney or liver failure, which contraindicates the parasite-specific therapy. The role of antiparasitic treatment in the chronic phase of Chagas disease is controversial [46]. The BENEFIT is the largest randomized trial on Chagas disease, involving 2854 patients at 49 centers in five Latin American countries [47•, 48]. The BENEFIT showed that, although benznidazole treatment of patients with moderate-to-severe chronic CC was able to reduce serum parasite detection, it did not reduce cardiac clinical decline through 5 years of follow-up [47•]. Nevertheless, it is noteworthy that patients receiving benznidazole had significantly fewer hospital admissions for cardiovascular causes than those receiving placebo [48]. Furthermore, the recent phase II randomized clinical trials CHAGASAZOL, STOP-CHAGAS, and the E1224 [49–51] demonstrated that the antifungal azoles, ergosterol biosynthesis inhibitors, are inferior to benznidazole in eliminating the *T. cruzi*. More clinical trials with either new drugs or different regimens of current standards of care, such as benznidazole, are necessary [40]. Until further evidence is available, treatment of patients with chronic Chagas disease without cardiomyopathy remains disputed [52, 53].

Anatomopathological Aspects in Explant Specimens

Since autopsy studies of confirmed Chagas patients are rare and no large autopsy series have been published recently, the pathology data of chronic Chagas are derived from explanted specimens in small series from transplant services [54•]. Herein, we also share some of our institutional experience in assessing gross and microscopic hearts from Chagas patients.

Hearts are grossly enlarged, with typical biventricular and biatrial dilatation. In a series, presented at the 2013 ESC Heart Failure Congress, the mean heart weight in Chagas explants was 465 g compared to 608 g in idiopathic-dilated cardiomyopathy hearts ($p < 0.05$) [55]. Chagas hearts also showed a lesser amount of interstitial fibrosis and myocyte hypertrophy in semi-quantitative evaluation.

Although the apical ventricular aneurysm is commonly described as a characteristic feature of CC [42], this was not true in our experience as we have detected apical aneurysm in less than 10% of our specimens. This rate is similar to the one described by Kransdorf in one of 11 patients, [56] but lower than the 36% described subsequently in 2016 by the same group. [54•]. We found LV endocardial fibrosis (Fig. 2), a

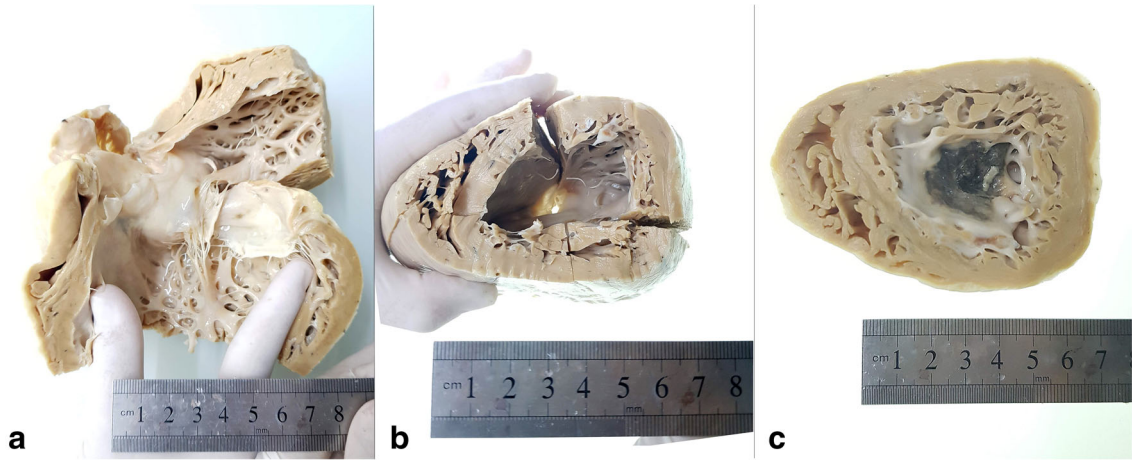

Fig. 2 Gross photographs of explanted Chagas cardiomyopathy hearts. **a** Left ventricular outflow tract in Chagasic explant. There is minimal endocardial fibrosis. The aortic valve seems unremarkable. **b** Cross-sectional biventricular short axis cut. There is left ventricular dilatation with mild to moderate endocardial fibrosis. The mitral valve has been transilluminated. **c** Apical section of the same explanted heart. There is moderate endocardial fibrosis and a dark thrombus at the tip

feature that may mimic tropical endomyocardial fibrosis, but epicardial coronary atherosclerosis was uncommon in our series. There was a fairly common rate of aortic root dilatation, as in any case of enlarged hearts, but without aortic valve leaflets disease. Mitral valve fibrosis with tissue redundancy was also common, which clinically correlates with a high incidence of mitral regurgitation [56].

Microscopically, the Chagas heart histology shows a variety of patterns. The most common is a combination of interstitial fibrosis, myocyte hypertrophy, and interstitial lymphoplasmacytic inflammation, without an area predilection, but more common in LV sections (Fig. 3). Scattered giant cells and poorly formed granulomas are seen in less than 5% of cases, with or without the identification of parasites within the tissue (amastigote forms). In one series, the authors described "myocarditis" in all explanted patients [54•]. In our experience, a second pattern with larger areas of fibrosis among scattered and less prominent lymphocytic infiltrates was also seen, which could be consistent with a "healed myocarditis" pattern. A third pattern, the least common, showed aggregated of inflammatory infiltrates in a perivascular distribution, similar to the histology of hypersensitivity myocarditis. Since all patients were on multiple drugs during the transplantation process, it was impossible to distinguish this latter pattern from drug-induced myocarditis, a process that is also seen in cases of idiopathic-dilated cardiomyopathy.

Heart Transplantation

Since Chagas disease is a chronic systemic infection, heart transplantation (HT) was formerly contraindicated for CC because of the potential risk of recurrence. However, early Brazilian experience in the 1980s established the viability of HT in patients with CC [2, 57, 58]. In fact, survival probability for Chagas HT recipients is better than that

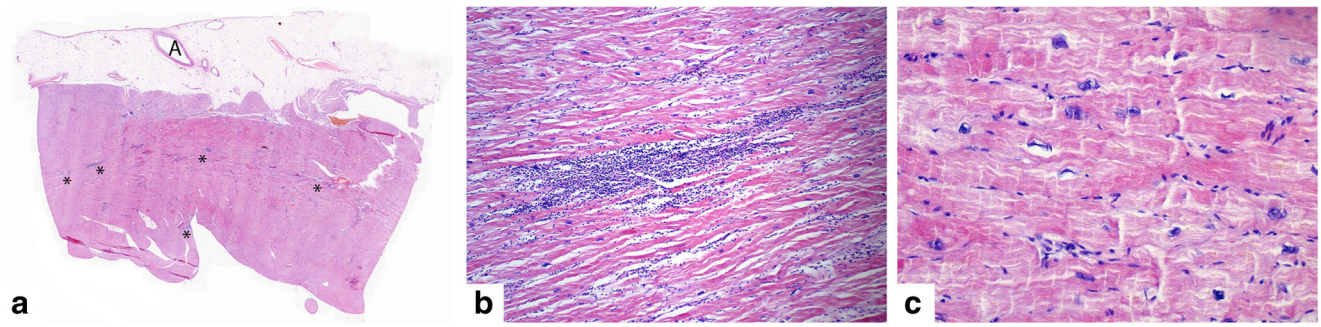

Fig. 3 Microscopic assessment of explanted Chagas cardiomyopathy hearts. **a** Panoramic histologic section of the left ventricular lateral wall. There is normal epicardial fat and an arteriole (A) with minimal intimal thickening. The myocardium has multiple foci of interstitial inflammation (*asterisk* indicates focal myocarditis). There is minimal interstitial fibrosis. **b** Higher power of the same case showing interstitial inflammation splaying myocardial fibers. The infiltrates are mostly lymphocytes with scattered plasma cells and macrophages. **c** There is several fold variation in length and diameter of myocyte nuclei and focal lipofuscin deposition (*brown pigment*). These findings are nonspecific

seen in other etiologies [59, 60], since the patients are younger, with few comorbidities and no reoperations or severe pulmonary hypertension [61].

Severe megaesophagus is a relative contra-indication to HT, because it could be associated with post-transplant malnourishment [62]. Most transplant centers in South America screen for Chagas megaesophagus with radiographic barium swallow and refer stable patients on the transplant list for elective surgical correction, if possible [2, 63].

Posttransplant *T. cruzi* reactivation is frequent; nevertheless, if treated appropriately, it rarely results in death or CC relapse [12•, 58]. The current evidence indicates that the probability of reactivation could be up to 90% at 2 years following HT [64]. Symptoms may be the same as in the acute phase of Chagas disease or even simulate acute allograft rejection. Aggressive immunosuppression plays an important role in *T. cruzi* reactivation, as it is associated with AIDS, chemotherapy, malignancy, and, particularly, with the immunosuppressive protocol [64–66]. There is an increased risk of reactivation after allograft rejection episodes, when immunosuppression intensification is required. Initial experience with HT for CC showed that reactivation episodes were reduced from to 2.3 to 0.25 per patient after cyclosporine trough levels were adjusted from 500–700 to 100–150 ng/mL [67]. Mycophenolate mofetil (MMF) has also been associated with higher incidence of *T. cruzi* reactivation when compared to azathioprine [66]. Some transplant centers in South America routinely substitute MMF for azathioprine in Chagas HT recipients, while others just choose to lower MMF doses.

A structured clinical and laboratory monitoring protocol is necessary to monitor for *T. cruzi* reactivation, so that specific treatment could be initiated before the development of clinically significant disease [68]. However, there is no scientific data defining exactly when that should be done. Some centers perform it along with the biopsies, while others recommend it weekly in the initial 2 months after HT, every 2 weeks up to the 6 months, and, finally, monthly until the first year [2, 69, 70].

Reactivation should be treated with benznidazole, at 5–10 mg/kg per day for 60 days. However, a strategy of universal anti-trypanosomal therapy for all recipients with CC should not be indicated, first, because not all patients will experience post-transplant reactivation and second, because of the drug toxicity and severe side effects such as peripheral neuropathy, anorexia, rash, insomnia, and bone marrow suppression [71].

In 2009, a systematic review of studies on Chagas HT population suggested that other post-transplant complications, such as infection, rejection, neoplasms, and cardiac allograft vasculopathy, have a similar incidence in recipients with or without Chagas disease [59].

Mechanical Circulatory Support

Survival of Chagas patients listed as UNOS Status 1 is lower than that observed for non-Chagas patients (NCP) in the same condition [72]. Although published data on mechanical circulatory support (MCS) in patients with CC is limited, it is important to contemplate a precocious indication as a bridge to transplantation (BTT) in these patients [73].

Due to the limited experience with MCS devices in Latin American countries, there are very few studies evaluating their feasibility and impact in CC. However, successfully BTT in CC with LV assist device and total artificial heart were previously described [56, 74, 75]. The

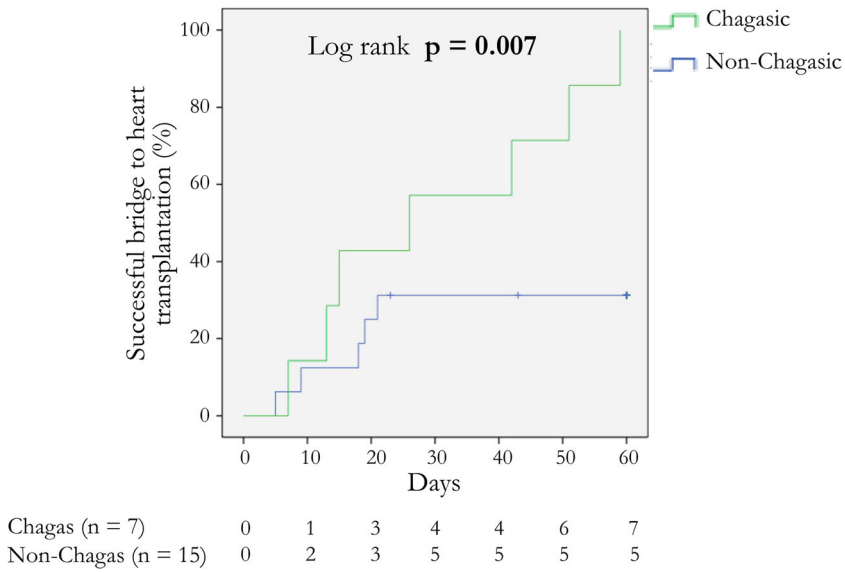

Fig. 4 Bridge to heart transplantation in Chagas cardiomyopathy: a single-center 10-year experience

favorable characteristics of Chagas patients could be an advantage for MCS indication in advanced HF. However, these patients should be monitored for right ventricular dysfunction, apical aneurysms, and mural thrombi [54•].

We retrospectively assessed our institutional experience with BTT in CC over a 10-year period (unpublished data). Information regarding the follow-up status was obtained from inpatient and outpatient clinical charts and telephone contact. From January 2008 to December 2017, we mechanically bridged to transplant 23 adults with refractory end-stage HF. Seven of these patients had CC. Bridged CC patients were all male ($p = 0.21$ vs. NCP), with a mean age of 44.6 ± 13.8 years ($p = 0.31$ vs. NCP). We used the Abiomed AB500™ ($n = 5$) and the CentriMag™ ($n = 2$; $p =$ NS vs. NCP for both MCS). Mean support time was 26 days (range 7–58; $p = 0.39$ vs. NCP). All CC patients were successfully bridged to HT in less than 60 days (log rank $p = 0.007$ vs. NCP, Fig. 4).

Conclusion

Chagas cardiomyopathy is a major public health disease that is becoming a worldwide health and economic burden. It is associated with worse outcomes when compared to other HF etiologies, including ischemic heart disease.

Despite the absence of evidence-based data, pharmacological treatment should be similar to other cardiomyopathies. Heart transplantation is an acceptable therapy for patients with end-stage Chagas cardiomyopathy, with short-term outcomes comparable to other etiologies. However, survival of Chagas patients listed under UNOS 1 Status is lower than that observed for non-Chagas patients in the same condition. Therefore, it is important to contemplate a precocious indication of mechanical circulatory support in these patients. The experience of our institution and others encourage the use of mechanical circulatory support for end-stage Chagas cardiomyopathy as a bridge to successful heart transplantation.

Compliance with Ethical Standards

Conflict of Interest Jefferson Luis Vieira, Fábio Rocha Fernandes Távora, Maria Gyslane Vasconcelos Sobral, Glauber Gean Vasconcelos, Germana Porto Linhares Almeida, Juliana Rolim Fernandes, Laura Leite da Escóssia Marinho, Daniel Francisco de Mendonça Trompieri, João David De Souza Neto, and Juan Alberto Cosquillo Mejia declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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