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Review

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Advances in the Understanding and Treatment of Chronic Chagas Cardiomyopathy

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Abstract

Chronic Chagas cardiomyopathy (CCC) poses significant health challenges not only in Latin America but also in non-endemic regions due to global migration. The complexity and severity of CCC call for an updated and thorough review to inform clinical practices and direct future research efforts. This review seeks to consolidate current knowledge on CCC, emphasizing diagnostic, therapeutic, and prognostic facets to facilitate better management and understanding of the disease. An exhaustive examination was conducted, analyzing peer-reviewed articles published between January 2020 and April 2024, sourced from prominent medical databases such as PubMed and Scopus. The review delineates crucial aspects of CCC pathophysiology, evaluates patient outcomes, identifies diagnostic challenges, and assesses treatment efficacy. Our findings prompt the need for revised clinical guidelines and stress the importance of continued research to enhance therapeutic strategies and disease comprehension. It is imperative that future studies address these identified gaps to advance patient care and treatment options for CCC.

Keywords: Chronic Chagas cardiomyopathy; Diagnostic challenges; Treatment efficacy; Patient outcomes; Pathophysiology

Introduction

Chagas disease, initiated by the protozoan parasite *Trypanosoma cruzi* (*T. cruzi*), has emerged as a leading cause of nonischemic cardiomyopathy in Latin America and now poses a significant global health challenge [1]. Chronic Chagas cardiomyopathy (CCC), the most severe cardiac manifestation of Chagas disease, progresses through distinct phases acute, indeterminate, and chronic - culminating in debilitating cardiomyopathy marked by extensive myocardial fibrosis and heart failure (HF) [2]. This introduction delineates the complex epidemiological and pathophysiological landscape of CCC, emphasizing the urgent need for comprehensive reviews that address diagnostic, management, and prognostic strategies to ameliorate this public health issue [3].

CCC is classified as a cardiomyopathy where *T. cruzi* infection leads to acute myopericarditis followed by chronic fibrosing myocarditis. The disease manifests in phases, starting with an acute phase that is frequently asymptomatic and lasting approximately 40 - 60 days [4]. This is followed by an indeterminate phase where the infected individual may remain symptom-free for years [5]. Approximately 20-30% of individuals infected with *T. cruzi* develop CCC after a latency period of 10 - 30 years [3, 4]. The chronic phase is characterized by progressive myocarditis, ventricular dilation, and HF, with increased expression and activity of matrix metalloproteinases (MMP-2 and MMP-9) and their inhibitors (TIMPs) associated with extensive heart remodeling and poorer prognosis in CCC patients [1]. Heart transplantation becomes a valuable therapeutic option for end-stage patients [2]. The severity of myocarditis in CCC is correlated with the number of infiltrating leukocytes expressing hypoxia-inducible factor (HIF)-1α and CD73, which are linked to tissue parasite persistence and immune response modulation [2]. The conversion rate from the indeterminate phase to Chagas cardiomyopathy is approximately 1.1% per year, with early predictors of disease progression including elevated B-type natriuretic peptide (BNP) levels and echocardiographic changes [4]. Genetic polymorphisms, such as the TT genotype at -819C>T, are associated with an increased risk of developing CCC, suggesting a genetic predisposition to disease progression [3]. Regulatory T cells (Tregs) and their interactions with co-stimulatory molecules (CD80 and CD86) play a role in modulating the immune response, with distinct patterns observed in asymptomatic and symptomatic patients [5, 6]. Understanding these stages and the underlying mechanisms can aid in early detection, improve patient management, and develop targeted interventions.

Detailed analyses reveal that prevalence rates vary significantly, influenced by factors such as disease phase, comorbidities, and genetic predispositions [7]. For instance, the cumulative progression rate to CCC in a Brazilian cohort was observed to be 6.9%, with a notable incidence rate of 1.48 cases per 100 patient-years [8]. Such variability is also pronounced in different regions, such as among Bolivians in Barcelona compared to those in rural Southern Bolivia, highlighting the impact of environmental and social factors on disease spread and progression [9].

The clinical significance of CCC cannot be overstated,

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given its impact on morbidity and mortality. The progression from a potentially asymptomatic condition to severe cardiomyopathy underscores the importance of early detection and effective management to reduce the healthcare burden [10]. Socioeconomic factors also play a critical role in disease management and outcomes, with disparities in access to care and treatment efficacy often observed across different regions and populations [11].

This review is justified by the variability in clinical outcomes and regional disparities in treatment, which suggest gaps in current research and practice. These gaps include a lack of standardized treatment protocols and an incomplete understanding of the pathophysiological mechanisms contributing to the variability in disease progression and outcomes [12].

The objectives of this review are to provide a comprehensive overview of the diagnosis, management, and outcomes of CCC, identify current gaps in research and healthcare delivery, and propose future directions for research and clinical practice. By focusing on these areas, this review aims to contribute significantly to the understanding of CCC, offering insights that could lead to more effective and tailored therapeutic interventions, thereby improving patient outcomes on a global scale.

Epidemiology

The prevalence and progression of CCC display significant geographic and demographic variability, reflecting the complexity of its epidemiological and pathophysiological landscape [13].

Detailed analyses reveal that the prevalence rates of CCC vary considerably across different regions, influenced by factors such as the phase of Chagas disease, comorbidities, and genetic predispositions. Notably, the annual rate of developing cardiomyopathy is estimated at 4.6% among patients with acute Chagas infection and 1.9% among those with the indeterminate chronic form of the disease [14]. Furthermore, the cumulative progression rate to CCC in a Brazilian urban cohort with an indeterminate form of Chagas disease was observed to be 6.9%, with an incidence rate of 1.48 cases per 100 patient-years [8].

Geographic variation in prevalence is also marked; for instance, in Barcelona, among the Bolivian population, the prevalence of *T. cruzi* infection stands at 18.3%, with a coinfection rate of 6% for *T. cruzi* and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [15]. In contrast, rural populations in Southern Bolivia exhibited a higher seroprevalence of Chagas disease (92%) compared to their urban counterparts (40%). These disparities are particularly pronounced in specific demographic groups; for example, the highest proportion of Chagasic cardiac anomalies occurs in the 50 - 59 age group [16-18].

The epidemiology of CCC is characterized by significant variability across different regions and populations, with genetic and environmental factors playing crucial roles in its development. Understanding these dynamics is essential for the development of targeted diagnostic and therapeutic strategies for this debilitating disease.

Pathophysiology

In Chagas cardiomyopathy, the acute phase, typically asymptomatic and lasting around 40 - 60 days, presents significant challenges for early detection and management [4]. Following this phase, individuals enter an indeterminate period, during which they may remain symptom-free for years [5]. Ultimately, approximately 30% of those infected progress to CCC, characterized by severe cardiomyopathy leading to HF, arrhythmias, and sudden cardiac death (SCD) [6].

The transition from acute to chronic Chagas disease is influenced by a multitude of factors including genetic predispositions and immunologic responses. Spatial metabolomics studies have demonstrated that *T. cruzi* infection induces localized chemical changes in heart tissue, contributing to the pathogenesis of CCC [12]. This chronic phase is marked by a sustained inflammatory response, characterized by the production of proinflammatory cytokines and reactive oxygen species by infected macrophages, which promote oxidative stress, fibrosis, and cellular apoptosis in cardiac tissues [19].

In terms of transmission dynamics, CCC's development involves multiple vectors and mechanisms, which vary significantly by region. The role of genetic factors is increasingly recognized, with research highlighting rare pathogenic variants in mitochondrial and inflammation-associated genes that may predispose individuals to CCC. These genetic factors, alongside mitochondrial dysfunction and chronic inflammatory processes, contribute significantly to the disease's pathogenesis [17].

Studies also emphasize the importance of immune response dynamics in CCC, with the production of proinflammatory cytokines and reactive oxygen species playing a central role. Bioinformatics analyses have identified key biological pathways and hub genes associated with inflammation in CCC, significantly correlating with Th1 and Th2 cell differentiation, cytokine-cytokine receptor interaction, nuclear factor (NF)-κB signaling pathway, and T cell receptor signaling pathway [18].

Genetic factors play a critical role in the susceptibility to and progression of CCC. Studies have identified rare pathogenic variants in mitochondrial and inflammation-associated genes that predispose individuals to mitochondrial dysfunction and an exaggerated inflammatory response to interferon-γ [17]. Furthermore, polymorphisms in the *PIK3CG* gene, which influences the PI3Kγ signaling pathway, are associated with an increased risk of developing CCC. These genetic elements, combined with immunological factors such as the activation of the NF-κB-dependent pathway, underline the complex interplay between host genetics and immune responses in disease progression [20].

Cardiac remodeling in CCC involves profound structural and functional alterations within the heart. Increased expression and activity of MMPs (MMP-2 and MMP-9) and their tissue inhibitors (TIMPs) indicate a shift toward extensive car-

diac remodeling [21]. These changes are accompanied by metabolic disturbances, as evidenced by metabolomic profiling, which reveals energy deficits and altered substrate utilization contributing to the severity of CCC. Additionally, elevated diastolic calcium levels and intracellular inositol 1,4,5-trisphosphate concentrations in cardiomyocytes from CCC patients are associated with contractile dysfunction, further complicating the disease progression [22].

The pathophysiology of CCC encompasses a transition from an acute, often unnoticed infection to a debilitating chronic condition. This progression is driven by a combination of genetic predispositions, immunological responses, and metabolic and structural changes in the heart. Understanding these intricate mechanisms is crucial for improving the diagnosis, treatment, and management of Chagas disease, ultimately aiming to mitigate the global burden of CCC.

Clinical Manifestations

CCC, primarily caused by *T. cruzi* infection, exhibits a diverse spectrum of clinical manifestations that evolve from asymptomatic to severe, life-threatening cardiovascular complications. This progression underscores the complexity of CCC and necessitates a nuanced understanding for effective diagnosis and management [2].

In the initial stages, CCC may be subtle or entirely asymptomatic, which presents significant challenges for early diagnosis. As the disease progresses, patients often experience a range of symptoms including dyspnea on exertion, fatigue, palpitations, dizziness, and syncope. These symptoms are indicative of underlying cardiac abnormalities such as ventricular arrhythmias, conduction system defects, sinus node dysfunction, and segmental wall-motion abnormalities. Other notable manifestations include chest pain, which may present as atypical or resemble angina, and peripheral edema [7].

A hallmark of CCC is the development of cardiac structural changes including apical aneurysms and mural thrombi, which have a high embolic potential. These structural changes can precipitate severe outcomes such as stroke, SCD, and HF [23]. SCD, which accounts for 55-65% of deaths in CCC patients, may occur unexpectedly and is often triggered by severe arrhythmic events such as ventricular tachycardia or fibrillation, asystole, or complete atrioventricular block (frequently during physical exertion) [24].

The transition to overt HF typically begins with isolated left ventricular failure and may progress to biventricular HF (HF). Patients with advanced disease often exhibit clinical signs of right-sided HF, such as increased jugular venous pressure, peripheral edema, ascites, and hepatomegaly. Diagnostic findings may include both systolic and diastolic dysfunction, the latter of which may be present without overt left ventricular systolic impairment [25].

Cardiac arrhythmias in CCC span a wide spectrum, from asymptomatic disturbances to symptomatic palpitations, syncope, and sudden cardiac arrest. These arrhythmias encompass virtually all types of atrial and ventricular disturbances, including persistent sinus node dysfunction, atrial fibrillation, intermittent complete atrioventricular block, and complex ventricular arrhythmias. The presence of ventricular arrhythmias and atrioventricular or sinus node dysfunction often co-occur, adding to the complexity of clinical management. In managing these arrhythmias, amiodarone and sotalol are commonly used due to their efficacy in reducing arrhythmia recurrence and improving patient outcomes. Amiodarone is often preferred for its broad-spectrum antiarrhythmic properties, despite its slower onset of action. Sotalol, a class III antiarrhythmic, is also effective but may be used in combination with other agents for enhanced efficacy [26]. Combining class I and class III antiarrhythmic drugs, such as amiodarone with beta-blockers, is a common strategy to enhance antiarrhythmic efficacy and reduce the risk of arrhythmias. This approach is particularly useful in cases where monotherapy is insufficient. Amiodarone is typically administered in a loading dose followed by a maintenance dose to achieve therapeutic levels quickly and maintain efficacy. Sotalol dosage must be carefully adjusted based on renal function and patient response to minimize the risk of adverse effects. Both amiodarone and sotalol have been shown to reduce the frequency of ventricular arrhythmias and the morbidity associated with recurrent implantable cardioverter-defibrillator (ICD) shocks in CCC patients. The combination of antiarrhythmic drugs can lead to better control of arrhythmias and improved patient outcomes compared to monotherapy [26].

Thromboembolic events represent a major cause of morbidity in CCC, contributing significantly to the incidence of stroke and other severe outcomes. Strokes in CCC are often cardioembolic in origin, related to emboli from dilated cardiac chambers or atrial fibrillation. Less frequently, strokes may result from atherothrombosis or small vessel disease. Pulmonary embolisms typically originate from venous or right heart thrombi, adding another layer of risk for these patients [27].

The initial diagnostic approach for CCC typically involves chest radiography and electrocardiography (ECG). Cardiomegaly is a classic radiographic finding, although many patients may present with a normal chest radiograph. ECG abnormalities are common and varied, including intraventricular blocks, particularly right bundle branch block and left anterior fascicular block, diffuse ST-T changes, ventricular premature beats, and various degrees of atrioventricular block. Despite their prevalence, these findings are not exclusive to CCC, necessitating further diagnostic evaluation [28].

Advanced imaging techniques, such as cardiac magnetic resonance (CMR), play a critical role in the evaluation of CCC. CMR can detect myocardial fibrosis, which is strongly associated with ventricular arrhythmias and an increased risk of SCD. Moreover, novel imaging modalities can identify early diffuse myocardial fibrosis and inflammation, crucial predictors of disease severity and prognosis [24].

The clinical manifestations of CCC are multifaceted and dynamic, ranging from asymptomatic to critical conditions that include severe arrhythmias, HF, and thromboembolic events. Given that sudden death is a major problem in CCC, specific consideration is given to the use of antiarrhythmic drugs to manage these arrhythmias. Ventricular arrhythmias, which are a major cause of SCD, are primarily targeted by antiarrhythmic drugs. Beta-blockers, particularly at doses greater

than 50% of the target dose, have been shown to significantly reduce the risk of major ventricular arrhythmias and SCD in patients with arrhythmogenic conditions similar to CCC [5]. Amiodarone and sotalol are also used to manage ventricular arrhythmias, although their efficacy varies and is often based on extrapolation from other cardiomyopathies [4, 5]. Additionally, the Na^+/Ca^{2+} exchanger (NCX) has been identified as a key player in the electrical remodeling of cardiomyocytes in CCC, suggesting that targeting NCX could be a potential therapeutic strategy [6]. However, the narrow therapeutic window of antiarrhythmic drugs poses a challenge, necessitating careful monitoring and individualized dosing to minimize adverse effects [1, 2].

Given the high risk of SCD in CCC patients, ICDs play a crucial role in reducing mortality and preventing sudden death, particularly in those with life-threatening ventricular arrhythmias. ICD implantation, combined with amiodarone, significantly reduces all-cause mortality and sudden death compared to amiodarone alone. The survival benefit is especially significant in patients with a left ventricular ejection fraction (LVEF) of less than 40% [1]. ICDs are used for both primary and secondary prevention in CCC patients with sustained ventricular tachycardia or ventricular fibrillation [3]. However, identifying predictors of sudden death remains challenging. Fragmented surface ECG is a poor predictor of appropriate ICD therapies in these patients [2]. CCC patients exhibit a higher frequency of appropriate ICD therapy and shorter event-free survival compared to non-Chagas patients, indicating a more arrhythmogenic substrate in CCC [4]. Chagas disease doubles the risk of requiring appropriate ICD therapy or experiencing death [4].

The implantation of cardiac defibrillators, particularly ICDs, significantly improves prognosis and quality of life for patients with CCC. Clinical studies have shown that ICD implantation significantly reduces the risk of SCD and improves survival rates in patients with various cardiomyopathies, including CCC. Patients report improved quality of life post-implantation, with positive changes in physical and social limitations, symptom frequency, and overall well-being [1-3]. However, device-related complications, such as inappropriate shocks, can significantly deteriorate quality of life, highlighting the importance of managing these complications effectively [1, 7]. Most patients adjust well to ICD implantation, though a subset may experience poor psychological outcomes, including anxiety and depression, particularly those with comorbidities or lower education levels [5, 8]. Effective management of complications and personalized patient care are crucial to maximizing the benefits of ICD therapy.

Comparative studies indicate that catheter ablation may be more effective than antiarrhythmic drugs in reducing recurrent atrial arrhythmias and hospitalizations, though this is more relevant to atrial fibrillation rather than the ventricular arrhythmias typical in CCC [3]. A thorough understanding of these manifestations, coupled with comprehensive diagnostic strategies, is essential for the effective management and treatment of CCC. This nuanced approach ensures that clinicians can better predict disease progression and tailor interventions to mitigate the significant morbidity and mortality associated with this challenging cardiomyopathy.

Diagnostic Criteria and Challenges

The diagnosis of CCC requires meticulous integration of clinical assessments, serological testing, and advanced imaging technologies. This comprehensive approach is vital to accurately identify and manage CCC, given its complexity and the significant morbidity associated with delayed or missed diagnosis [29].

Approach to diagnosis

The diagnostic process for CCC begins with the identification of individuals at potential risk. This includes those who have resided in endemic areas of Latin America or are descendants of individuals from these regions. Due to the often-asymptomatic nature of chronic Chagas disease, proactive screening is essential. Serologic testing for immunoglobulin G (IgG) antibodies against *T. cruzi* is the cornerstone for confirming infection, irrespective of symptom presentation [30].

Following serological confirmation, a thorough cardiac assessment is mandatory. This assessment should comprise a detailed medical history review, physical examination, resting 12-lead ECG with a 30-s lead II rhythm strip, and chest radiography. While these initial tests are fundamental, their normal findings do not rule out CCC, thereby necessitating further detailed cardiac evaluation [31]. Differential diagnosis is essential as CCC can mimic other cardiomyopathies, notably arrhythmogenic cardiomyopathy (AC). CCC is primarily caused by infection with the protozoan parasite *T. cruzi*, presenting with HF, ventricular arrhythmias, and thromboembolic events. AC, a genetic disorder often inherited in an autosomal dominant pattern, primarily features fibrofatty replacement of the right ventricular myocardium and does not typically present with thromboembolic events. Imaging modalities such as strain echocardiography, nuclear medicine, computed tomography (CT), and CMR imaging are crucial in distinguishing CCC, which often shows myocardial fibrosis and inflammation, from AC, which is characterized by fibrofatty myocardial replacement (Table 1).

Standardized diagnostic criteria

The clinical diagnosis of CCC hinges on identifying specific cardiac abnormalities that are indicative of Chagas heart disease. Diagnostic criteria include ECG or ambulatory ECG abnormalities, such as sinus bradycardia, right bundle branch block with left anterior hemiblock, ventricular premature beats, and varying degrees of atrioventricular block. These findings must be evaluated alongside other potential cardiac conditions to ensure CCC is the primary diagnosis [32].

Cardiac imaging further enriches the diagnostic landscape. Echocardiography and CMR are pivotal, revealing abnormalities from regional wall motion issues to more pronounced features such as ventricular aneurysms or intracavity thrombi. These imaging modalities are essential for a definitive diagnosis and for monitoring disease progression [29].

Table 1. Comparison of Chronic Chagas Cardiomyopathy (CCC) and Arrhythmogenic Cardiomyopathy (AC)

Features	Chronic Chagas cardiomyopathy (CCC)	Arrhythmogenic cardiomyopathy (AC)
Risk factors	Rural Latin America	Family history (autosomal dominant)
Causes	*Trypanosoma cruzi* infection	Genetic mutations
Pathophysiology	Dysautonomia	Fibrofatty infiltration
Heart failure	Common	Common
Ventricular arrhythmias	Common	Common
Thromboembolism	Common	Rare
Ventricular aneurysms	Common (apical aneurysms)	Rare
Right ventricular involvement	Rare	Common (dilation)
Heart block	Common (complete)	Rare (first-degree)
Chest pain	Common (atypical)	Rare
Disease-specific finding	Common (megaesophagus, megacolon)	Rare
Diagnostic test	Transthoracic echocardiogram	Cardiac MRI
Treatment	Benznidazole, angiotensin-converting enzyme inhibitors, beta-adrenergic blockers, diuretics	Beta-adrenergic blockers, angiotensin-converting enzyme inhibitors, antiarrhythmic drugs, implantable cardioverter-defibrillators
Complications	Heart failure	Sudden cardiac death

MRI: magnetic resonance imaging.

Key diagnostic tests

Echocardiography remains a fundamental diagnostic tool by detailing structural and functional cardiac changes. Early-stage disease may show mild segmental wall motion abnormalities, which are significant predictors of future cardiac events and overall disease progression. Advanced stages are characterized by more severe global ventricular dilatation and systolic dysfunction, often accompanied by valvular disturbances [33].

Ambulatory ECG monitoring is indispensable for capturing transient cardiac events and arrhythmias that a standard ECG might miss. This test is crucial for assessing the arrhythmic risk and other related cardiac symptoms, providing a continuous overview of the cardiac rhythm that informs both diagnosis and management strategies [29].

Advanced diagnostic tools and innovations

When echocardiography does not provide conclusive results, CMR is the recommended next step. It offers a detailed assessment of ventricular size, function, and myocardial fibrosis, providing a clear picture of the extent of myocardial damage. In scenarios where CMR is inaccessible or contraindicated, radionuclide imaging serves as a viable alternative, enabling comprehensive evaluation of cardiac function and identification of fibrotic changes [29].

Differential diagnosis

Accurately distinguishing CCC from other cardiomyopathies and cardiac conditions is critical. This differentiation involves detailed comparative analysis against ischemic heart disease, hypertrophic cardiomyopathy, and dilated cardiomyopathy. Stress testing and coronary angiography are employed to exclude ischemic conditions, especially in patients presenting with chest pain or those with inconclusive stress imaging results. The differentiation process is guided by both clinical judgment and a range of diagnostic tools to ensure precise diagnosis and appropriate management [34].

In conclusion, the diagnosis of CCC encompasses a broad spectrum of diagnostic strategies, from initial risk assessment and serologic testing to advanced imaging and careful differentiation from other cardiac conditions. This comprehensive approach ensures accurate diagnosis, informs effective management strategies, and ultimately improves patient outcomes in CCC. This meticulous diagnostic journey underscores the complexities of CCC and highlights the necessity for robust clinical protocols and advanced diagnostic tools in managing this life-threatening condition.

Management and Treatment

The management of CCC requires a vigilant and structured approach to actively monitor disease progression. Patients diagnosed with CCC should undergo annual clinical evaluations, which include a detailed history and physical examination, complemented by an electrocardiogram to detect new or progressive cardiac abnormalities. These regular assessments help in the timely identification of complications such as HF or arrhythmias, which may necessitate adjustments in therapeutic strategies [35].

Echocardiographic monitoring is pivotal and should be

performed with a frequency tailored to disease severity. Patients exhibiting a normal LVEF and no regional wall motion abnormalities are advised to undergo echocardiography every 3 -5 years. Conversely, those displaying reduced ejection fractions or evident wall motion abnormalities should receive more frequent evaluations, typically on an annual or biennial basis, to closely monitor progression and guide treatment adjustments [25].

Pharmacological and antitrypanosomal therapy

Pharmacological management in CCC is twofold, focusing on symptomatic relief of HF symptoms and specific antitrypanosomal treatment to address the underlying infection. For early-stage HF (American Heart Association/American College of Cardiology (AHA/ACC) stages A and B) with a Rassi score indicating low mortality risk, antitrypanosomal therapy with either benznidazole or nifurtimox is recommended. Benznidazole is typically administered at a dose of 5 - 7 mg/kg/day in adults, divided into two doses for 60 days, while nifurtimox is given at a dose of 8 - 10 mg/kg/day in adults, divided into three doses for 60 - 90 days. These doses may vary based on patient factors such as age, weight, disease stage, and comorbidities. However, the use of these medications in the chronic phase of CCC is limited due to their high toxicity and limited efficacy. Combination therapies, such as benznidazole with aspirin or curcumin, have shown promise in reducing cardiac fibrosis and inflammation. Immunomodulatory and anti-inflammatory approaches, including low-dose aspirin, resolvins, and natural compounds like resveratrol and curcumin, can also play a crucial role in managing CCC. Advanced therapeutic strategies targeting specific pathways such as transforming growth factor (TGF)-β and miR-21, along with the development of vaccines linked to chemotherapy, offer potential benefits. The selection of specific agents and dosing schedules is critical and should be adjusted based on therapeutic response and potential side effects. The use of anti-parasitic medications should be carefully considered, with a preference for combination therapies and advanced management options in chronic cases [35].

The use of these drugs in later stages (AHA/ACC stages C and D) is generally avoided due to diminished benefits and heightened risks of drug toxicity. Additionally, the management of HF follows standard guidelines applicable to other etiologies, emphasizing neurohormonal blockade to improve survival and reduce morbidity [35].

Non-pharmacological interventions

Non-pharmacological strategies form a crucial component of CCC management. These include lifestyle modifications such as dietary adjustments and tailored physical activity programs, which help mitigate HF symptoms and improve quality of life. Surgical interventions and device therapies, such as the implantation of pacemakers or defibrillators, are reserved for patients with severe arrhythmic complications or those at high risk for SCD [36].

Advanced management options

For patients with refractory HF or those ineligible for or unresponsive to conventional therapies, advanced treatment options such as heart transplantation are considered. This approach necessitates comprehensive preoperative evaluation and meticulous postoperative care to prevent reactivation of *T. cruzi* infection, facilitated by immunosuppressive therapy. Anti-parasitic medications, particularly benznidazole and nifurtimox, are used post-transplant to manage parasitic infection and prevent cardiac deterioration. However, these drugs have significant side effects and high rates of treatment discontinuation. Research into alternative drugs and new treatment strategies, including combinations of anti-parasitic and immunomodulatory drugs, is ongoing to improve outcomes and reduce side effects. Prophylactic anti-parasitic therapy or the use of allopurinol alone is currently limited by evidence, necessitating further research to establish effective measures. Adjusted immunosuppressive regimens, including lower doses of corticosteroids, adjusted cyclosporine levels, and the use of azathioprine rather than mycophenolate mofetil, are recommended to reduce the risk of *T. cruzi* reactivation and rejection episodes [37].

Treatment challenges

The effective treatment of CCC is hindered by several challenges, including logistical issues such as access to care in endemic areas, economic barriers limiting the availability of medications and advanced therapies, and the inherent toxicity and limited efficacy of current antitrypanosomal drugs in chronic disease stages. Additionally, patients with CCC exhibit resistance to standard HF therapies due to unique pathogenic mechanisms and clinical characteristics. Studies have shown that CCC patients have altered intestinal permeability, leading to potential differences in drug absorption and response. Metabolomic profiling of CCC patients' failing myocardium revealed significant metabolic alterations, including dysregulation of energy pathways, increased oxidative stress, and chronic inflammation, contributing to disease progression and severity [3]. Furthermore, research on microRNAs in CCC patients demonstrated associations between specific circulating microRNAs and markers of myocardial function, suggesting a potential link between microRNA levels and disease severity [5]. Addressing these challenges is essential for improving outcomes and requires enhancements in healthcare infrastructure, patient education, and the development of new therapeutic agents with better efficacy and safety profiles [2].

In conclusion, the management of CCC involves a multifaceted approach that emphasizes regular monitoring, appropriate use of pharmacological therapies, supportive non-pharmacological interventions, and advanced treatment options for severe cases. Overcoming the challenges associated with the management of CCC requires ongoing efforts in medical research, healthcare policy, and patient-centered care strategies to enhance the quality of life and prognosis for affected individuals.

Prognosis

CCC represents a severe manifestation of Chagas disease, primarily characterized by its impact on the cardiovascular system and significant implications for patient morbidity and mortality. The prognosis of CCC is influenced by a multifaceted interplay of clinical, metabolic, and molecular factors, which necessitate a comprehensive understanding to enhance patient outcomes [12].

Predictive factors for mortality in CCC encompass both clinical presentations and underlying pathophysiological mechanisms. A prominent risk factor is HF, which notably influences mortality rates. Observational studies suggest that mortality in patients presenting with HF due to CCC is higher compared to other etiologies of HF. This heightened risk is underscored by the presence of left ventricular dilatation or systolic dysfunction, and nonsustained ventricular tachycardia (NSVT). Furthermore, the disease stage critically affects prognosis, with advanced cardiomyopathy stages showing significantly higher mortality rates. Meta-analysis indicates annual mortality rates of 4.8% to 22.4% escalating with disease severity from early to advanced stages [14]. Additionally, male sex and older age have been identified as demographic factors associated with poorer outcomes [38].

The Rassi score is instrumental in prognostic assessments, offering a quantifiable method to stratify mortality risk among patients. Developed and validated through longitudinal studies, this score incorporates multiple predictors including New York Heart Association (NYHA) class III or IV, cardiomegaly on chest radiograph, and segmental or global left ventricular systolic dysfunction, among others [34]. Patients with higher scores on this scale exhibit substantially increased risks of mortality, with 10-year mortality rates ranging from 9% to 85% based on score stratification [39].

Prognostic assessments also involve a range of diagnostic tools that provide critical insights into the disease's progression and patient prognosis. Echocardiography and CMR are pivotal in this regard. Echocardiography frequently identifies impaired left ventricular function, a significant predictor of poor outcomes. CMR further elaborates on this by detailing the extent of myocardial fibrosis, which is strongly correlated with increased mortality and morbidity rates [29].

Emerging research highlights the potential of metabolic and molecular alterations in influencing the disease course. Chronic inflammatory states, driven by metabolic dysfunctions such as altered amino acid levels and increased oxidative stress, play a crucial role in disease progression. These findings advocate for the integration of these biomarkers in routine clinical assessments to anticipate disease trajectory and tailor patient management strategies [40].

In conclusion, the prognosis of CCC is dictated by a complex array of factors that span clinical manifestations, disease staging, and underlying molecular alterations. Effective management hinges on the utilization of comprehensive risk assessments like the Rassi score and the judicious application of diagnostic imaging to guide therapeutic decisions. As research continues to evolve, integrating new biomarkers and molecular insights holds promise for refining prognostic evaluations and enhancing therapeutic outcomes in this patient population.

Gaps in the Literature

Research on CCC has identified significant insights into the disease's progression, demographic influences, and potential therapeutic interventions. Nonetheless, several critical gaps remain, particularly in understanding the long-term outcomes and the impacts of early interventions. These shortcomings not only hinder the refinement of therapeutic strategies but also limit the overall advancement in patient care and disease management within this field [34].

Research shortcomings are evident, particularly in the underrepresentation of specific demographic groups within longitudinal studies. Insights from recent research underscore that older age and male sex are associated with a higher risk of progressing to CCC. Additionally, the increasing prevalence of comorbidities such as arterial hypertension, diabetes mellitus, and pulmonary hypertension among Chagas patients highlights the need for a nuanced understanding of how these factors influence disease progression and patient outcomes [14]. However, current studies tend to overlook younger individuals and females, which could skew the understanding of CCC across the broader population. This gap suggests a pressing need for inclusive research designs that encompass a wider range of demographic variables to provide a more comprehensive understanding of the disease dynamics [7].

The methodological limitations in CCC research further complicate the ability to draw robust conclusions about the efficacy of treatments and the pathophysiology of the disease. While recent studies have started to explore the potential of immunomodulatory agents, cell therapies, and innovative pharmaceutical approaches, there remains a substantial gap in evidence concerning the long-term efficacy and safety of these treatments [10]. The limitations are particularly pronounced in the context of randomized controlled trials (RCTs), which are crucial for validating the effectiveness of new therapies [12]. Despite the potential shown by various emerging therapies, such as nano-immunotherapy and therapeutic silencing of miR-21, the current research landscape lacks a sufficient number of comprehensive RCTs that could substantiate their benefits and guide clinical practice [41].

Furthermore, the existing methodologies for detecting and monitoring CCC are not without flaws. Advanced diagnostic techniques such as speckle tracking echocardiography and CMR imaging offer promising avenues for early detection of myocardial damage and fibrosis. However, these technologies are not yet widely incorporated into routine clinical evaluations, leading to potential delays in diagnosis and suboptimal monitoring of disease progression. Additionally, the need for a multi-therapeutic strategy that encompasses both pharmacological and non-pharmacological interventions remains inadequately addressed in the current research framework [42].

In summary, the gaps in the literature concerning CCC are significant and multifaceted. The underrepresentation of broader demographic groups in research studies and the methodological limitations in both diagnostics and treatment evaluations pose considerable challenges. Addressing these gaps is crucial for advancing the understanding and management of CCC, which in turn could lead to more effective and tailored therapeutic inter-

ventions for affected individuals. The enhancement of methodological approaches and the expansion of demographic inclusivity in research are imperative for overcoming these challenges and improving patient outcomes in the realm of CCC.

Future Directions

Future research in CCC should prioritize multi-therapeutic strategies targeting both the parasite and inflammation-related alterations, utilizing immunomodulatory drugs [43]. Identifying novel biomarkers for disease progression and mortality can improve diagnostic and prognostic tools, aiding early detection and management [25]. Investigations should focus on cardiometabolic and inflammatory markers like interleukin (IL)-33, CD40, and regenerating islet-derived 1 alpha (REG1A) for better patient stratification and targeted therapies [44, 45]. Public health policies need to enhance CCC prevention and management, integrating surveillance systems and treatment protocols, especially for vulnerable populations like human immunodeficiency virus (HIV)-infected patients [46]. Policy changes should also consider heart transplantation for advanced cases and strategies against thromboembolic events [47]. New imaging parameters, such as strain echocardiography and CMR imaging, are recommended for predicting and managing SCD risks, facilitating early detection of myocardial fibrosis and inflammation [48]. Enhancing research into diagnostic biomarkers and targeted therapies, alongside strategic public health policy updates, is crucial for improving CCC prevention, management, and patient outcomes.

Conclusions

This review has delineated the complex epidemiology and pathophysiology of CCC, highlighting the disease's progression from an often-asymptomatic acute phase to a debilitating chronic state characterized by severe cardiomyopathy. Our comprehensive analysis underscores the critical role of early detection and the implementation of targeted diagnostic and therapeutic strategies to mitigate the impact on patient morbidity and mortality. The variability in disease expression and progression, influenced by genetic predispositions and regional disparities in treatment efficacy, points to significant gaps in current research and healthcare delivery. It is imperative that future studies focus on closing these gaps through rigorous research, particularly involving underrepresented demographics and innovative treatment modalities. Enhanced public health policies and ongoing research support are crucial to improve CCC management and patient outcomes globally. Therefore, we urge for continued advancement in the understanding of CCC's clinical, metabolic, and molecular dynamics to foster the development of more effective therapeutic interventions and healthcare strategies.

Learning points

The review has the following learning points: 1) addresses the escalating global burden of CCC due to migration patterns, emphasizing the urgency for enhanced intervention strategies; 2) provides novel insights into CCC's pathophysiological mechanisms, advancing understanding of disease progression through genetic, immunological, and metabolic perspectives; 3) evaluates advancements in diagnostic methodologies, facilitating early detection and precise disease monitoring with advanced imaging techniques; 4) assesses the efficacy of current treatment modalities, emphasizing the need for tailored therapeutic interventions to optimize patient outcomes; 5) identifies critical gaps in research and clinical practice, advocating for updated treatment guidelines and proposing future research directions to enhance CCC management globally.

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Conflict of Interest

The author declares no conflict of interest to ensure the impartiality of the review.

Author Contributions

Jordan Llerena-Velastegui, MD: conceptualization, supervision, project administration, writing - review and editing. Almendra Lopez-Usina, medical student: data curation, formal analysis, writing - review & editing. Camila Mantilla-Cisneros, medical student: conceptualization, writing - original draft, writing - review & editing, methodology.

Data Availability

All data generated or analyzed during this study are included in this published article, and further inquiries should be directed to the corresponding author.

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