Chagas Disease: An Overview of Current Understanding and Future Perspectives

09

Chanda Naseem[1*], Warda Irfan[1], Ammal Ali[1], Syeda Wajeeha Masud[1], Bilal Khan[2], Asad Ullah[2], Muhammad Rizwan[3], Syed Bilal Tahir[4, 5] and Muhammad Arslan Yousaf Rehan[2]

ABSTRACT

Chagas disease (CD), caused by the protozoan parasite Trypanosoma cruzi, is a life-threatening infection transmitted primarily by triatomine bugs. Originating in rural Latin America, CD has spread globally through various transmission routes, including organ transplantation, blood transfusion, contaminated food and drink, and hereditary transfer. Millions in vulnerable stages face poverty and inadequate medical care due to unawareness and resource constraints. The acute phase presents symptoms like fever, anorexia, fatigue, and tachycardia, progressing to the chronic phase with severe health issues, including congenital heart diseases and neurological damage. It remains a neglected tropical disease recognized by the World Health Organization. Diagnosis involves serological, molecular, and parasitological tests, with challenges such as underdiagnosis. Antiparasitic medications, including Benznidazole and Nifurtimox, offer limited effectiveness, and drug resistance is emerging. Ongoing research explores new drugs, immunotherapies, gene therapy, and combination therapies. Diagnostic advances include nucleic acid amplification tests and serological tests with recombinant antigens. Vector control is crucial, focusing on insecticide use, housing improvements, and community education. Blood screening, organ transplantation screening, and prenatal interventions contribute to prevention. The disease's global burden affects millions, with challenges in endemic and non-endemic regions. Future research must address disease mechanisms, enhance diagnostic methods, explore new treatment options, and develop effective prevention strategies. Genomics, drug discovery, immunotherapy, vector control, and health system strengthening offer opportunities. Eradication potential lies in comprehensive public health strategies, targeting vectors, blood screening, and prenatal care, underscoring the need for sustained efforts and research innovations in the fight against Chagas disease.

Key words: Chagas Disease, Trypanosoma cruzi, Vector-borne Infection, Antiparasitic Medications, Global Health Challenges

CITATION

Irfan W, Ali A, Masud AW, Khan B, Ullah A, Hussain A, Rizwan M, Tahir SB, Rehan MAY and Naseem C,2023. Chagas Disease: An Overview of Current Understanding and Future Perspectives. In: Abbas RZ, Hassan MF, Khan A and Mohsin M (eds), Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, Vol. 2: 113-125. https://doi.org/10.47278/book.zoon/2023.56

CHAPTER HISTORY Received: 25-June-2023 Revised: 27-July-2023 Accepted: 03-Aug-2023

[1]Department of Emerging Health Professional Technologies, Faculty of Allied Health Sciences, Superior University, Lahore

[2]Shaheed Benazir Bhutto University of Veterinary and Animal Sciences, Sakrand
[3]Faculty of Veterinary Science, University of Agriculture Faisalabad
[4]Veterinary Research Institute, Lahore
[5]Institute of Microbiology, University of Veterinary Animal Sciences, Lahore
[6]Department of Physiology, University of Veterinary and Animal Sciences, Lahore
***Corresponding author:** chanda.naseem@uvas.edu.pk; chanda.naseem@superior.edu.pk

1. INTRODUCTION

Chagas disease (CD) is an immedicable infection caused by an American vector-borne protozoan parasite, *Trypanosoma cruzi*. It is a life-threatening human disease when the infected parasite's feces enter a mammalian host's mucous membrane. It is mainly transmitted by the bite of an infected triatomine bug, commonly known as a kissing bug. Other transmission means are organ transplantation, blood transfusion, contaminated food and drink usage, and hereditary transfer (Bern et al. 2019). The original roots of CD belong to rural Latin America, and it emerged across the borders from infected immigrants from their countries of origin (Perez and Israel 2018). Millions of people who get infected with this infection at the most yielding stage are susceptible to poverty and cannot get proper medical treatment due to unawareness and lack of resources (Olivera et al. 2019). Symptoms like fever, anorexia, fatigue, body aches, tachycardia, *etc*., come under the umbrella of the acute phase. Most of the infected individuals remain asymptomatic as long as the chronic stage of the disease evolves. The chronic phase is characterized by dangerous health issues, including congenital heart diseases, heart failure, gastrointestinal disorders, and neurological damage (Lidani et al. 2019).

The World Health Organization (WHO) recognizes CD as a Neglected Tropical Disease (NTD) around the globe. A Brazilian physician, Carlos Chagas, discovered this disease while working in Brazil's Ministry of Public Health and Hygiene. He was also the first who apply intra-household vectors against malaria. As he succeeded in his work, he was honored with many awards from institutions in different countries. He also became a member of the National Academy of Medicine of Brazil. His unusual discovery was not accepted and understood by the researchers of that time. Chagas had already organized the essential characteristics of this new disease and published his discovery in a journal. Later, he consulted a patient who was the first CD case. Before 1909, CD was not mentioned in history, making his work a remarkable gain in medicine and parasitology. He narrated the principal features of a new tropical disease (Lidani et al. 2019). The CD gives rise to heart failure and even leads to death in some cases.

Identification and cure of the infection are challenging. Disease control demands the removal of the causative agents, the reduviid bugs. Control has proved successful in South American Countries but falls behind in Northern (Central) American countries (Mills 2020). Despite vector transmission, it also spreads through vertical transmission, especially in non-endemic areas with a high ratio of pregnant women infected with the parasite, most of whom were immigrants. These women can be considered latent transmitters of Congenital CD (CCD). CCD has gained attention due to its high childhood morbidity and mortality risk. Early diagnosis and mediation may improve the quality of life and low morbidity and mortality (Santana et al. 2020). Cure rates in children are considerable, and in adults, they are unsure. The test used for the reversal of CD is a negative serological test. The results are inversely proportional to the duration of the infection (Irish et al. 2022).

2. MODE OF TRANSMISSION

The CD is transmitted in many ways, such as through direct contact with kissing bugs (carriers of *T. cruzi*). Like in some areas of the world, they are freely present in their homes as family members. Feeding food

contaminated with the feces/urine of bugs is another transmission route. Wastes of the bugs carry most of the infectious form of the parasite (Eduardo et al. 2021). Vector transmission also occurs by touching the animals. These vectors enter through the mouth, open wound, or mucous membrane. The male parasite bites only at night, but the female parasite needs the host's blood to nourish eggs. Vertical transmission occurs when the baby is in direct contact with the mother's fluid. Other passages are through the transfusion of blood, the transplant of infectious organs, or unsterilized lab equipment (Han et al. 2020; Klotz and Schmidt 2020; Nguyen and Waseem 2021).

3. LIFE CYCLE OF PARASITE

The two forms of the *T. cruzi* parasite (amastigotes and epimastigotes) are divided by binary fission and are observed as clonal organisms. By the time they evolve, they undergo many changes. First, the vector enters a mammalian host through a vector bite wound and mucosal membrane. It is found in the bloodstream plasma and then binds to different cell receptors. After that, it moves into a parasitophorous vacuole (Escolano et al. 2022). After entry, it differentiates into a protist cell with unclear flagella or cilia (amastigotes) and escapes from the vacuole into the cytoplasm, where it multiplies, and here the transformation ends as it becomes flagellated. The trypomastigotes in the blood traveling through the heart, arteries, veins, and capillaries have both slender and broad forms. After completing this cycle, the parasite again undergoes the cell cycle and creates many copies until the cell becomes filled with them (Ngyen and Waseem 2021).

4. IMMUNE RESPONSE AND DISEASE PROGRESSION

CD directly targets the thymus gland, the site of maturation of T and B cells, leading to the depletion of T cells, which then damages a person's immunity. Thymus atrophy, weight loss of the thymus, is caused in the acute phase. Abnormal thymocyte is also observed in the thymus. The CD is a silent killer with three phases: acute, indeterminate, and chronic. The acute phase is symptomatic and leads to fever, diarrhea, swollen lymph nodes, headache, muscular pain, and many severe diseases like myocarditis, pericarditis, hepatosplenomegaly, lymphadenopathy, meningoencephalitis, etc. These parasites throughout the body affect many other parts of the body like glands, skeletal, nervous, lymphoid, etc. Most patients during the acute phase are asymptomatic, while the chronic symptomatic phase appears years later, with around 30% progressing toward detectable organ damage affecting mainly the cardiovascular and digestive systems. Chagas cardiomyopathy is the leading cause of nonischemic cardiomyopathy (NICM) in Latin America and affects around 30% of infected patients (Echavarria et al. 2021).

5. CLINICAL MANIFESTATIONS

The CD has an asymptomatic acute phase with higher parasitemia levels; it then enters an indeterminate chronic phase without clinical symptoms of visceral involvement (Maite et al. 2020).
Up to 30% of chronically infected people develop cardiac alterations, and up to 10% develop digestive, neurological, or mixed alterations, which may require specific treatment. In chronic patients, antiparasitic treatment can potentially prevent or curb disease progression. Recent studies have shown that treating infected women before pregnancy eliminates vertical transmission of *T. cruzi*, while treatment efficacy is also incredibly high in congenitally infected newborns, with a cure rate of 100%. In the chronic and symptomatic phase of the disease, the heart and digestive system suffer significant clinical impairment. In the digestive system, esophagopathy causes the most frequent clinical manifestations due to the destruction of the myenteric plexus of the esophagus. It triggers functional motility changes, such as hypo-

contractility, loss of peristalsis, achalasia of the lower esophageal sphincter, and megaesophagus. Esophageal motility disorder causes dysphagia, possible regurgitation of the swallowed material, heartburn, and weight loss. Dysphagia, which means swallowing difficulty, is the most frequent digestive symptom, occurring during ingesting solid and liquid foods – though most often intense with solid foods (Barja et al. 2021).

6. CLINICAL MANAGEMENT

In most cases, CD is asymptomatic and cannot be detected earlier. For this purpose, there must be a test for the early assessment of CD. When the disease remains undiagnosed, it remains untreated and thus destroys the lives of thousands of patients. Similarly, that kind of test should also be present to critically analyze the response to the pharmaceutical treatment of CCD. TPP tests (Target Product Profile) are used in different aspects: to diagnose the patients suffering in the acute phase or those who are in the chronic phase (Symptomatic or Asymptomatic) and to evaluate the feedback of antiparasitic treatment of the disease (Padilla et al. 2020). Introducing vaccines against CD will also prove beneficial in setting up a robust immune system during the infection. BNZ and NF are used in America to treat CD but show unfortunate side effects within a few weeks. So, there is a high need to research, revamp pharmaceutical compounds, generate alternative drugs, and develop innovative strategies to treat patients bearing cardiac and esophageal diseases (Ribeiro et al. 2020).

7. DIAGNOSIS

7.1. SEROLOGICAL TESTS

- Enzyme-linked immunosorbent Assay (ELISA) identifies specific antibodies against *Trypanosoma cruzi* antigens in the blood.
- Immunoblot or Western Blot identifies specific antibodies against multiple *T. cruzi* antigens (Jeffrey et al. 2019).

7.2. MOLECULAR TESTS

- Polymerase Chain Reaction (PCR) amplifies and detects *T. cruzi* DNA in blood clot samples, which is especially useful during the acute phase (Kell et al. 2021).
- Real-time PCR provides quantitative results and helps monitor treatment effectiveness (Schijman et al. 2022).

7.3. PARASITOLOGICAL TESTS

- Direct Microscopy: Examines blood smears or other fluids under a microscope for the presence of *T. cruzi* parasites, particularly during the acute phase.
- Xenodiagnosis: Involves allowing laboratory-reared triatomine bugs (vectors of CD) to feed on the patient and then examining the bugs for *T. cruzi* (Guillermo et al. 2019).

8. CHALLENGES FOR DIAGNOSIS

Limited awareness among healthcare providers, particularly outside endemic regions, can lead to underdiagnosis or misdiagnosis of CD (Amanda et al. 2020).

The disease can manifest in a range of clinical symptoms, which are generally absent or nonspecific, similar to a viral illness, specifically to CD (Amanda et al. 2018).

9. NEW DIAGNOSTIC APPROACHES

9.1. NUCLEIC ACID AMPLIFICATION TESTS (NAATS)

PCR and other NAATs have demonstrated improved sensitivity and specificity in detecting *Trypanosoma cruzi* DNA. These tests can identify the parasite during the acute and chronic phases of infection (Caryn et al. 2019; Dhésmon et al. 2021).

9.2. SEROLOGICAL TESTS WITH RECOMBINANT ANTIGENS

Newer serological tests use recombinant antigens specific to *Trypanosoma cruzi*, reducing cross-reactivity with other parasites (Carine et al. 2021). This enhances the accuracy of results and improves sensitivity and specificity compared to tests using whole parasite extracts (Gabriel et al. 2022; Pilar et al. 2023).

9.3. POINT-OF-CARE (POCS) RAPID DIAGNOSTIC TESTS

POCs for CD have been developed to enable quick and accessible diagnosis in resource-limited settings. Based on lateral flow immunoassay technology, these tests detect specific antibodies against *Trypanosoma cruzi* and provide rapid results within minutes without requiring specialized equipment (Daniel et al. 2019).

10. TREATMENT

Available therapies are the following:

10.1. ANTIPARASITIC MEDICATIONS

Standard treatment involves the use of drugs like Benznidazole and Nifurtimox. These medications attenuated or degenerated the parasite and reduced the infection's severity. They are most effective during the acute phase of the disease but can also be used in the early chronic stage (Julio et al. 2020).

10.2. SYMPTOMATIC TREATMENT

CD can cause different symptoms and complications. Managing these symptoms is essential to improving the patient's quality of life (Falk et al. 2022). Symptomatic treatment may involve medications to control cardiac symptoms, such as beta-blockers, angiotensin-converting enzyme inhibitors, and antiarrhythmics for heart rhythm abnormalities. Medications to manage digestive problems, like prokinetic agents and antacids, may also be prescribed (Jose et al. 2021).

10.3. SUPPORTIVE CARE

CD can affect multiple organs, including the heart, digestive, and nervous systems. Supportive care addresses specific symptoms and complications associated with organ involvement (García-Huertas et al.

2021). This may include interventions like pacemakers or implantable cardioverter-defibrillators (ICDs) for cardiac issues or medications to control gastrointestinal symptoms (Caldas et al. 2019).

10.4. REGULAR MEDICAL MONITORING

Patients with CD require regular medical monitoring to assess disease progression, evaluate organ function, and detect potential complications. This involves periodic blood tests, electrocardiograms (ECGs), echocardiograms, and other diagnostic procedures to assess cardiac and gastrointestinal involvement (Sulleiro et al. 2020).

10.5. VECTOR CONTROL

The CD is primarily transmitted through infected triatomine bugs. Implementing vector control measures, such as insecticide spraying, improving housing conditions, and using bed nets, is crucial for preventing new infections (Julio et al. 2019).

11. DRUG RESISTANCE

11.1. RESISTANCE TO BENZNIDAZOLE AND NIFURTIMOX

Benznidazole and Nifurtimox are the primary drugs used to treat CD. However, the parasite's resistance to these medications has been reported. The emergence of drug-resistant strains of *T. cruzi* is a concern and hampers successful treatment (Correia 2022; Juliana et al. 2022; Duschak et al. 2023).
The specific mechanisms underlying drug resistance in CD are not yet fully understood. It is believed that various factors, including genetic variations in the parasite and drug changes (Santi et al. 2022).
Drug resistance can have a significant impact on the effectiveness of treatment. Patients with drug-resistant strains may not respond well to standard therapy, leading to persistent infection and disease progression. This can result in prolonged or recurring symptoms and an increased risk of complications (Julio et al. 2019).
The emergence of drug resistance underscores the need for alternative treatment approaches. Currently, there are limited alternative drugs available to combat drug-resistant strains. Research focuses on developing new drugs or combination therapies to overcome drug resistance and improve treatment outcomes (Dumonteil et al. 2019).

12. EMERGING THERAPIES

12.1. DEVELOPMENT OF NEW ANTIPARASITIC DRUGS

Scientists are searching for novel antiparasitic drugs that effectively target and eliminate the *Trypanosoma cruzi* parasite. This involves exploring new drug compounds, repurposing existing drugs for CD, and investigating drug combinations to enhance efficacy and overcome drug resistance (de Araujo-Jorge et al. 2022).

12.2. IMMUNOTHERAPIES

Immunotherapies aim to enhance the immune response against the parasite. Researchers are developing vaccines to prevent infection or reduce disease severity. Various vaccine candidates, such

as DNA, protein-based, and vector, are being investigated to stimulate immune protection against *T. cruzi* (Subhadip et al. 2021).

12.3. HOST-DIRECTED THERAPIES

Host-directed therapies focus on modulating the host immune response to control the infection and minimize tissue damage caused by CD. These therapies seek to boost the immune system's ability to eliminate the parasite and prevent disease progression (Timothy et al. 2021).

12.4. COMBINATION THERAPIES

Combination therapies involving the use of multiple drugs with distinct mechanisms of action are being studied as a strategy to enhance treatment effectiveness and overcome drug resistance. By simultaneously targeting the parasite through numerous pathways, combination therapies can improve treatment efficacy and reduce the risk of treatment failure (Santo et al. 2020).

12.5. GENE THERAPY

Gene therapy involves modifying the genetic material of host cells to enhance their resistance to the parasite or improve the immune response against *T. cruzi*. Preclinical studies are underway to investigate the feasibility and effectiveness of gene therapy approaches in CD (Ana Lia et al. 2020).

12.6. DRUG DELIVERY SYSTEMS

Developing targeted drug delivery systems can enhance the effectiveness of antiparasitic drugs while minimizing side effects. Scientists are exploring using nanoparticles, liposomes, and other drug delivery systems to improve drug stability, increase drug accumulation in infected tissues, and optimize treatment outcomes (Nuria et al. 2022).

12.7. BIOMARKERS AND DIAGNOSTIC TOOLS

Identifying reliable biomarkers and developing improved diagnostic tools are essential for early detection, accurate diagnosis, and monitoring of CD (Carlier et al. 2019).

13. PREVENTION AND CONTROL

13.1. PUBLIC HEALTH STRATEGIES

- Vector control should be a key focus in public health strategies for CD. This involves identifying and eliminating breeding sites of triatomine bugs, improving housing conditions, and using insecticides to kill or repel the bugs.
- Screening blood and organ donors is crucial to prevent parasite transmission through transfusions and organ transplantation (Bern et al. 2019).
- Prevention of maternal and congenital transmission is essential. Pregnant women with CD should receive appropriate treatment, and newborns should be screened for early detection and intervention.
- Educating communities, healthcare providers, and the public about CD is essential. This includes raising awareness about transmission routes, prevention measures, and the importance of early diagnosis and treatment.

- Improving access to diagnostic tests and effective treatment is necessary for controlling CD (Calderón et al. 2020).

14. BLOOD SCREENING AND ORGAN TRANSPLANTATION

- Blood screening plays a critical role in preventing the transmission of CD through blood transfusions. Rigorous screening of blood donors is essential, typically involving tests to detect CD antibodies. If a donor tests positive, their blood should not be used for transfusion.
- Organ transplantation, particularly involving solid organs like the heart or liver, requires careful screening to prevent CD transmission. Donor screening includes serological tests to determine their CD status. Transplantation may be contraindicated if the donor tests are positive unless specific measures are taken, such as pre-transplantation or post-transplantation follow-up and treatment (Suárez et al. 2022).
- International guidelines provided by organizations like the World Health Organization (WHO) and the Pan American Health Organization (PAHO) offer recommendations for blood screening and organ transplantation concerning CD (Iglesias et al. 2023).

15. VECTOR CONTROL

- Effective vector control is essential in the fight against CD. It involves implementing measures to prevent the transmission of the parasite by triatomine bugs, also known as kissing bugs.
- Identifying and eliminating the breeding sites of triatomine bugs is a crucial step (Ribeiro-Jr et al. 2021). These bugs tend to inhabit poorly constructed houses, cracks in walls, animal burrows, and nests.
- The use of insecticides is a critical component of vector control. Proper application of insecticides can kill or repel triatomine bugs, preventing their bites and interrupting the transmission cycle. The choice of insecticides should be based on their effectiveness, safety, and suitability for the local context (Gürtler et al. 2021).
- Community involvement and awareness are vital for successful vector control. They are educating affected communities about and promoting the risks of triatomine bugs.
- Integrated approaches to vector management are recommended (Castro et al. 2020). This involves combining multiple strategies, such as insecticide spraying, housing improvements, and education.
- Continued triatomine bug biology, behavior, and insecticide resistance research is necessary to develop improved vector control strategies. Understanding the specific characteristics of local bug populations can inform targeted interventions.
- Collaboration among health authorities, policymakers, and communities is essential for successfully implementing vector control programs (Jennifer et al. 2019).

16. GLOBAL BURDEN AND FUTURE DIRECTION

Current Status Of Cd World Wild

16.1. ENDEMIC REGIONS

CD remains a significant public health concern in 21 Latin American countries, predominantly in Central and South America. These countries, including Argentina, Bolivia, Brazil, Colombia, Ecuador, Paraguay, Peru, and Venezuela, have a high disease prevalence and a large population at risk of infection.

16.2. GLOBAL DISTRIBUTION

Due to migration and travel, the CD has also been reported in non-endemic regions. Cases have been identified in North America, Europe, and certain parts of Asia. However, the prevalence of CD in these regions is generally lower compared to endemic areas (Amanda et al. 2020).

16.3. DISEASE BURDEN

It is estimated that CD affects 6 to 7 million people worldwide. However, the actual number of cases is believed to be much higher due to underdiagnosis and the often asymptomatic nature of the disease (Lidani et al. 2019).

17. CHALLENGES AND OPPORTUNITIES FOR FUTURE RESEARCH

17.1. DISEASE MECHANISMS

Future research should aim to deepen our understanding of the underlying mechanisms of CD, including parasite-host interactions, immune responses, and disease progression. This knowledge is crucial for developing targeted interventions (Jadel et al. 2022).

17.2. DIAGNOSTIC METHODS

There is a need to improve diagnostic tools for CD. Future research should focus on developing more accurate, affordable, and accessible diagnostic methods, including point-of-care tests and serological markers (Francisco et al. 2020).

17.3. TREATMENT OPTIONS

Current treatment options for CD have limitations. Future research should explore new therapeutic approaches, such as novel drugs or combination therapies, to improve treatment outcomes, reduce side effects, and address the chronic phase of the disease (Passos et al. 2020).

17.4. PREVENTION STRATEGIES

Developing effective prevention strategies is essential, especially in endemic areas. Future research should investigate innovative vector control methods, evaluate the impact of housing improvements, and explore interventions like vaccines or vector-targeted approaches to interrupt transmission (Jadel et al. 2022).

18. OPPORTUNITIES FOR FUTURE RESEARCH

18.1. GENOMICS AND PROTEOMICS

Advancements in genomics and proteomics offer opportunities to gain insights into the biology of the parasite, host immune responses, and disease progression. These technologies can aid in identifying drug targets, vaccine candidates, and diagnostic biomarkers (Jadelet al. 2022).

18.2. DRUG DISCOVERY AND REPURPOSING

Future research should explore new compounds and repurpose existing drugs for CD treatment. High-throughput screening and computational approaches can help identify potential candidates for further development.

18.3. IMMUNOTHERAPY AND VACCINES

Investigating immunotherapeutic approaches and developing an effective vaccine against CD are essential research opportunities. Enhancing the host immune response and preventing infection can significantly impact disease control (Kathryn et al. 2022).

18.4. VECTOR CONTROL STRATEGIES

Research should evaluate the effectiveness of existing vector control methods, explore novel insecticides and formulations, and understand the ecological factors influencing vector populations. Based on these findings, evidence-based vector control strategies can be developed (Johan et al. 2020).

18.5. HEALTH SYSTEM STRENGTHENING

Research should assess barriers and facilitators in the implementation of CD control measures. This includes evaluating cost-effectiveness, health-seeking behavior, and strategies for integrating CD into existing health programs (Batista et al. 2019).

19. POTENTIAL FOR ELIMINATION AND ERADICATION

Vector control is a primary approach, aiming to reduce the population of triatomine bugs through insecticide spraying, improved housing conditions, and community education. Blood screening programs help prevent transmission through transfusions and organ transplants (Koh, Carolina Cattoni, et al. 2023). Preventive measures, such as prenatal screening and treatment, aim to minimize vertical transmission from mother to child. Early diagnosis and treatment are crucial, and antiparasitic medications are available (Rita de Cássia Moreira de et al. 2022).

20. CONCLUSION

In conclusion, CD is a serious and potentially life-threatening infection caused by the *Trypanosoma cruzi* parasite. Infected triatomine bugs primarily transmit it, but can also be transmitted through other means, such as blood transfusions and congenital transmission. The disease has two phases, acute and chronic, with the latter leading to severe cardiac and digestive complications if left untreated. Diagnosis involves laboratory tests; treatment mainly relies on antiparasitic medications during the acute phase. Prevention and control efforts focus on insecticide spraying, improved housing conditions, bed nets, hygiene practices, and screening of blood and organ donors. While there are challenges in understanding and managing CD, future perspectives involve ongoing research to develop more effective treatments and prevention strategies to combat this global health issue.

REFERENCES

Juliana AS et al., 2022. The repositioned drugs disulfiram/diethyldithiocarbamate combined to benznidazole: Searching for Chagas disease selective therapy, preventing toxicity and drug resistance. Frontiers in Cellular and Infection Microbiology 12: 926699.

Alonso-Padilla J et al., 2020. Target product profile for a test for the early assessment of treatment efficacy in Chagas disease patients: An expert consensus. PLoS Neglected Tropical Diseases 14(4): e0008035.

Julio AP et al., 2019. Strategies to enhance access to diagnosis and treatment for Chagas disease patients in Latin America. Expert Review of Anti-infective Therapy 17(3): 145-157.

Carolina B et al., 2019. A four-step process for building sustainable access to diagnosis and treatment of Chagas disease. Revista Panamericana de Salud Publica 43.

Caryn (B) et al., 2019. Chagas disease in the United States: a public health approach. Clinical microbiology reviews 33(1): e00023-19.

Eduardo GB et al., 2021. Case-fatality from orally transmitted acute Chagas disease: a systematic review and meta-analysis. Clinical Infectious Diseases 72(6): 1084-1092.

Caldas et al., 2019. An evaluation of Benznidazole as a Chagas disease therapeutic. Expert opinion on pharmacotherapy 20(15): 1797-1807.

Johan MC et al., 2020. Deltamethrin resistance in Chagas disease vectors colonizing oil palm plantations: implications for vector control strategies in a public health-agriculture interface. Parasites & vectors 13(1): 1-10.

Yves C et al., 2019. Congenital Chagas disease: updated recommendations for prevention, diagnosis, treatment, and follow-up of newborns and siblings, girls, women of childbearing age, and pregnant women. PLoS neglected tropical diseases 13(10): e0007694.

Castro-Arroyave et al., 2020. Integrated vector control of Chagas disease in Guatemala: a case of social innovation in health. Infectious Diseases of Poverty 9(1): 1-9.

Subhadip C et al., 2021. Oxidative stress implications for therapeutic vaccine development against Chagas disease. Expert review of vaccines 20(11): 1395-1406.

Nuria CS et al., 2022. Extracellular vesicles in *Trypanosoma cruzi* infection: Immunomodulatory effects and future perspectives as potential control tools against chagas disease. Journal of Immunology Research 2022.

de Araujo-Jorge et al., 2022. Translational research in Chagas disease: perspectives in nutritional therapy emerging from selenium supplementation studies as a complementary treatment. Memórias do Instituto Oswaldo Cruz 117: e220001.

Dumonteil et al., 2019. A therapeutic preconceptional vaccine against Chagas disease: A novel indication that could reduce congenital transmission and accelerate vaccine development. PLoS Neglected Tropical Diseases 13(1): e0006985.

Duschak et al., 2023. Chagas disease novel drug targets and treatments. Frontiers in Cellular and Infection Microbiology 13: 572.

Echavarria NG et al., 2021. Chagas disease: chronic Chagas cardiomyopathy. Current problems in cardiology. 46(3):100507.

Falk N et al., 2022. Effectiveness of Nifurtimox in the treatment of Chagas disease: a long-term retrospective cohort study in children and adults. Antimicrobial agents and chemotherapy 66(5): e02021-21.

Amanda FF et al., 2020. Challenges in Chagas disease drug development. Molecules 25(12): 2799.

García-Huertas et al., 2021. Advances in the treatment of Chagas disease: Promising new drugs, plants and targets. Biomedicine & Pharmacotherapy 142: 112020.

Gürtler et al., 2021. Chagas disease vector control. In: Guarneri A, Lorenzo M, editors. Triatominae-The biology of chagas disease vectors: Cham, Springer International Publishing; pp: 491-535.

Han CY et al., 2020. A voluntary use of insecticide treated nets can stop the vector transmission of Chagas disease. PLoS Neglected Tropical Diseases 14(11): e0008833.

Laura IR et al., 2023. Diagnostic pathways of Chagas disease in Spain: a qualitative study. BMC Public Health 23(1): 1-12.

Irish A et al., 2022. Updated estimates and mapping for prevalence of Chagas disease among adults, United States. Emerging Infectious Diseases 28(7): 1313.

Kathryn MJ et al., 2022. Preclinical advances and the immunophysiology of a new therapeutic Chagas disease vaccine. Expert Review of Vaccines 21(9): 1185-1203.

Emily AK et al., 2021. Comparative performance of latest-generation and FDA-cleared serology tests for the diagnosis of Chagas disease. Journal of Clinical Microbiology 59(6): e00158-21.

Klotz SA and Schmidt JO, 2020. Autochthonous Chagas disease: how are these infections happening? The American Journal of Medicine 133(12): e683-6.

Carolina Cattoni K et al., 2023. Cytokine Networks as Targets for Preventing and Controlling Chagas Heart Disease. Pathogens 12(2): 171.

Jadel MK et al., 2022. The translational challenge in Chagas disease drug development. Memórias do Instituto Oswaldo Cruz 117.

Lidani KC et al., 2019. Chagas disease: from discovery to a worldwide health problem. Frontiers in public health 7: 166.

Dhésmon L et al., 2021. Electrochemical sensing of trypanosome-and flavivirus-related neglected tropical diseases. Current Opinion in Electrochemistry 30: 100838.

Daniel L et al., 2019. Use of rapid diagnostic tests (RDTs) for conclusive diagnosis of chronic Chagas disease–field implementation in the Bolivian Chaco region. PLOS Neglected Tropical Diseases 13(12): e0007877.

Passos M et al., 2020. Chagas disease: perspectives on the past and present and challenges in drug discovery. Molecules 25(22): 5483.

Martín-Escolano J et al., 2022. An updated view of the *Trypanosoma cruzi* life cycle: Intervention points for an effective treatment. ACS Infectious Diseases 8(6): 1107-15.

Ana Lia M et al., 2020. Benznidazole self-emulsifying delivery system: A novel alternative dosage form for Chagas disease treatment. European Journal of Pharmaceutical Sciences 145: 105234.

Mills RM, 2020. Chagas disease: epidemiology and barriers to treatment. The American journal of medicine 133(11): 1262-5.

Guillermo M et al., 2019. Longitudinal follow up of serological response in children treated for Chagas disease. PLoS neglected tropical diseases 13(8): e0007668.

Myemandi S et al., 2018. Treatment of Chagas disease in the United States. Current treatment options in infectious diseases 10: 373-388.

Nguyen T and Waseem M, 2021. Chagas disease. InStatPearls. StatPearls Publishing.

Oliveira JD et al., 2021. Symptoms associated with different degrees of megaesophagus in Chagas disease. Arquivos de Gastroenterologia 58: 491-4.

Olivera MJ et al., 2019. Prevalence of Chagas disease in Colombia: A systematic review and meta-analysis. PloS one 14(1): e0210156.

Rito Santo P et al., 2020. Combination therapy using Benznidazole and aspirin during the acute phase of experimental chagas disease prevents cardiovascular dysfunction and decreases typical cardiac lesions in the chronic phase. Antimicrobial Agents and Chemotherapy 64(7): e00069-20.

Pérez-Mazliah et al., 2021. Host-parasite dynamics in Chagas disease from systemic to hyper-local scales. Parasite immunology 43(2): e12786.

Pérez-Molina JA and Molina I, 2018. Chagas disease. The Lancet 391(10115): 82-94.

Jose APM et al., 2021. Trypanocidal treatment of Chagas disease. Enfermedades infecciosas y microbiologia clinica (English ed.) 39(9): 458-470.

Jennifer KP et al., 2019. Chagas disease in Central America: recent findings and current challenges in vector ecology and control. Current Tropical Medicine Reports 6: 76-91.

Ribeiro AL et al., 2012. Diagnosis and management of Chagas disease and cardiomyopathy. Nature Reviews Cardiology 9(10): 576-89.

Gilmar R et al., 2021. TriatoScore: an entomological-risk score for Chagas disease vector control-surveillance. Parasites & Vectors 14: 1-15.

Pilar RB et al., 2023. Acute Phase Proteins in Dogs with Natural Infection by *Trypanosoma cruzi*. Tropical Medicine and Infectious Disease 8(6): 299.

Romay-Barja M et al., 2021. Key Chagas disease missing knowledge among at-risk population in Spain affecting diagnosis and treatment. Infectious Diseases of Poverty 10(1): 55.

Santana KH et al., 2020. Epidemiology of Chagas disease in pregnant women and congenital transmission of *Trypanosoma cruzi* in the Americas: Systematic review and meta-analysis. Tropical Medicine & International Health 25(7): 752-63.

Santi et al., 2022. Antioxidant defence system as a rational target for Chagas disease and Leishmaniasis chemotherapy. Memórias do Instituto Oswaldo Cruz 117: e210401.

Alejandro Gabriel S et al., 2022. Parasitological, serological and molecular diagnosis of acute and chronic Chagas disease: from field to laboratory. Memórias do Instituto Oswaldo Cruz 117: e200444.

Timothy DS et al., 2021. Mesenchymal Stromal Cells: An Antimicrobial and Host-Directed Therapy for Complex Infectious Diseases. Clinical microbiology reviews 34(4): e00064-21.

Soeiro and Maria de Nazaré Correia, 2022. Perspectives for a new drug candidate for Chagas disease therapy. Memórias do Instituto Oswaldo Cruz 117

Rita de Cássia Moreira de S et al., 2022. Chagas disease in the context of the 2030 agenda: Global warming and vectors. Memórias do Instituto Oswaldo Cruz 117: e200479.

Cristina S et al., 2022. Diagnosis and clinical management of Chagas disease: An increasing challenge in non-endemic areas. Research and Reports in Tropical Medicine: 25-40.

Elena S et al., 2020. Usefulness of real-time PCR during follow-up of patients treated with Benznidazole for chronic Chagas disease: experience in two referral centers in Barcelona. PLoS neglected tropical diseases 14(2): e0008067.

Carine T et al., 2021. Geographic variations in test reactivity for the serological diagnosis of *Trypanosoma cruzi* infection. Journal of Clinical Microbiology 59(12): e01062-21.

Maite V et al., 2020. Trypanocidal drugs for late-stage, symptomatic Chagas disease (*Trypanosoma cruzi* infection). Cochrane Database of Systematic Reviews 12.

Jeffrey DW et al., 2019. Chagas disease erological test performance in US blood donor specimens. Journal of Clinical Microbiology 57(12): e01217-19.