BMJ Best Practice

Chagas disease

Straight to the point of care

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Summary

Chagas disease is a chronic and neglected infectious disease associated with poverty, migration, and poor housing conditions with a high burden of morbidity and mortality.

Leading cause of cardiac lesions in young, economically productive adults in endemic Latin American countries in terms of disability-adjusted life years lost. It is a frequent cause of sudden cardiac death, but often goes undiagnosed.

Patients with acute-phase disease are generally asymptomatic or present with mild symptoms, although these may be more severe in immunocompromised patients, or in disease due to oral transmission. Chronic-phase disease has cardiac, gastrointestinal, indeterminate, and mixed (cardiac and gastrointestinal) forms. Reactivation occurs in immunosuppressed patients and presents as myocarditis or severe meningoencephalitis.

Objectives of aetiological treatment include parasite elimination and reduction of disease progression. Careful management of the different clinical syndromes resulting from irreversible lesions is important, as well as comprehensive multidisciplinary care encompassing psychosocial support.

Definition

Chagas disease, also known as American trypanosomiasis, is an anthropozoonosis (a disease maintained by animals and transmitted from animals to humans) caused by the obligate intracellular flagellate protozoon *Trypanosoma cruzi* *(T. cruzi)* , which infects humans and other mammals.[1]

It is a heterogeneous condition with a wide variation in clinical presentation, and the majority of patients remain asymptomatic throughout their life. The American Heart Association has warned that it is a frequent cause of sudden cardiac death, but often goes undiagnosed.[2] [3]

Clinically, there are acute and chronic phases. If the acute phase remains untreated, *T. cruzi* infection is lifelong. The chronic phase can manifest in various forms: indeterminate, cardiac, gastrointestinal, and mixed (cardiac and gastrointestinal).[1] [4] Reactivation of infection can occur in patients with induced or acquired immunosuppression (such as in advanced HIV infection or after organ transplantation), causing myocarditis or severe meningoencephalitis.[5][6] [7] [8]

The term ‘Chagas disease’ is used for the general disease, whereas the term ‘Chagas cardiomyopathy’ encompasses all cases of Chagas disease with cardiac involvement.[2]

Epidemiology

Chagas disease is endemic in 21 Latin American countries and it is estimated that 6-7 million people worldwide are infected with *Trypanosoma cruzi,* including 300,000 people residing in the US and 80,000 in Spain.[11] [WHO: Chagas disease (American trypanosomiasis)] (https://www.who.int/news-room/fact-sheets/detail/chagas-disease-%28american-trypanosomiasis%29) Infected residents have also been reported in Switzerland, France, Italy, Canada, Australia, and Japan.[2] Globally, there are 30,000-40,000 new cases per year.[27] [28]

The disease is associated with poverty and poor housing conditions. As a consequence of a co-ordinated multi-country programme, targeting reduction of transmission by vectors and via blood transfusion in the Southern Cone, Andean, Amazonian, and Central American countries, the transmission of Chagas disease has been significantly reduced. The incidence of new infections by *T. cruzi* across the South American continent has decreased from an estimated 700,000 new cases per year in the region to 29,925 in 2010 (96% reduction).[27] [29] However, oral transmission has significantly increased in many endemic countries.[9][30]

Human migration and travel from endemic areas contributes to the increasing prevalence of Chagas disease in non-endemic countries, including the US, Canada, and some European and Western Pacific countries.[31] [32] [33] [34] [35] However, the US cannot be classified as a typically non-endemic country as the southern states (from Georgia to California) have established enzootic cycles of *T. cruzi* , involving several triatomine vector species and mammalian reservoir hosts (e.g., raccoons, opossums, domestic dogs).[36] [37] Enzootic *T. cruzi* transmission has also been reported in states as far north as Virginia and Maryland. Despite the presence of these triatomine bugs (mostly *Triatoma sanguisuga*), vector-borne human cases of Chagas disease have only rarely been documented in the US.[38] In general, the probability of infection has reduced (due to measures such as better housing), but some populations continue to be at risk (e.g., migrant populations living in temporary housing along the US/Mexico border). Considering the increasing domestic presence of vectors, globalisation, and possible future rises in temperature, the disease has the potential to become well established in the US.[39] [40] [41]

Aetiology

Trypanosoma cruzi has sylvatic (occurring in wild animals), peridomestic, and domestic cycles. The domestic cycle is maintained by triatomines adapted to human dwellings, transmitting the parasite from domestic animals to humans and between humans.[12] [42] [43] The sylvatic cycle is maintained by triatomines and wild animals. In the peridomestic cycle, the infection is maintained among domestic animals in areas surrounding human dwellings, by peridomestic triatomines (and occasionally through exchange with the sylvatic cycle, such as dogs and cats hunting wild animals, or sylvatic animals invading areas surrounding human dwellings).[44] [45] [46] [47] Birds and cold-blooded animals are resistant to infection.

The classic mode of transmission of *T cruzi* is by contact with the faeces or urine of blood-sucking triatomine bugs (commonly known as kissing bugs in the US), which typically attack at night.[29] [48] More than 150 triatomine species have been described in endemic areas, and include *Alberprosenia* species; *Belminus* species; *Eratyrus* species; *Microtriatoma* species; *Panstrongylus* species; *Psammolestes* species; *Rhodnius* species; and *Triatoma* species.[42] [49] [50] [51] The principal vector in the US is *T. sanguisuga* .[52] [53] There are very few reports of transmission by vectors in humans in the US; however, increased domestic vector presence, globalisation, and potential future rises in temperature have raised awareness that vector-borne transmission may become established in the US.[39] [54]

Other primary modes of transmission include blood transfusions, consumption of contaminated food or drink, and vertical transmission (causing congenital disease). Secondary modes of transmission include organ transplantation, laboratory accidents, handling infected animals, sexual activity (via wounds, sperm, or menstrual fluids), and criminally induced infection (inoculation or oral).[9] [42] [55] [56] It is important to note that sexual transmission is possible in the case of acute Chagas disease due to the high level of parasitaemia but, unlike the other mechanisms, this pathway does not occur in the context of chronic disease.

An increased number of cases and micro-epidemics of oral transmission have been observed in Latin American countries (mainly in the Amazon region of Brazil). Several outbreaks of acute Chagas disease involving groups of people, often families, have been reported from endemic areas. Most commonly, oral ingestion occurs via home-made açaí, other palm products, and sugar cane juice. However, it may also occur after ingestion of water contaminated with fruit juice and after eating the raw meat of sylvatic animals.[9]

Triatoma sanguisuga : vector species with wide distribution in the US

Cleber Galvao, PhD, Laboratório Nacional e Internacional de Referência em Taxonomia de Triatomíneos, Instituto Oswaldo Cruz, Rio de Janeiro, Brazil; used with permission

Pathophysiology

The parasite is classically transmitted by an infected triatomine bug. Triatomines hide in the nests or resting places of wild animals and feed on blood while the animal is sleeping (sylvatic cycle). Some of these insect species have adapted to human dwellings where they hide in crevices, emerging at night for their blood meal (domestic cycle). Within the vector's intestine, *Trypanosoma cruzi* undergoes several successive developmental stages, the last of which is a flagellated form living in the vector's rectum. Ingestion of the blood meal causes the vector to defecate and deposit faeces containing infectious metacyclic

trypomastigotes onto the victim's skin, close to the bite wound. Upon awakening, the victim commonly rubs the itching bite area, pushing the trypanosome-laden faeces into the bite wound or onto the conjunctiva. Metacyclic trypomastigotes enter the victim's bloodstream through the bite wound or penetrate mucous membranes such as the conjunctiva (leading to Romaña's sign). This initiates the acute stage of disease.[4] [26] [42] This infective form of the parasite invades macrophage cells and transforms into intracellular amastigotes. The amastigotes multiply by binary fission and are released as trypomastigotes into the bloodstream and tissues.[4][12][26]

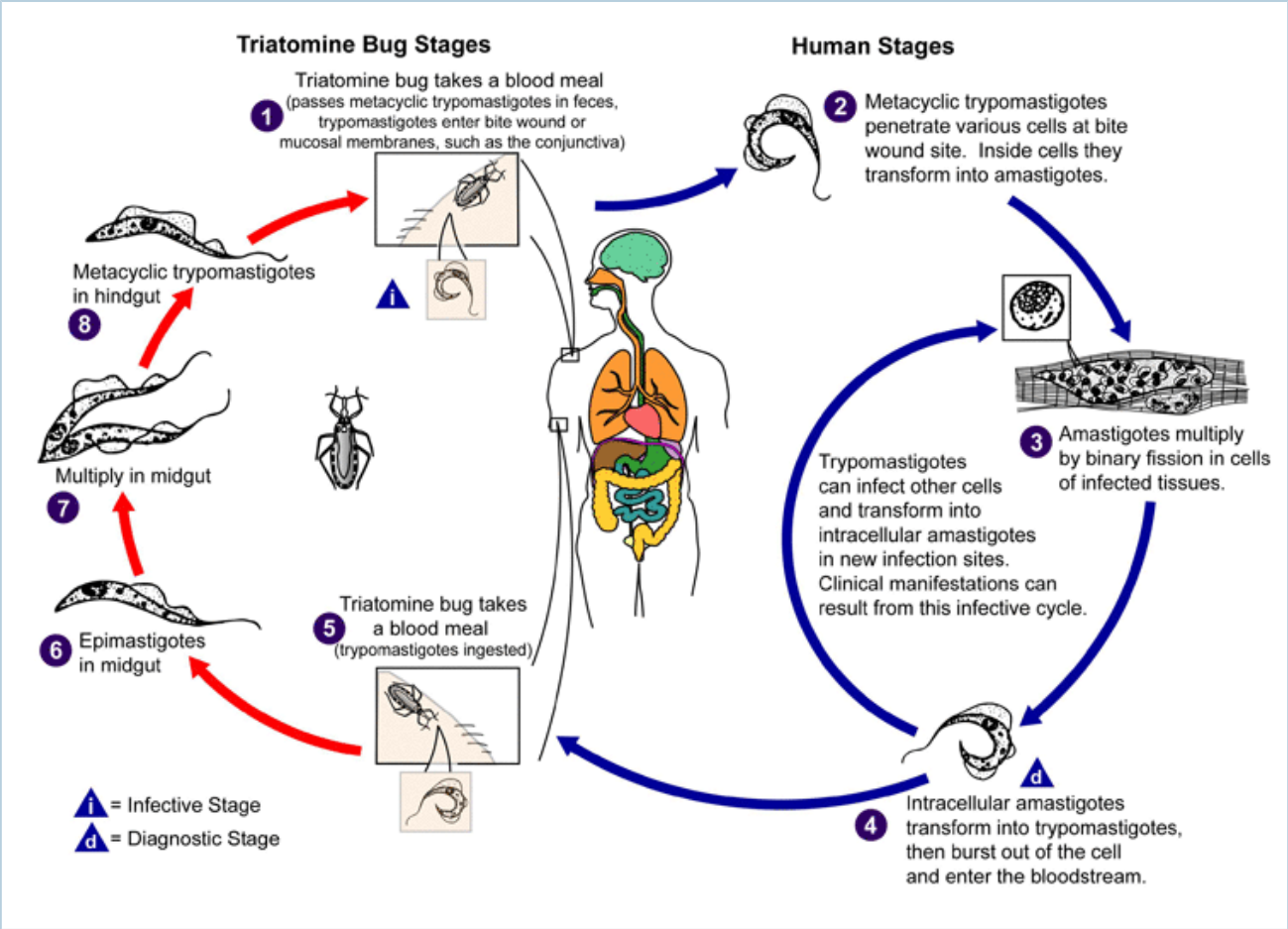
The incubation period varies according to the mode of transmission. The incubation period after vectorial transmission is 4 to 15 days; after transfusional transmission, it is 30 days or more (up to 4 months); after ingestion of contaminated food or drink, 3 to 22 days; and after accidental transmission, up to 20 days. Vertical transmission can occur in any gestation period, or during delivery.[57] [58] [59] [60] [61]

Trypomastigotes infect new cells of various tissues (e.g., reticuloendothelial system, myocardium, muscles, nervous system) and transform into intracellular amastigotes. After infection, inflammatory responses, cellular lesions, and fibrosis occur sequentially (mainly in the heart, oesophagus, and colon). In the acute phase, multiple cycles of intracellular parasite multiplication occur. This leads to high parasitaemia which further amplifies inflammation and cell lesions although, this process is less intense during chronic Chagas disease.

Myocytes and nerve cells (causing autonomic denervation) are typically affected. Direct destruction occurs by intracellular parasitism, necrosis related to inflammation, and other cytotoxic mechanisms. Fibrosis in Chagas cardiomyopathy is more intense than the fibrosis associated with any other cardiac disease. Cardiac involvement in the chronic phase is due to destruction of the conduction system, myocytes, and parasympathetic cardiac nerves. In association with the appearance of arrhythmogenic electric foci in the inflammatory areas, it gives rise to arrhythmic syndrome.[4] [62] [63] [64] [65] The hypertrophy of myocytes, and the intense fibrosis replacing the destroyed cells, predispose to cardiac dilation and failure. The left ventricular wall thins, typically allowing for the formation of an apical aneurysm. Thrombi are often present in such aneurysms, easily explaining the common occurrence of systemic and pulmonary thromboembolism.[4] [14] [64]

Parasympathetic intramural denervation is irregularly found within the gastrointestinal system and mainly affects the oesophagus and colon (most frequently the sigmoid colon). The affected intestine may have a normal macroscopic appearance with functional peristaltic disturbance but may also dilate, leading to mega-oesophagus or megacolon. Volvulus of the sigmoid colon is a rare complication appearing in advanced cases, and is associated with a high risk of intestinal necrosis.[66] [67] [68] [69] [70]

The factors that predispose a patient in the indeterminate phase of *T. cruzi* infection to develop symptomatic disease are not defined. Many factors may contribute.[71] [72] These include: exposure to *T. cruzi* reinfection in areas with sustained vector transmission; male sex; parasite load; host genetic factors; nutritional status; patients' social context and quality of life; and presence of comorbidities (important in the pathogenesis of chronic symptomatic/determinate Chagas disease).[72]



Life cycle of Trypanosoma cruzi , the causative parasite of Chagas disease

Centers for Disease Control and Prevention, Atlanta, GA, USA: Public Health Image Library ID # 3384 (Alexander J. da Silva, PhD/Melanie Moser, 2002)

Classification

Clinical phases of infection

Acute phase

- Usually lasts 3-8 weeks (up to 12 weeks in some cases), and is defined by evidence of *Trypanosoma cruzi* in the peripheral blood. Patients remain infected for life if not treated during this phase. Most patients have no symptoms, mild symptoms, or a non-specific febrile syndrome. Rarely, they may present with more severe symptoms such as myocarditis or meningoencephalitis.[9] [10]

Chronic phase

- Develops after many decades if suitable treatment is not given during the acute phase. Approximately 60% to 70% of infected individuals remain asymptomatic throughout their lifetime, while 20% to 30% of patients develop symptomatic disease.[2] [11] Asymptomatic disease progresses to chronic symptomatic disease at a rate of 1.85% to 7.00% annually.[2]
- The various clinical forms of disease may occur separately or simultaneously:

- Indeterminate form: the most common form. Patients can be asymptomatic for decades after the acute phase. While serology is positive for *T. cruzi* these patients have anatomically and physiologically normal x-ray results of the heart, oesophagus, and colon, and no abnormal changes on echocardiography.[12]
- Cardiac form: occurs between the 2nd and 4th decades of life, typically 5-15 years after the initial infection, and affects up to 30% of patients.[4] [13] [14]
- Gastrointestinal form: uncommon in countries north of the equator. Oesophagopathy affects 5% to 10% of patients, and colonopathy affects 3% to 5% of patients.[13]
- Mixed form (cardiac and gastrointestinal).

Reactivation phase

- Chronic disease may become acute in immunocompromised patients (e.g., AIDS, haematological cancers, post-organ transplantation, high-dose immunosuppressive therapy) due to *T. cruzi* reactivation.[15] Patients usually present with meningoencephalitis or myocarditis; however, dermatological manifestations may also occur.[8][16]
- Chagas disease reactivation is part of the diagnostic criteria for AIDS in Brazil.[17] [18]

Case history

Case history #1

A 40-year-old man originally from Brazil, who has been living in London for 22 years, presents with positive serology for *Trypanosoma cruzi* . This was detected by enzyme-linked immunosorbent assay and confirmed by radio-immunoprecipitation assay after a routine screening process for blood donors. He had been a blood donor for 14 years, but has now been excluded from the donation process. He denies cardiac or gastrointestinal symptoms, and there are no specific signs on physical examination.

Case history #2

A 50-year-old man from Australia has been living and working in a rural area of Argentina (Chaco province) since 1985. During a holiday visit to his family in Australia, he is admitted to an emergency unit with reports of palpitations and syncope. He denies digestive symptoms. Physical examination reveals hypotension, cardiomegaly, and generalised oedema.

Other presentations

Patients who are immunosuppressed (e.g., AIDS, haematologic cancers, post-organ transplantation, high-dose immunosuppressive therapy) may present with meningoencephalitis, myocarditis, or, less commonly, dermatological manifestations, due to reactivation of *Trypanosoma cruzi* infection.[8][16] [19] [20] [21] However, these are less common in people living with HIV who are on modern antiretroviral therapy.

Outbreaks of acute orally transmitted Chagas disease can present with atypical signs and symptoms, including rash, gastrointestinal bleeding, jaundice, elevated liver function tests, and cardiac failure. More severe manifestations, including pericardial effusion, myocarditis, and haemorrhagic symptoms have also been reported in patients in the Amazon and adjacent regions due to inoculation with a high number

of parasites.[9] [22][23] [24] [25] Morbidity and mortality rates in these patients are higher than in acute cases caused by other modes of transmission.[9]

Gastric dilation and megaureter have been described in immunocompetent patients with Chagas disease. However, these manifestations are rare.[26]

Approach

More than 99% of patients with Chagas disease remain undiagnosed in the US and Latin America.[127] Assessment of suspected or confirmed Chagas disease should include a thorough medical history (including identification of risk factors for exposure to the vector and parasite in endemic or non-endemic settings), a full review of systems with a focus on signs characteristic of Chagas disease, serological testing, and, in some cases, parasitological evaluation. A 12-lead ECG with a 30-cm lead II rhythm strip is necessary for all patients, and additional examinations (e.g., echocardiogram, 24-hour ambulatory ECG monitoring, barium studies of the oesophagus or colon) may be performed if symptoms or signs indicate the need. Histology or biopsy is not recommended for diagnosis; histology is only carried out at autopsy for fatal cases.

Chagas disease is a reportable condition in some countries.

History

Careful history-taking, identifying possible risks for infection, is helpful. Risk factors include exposure to *Triatoma* species and the presence of infected reservoirs; travel to or living in rural areas of endemic regions (recently or in the past); deforestation; poor housing and low socio-economic status; oral ingestion of possibly contaminated food; transfusion with possibly infected blood; organ transplantation from an infected donor; accidental exposure to infected material (surgical, laboratory); Chagas disease during pregnancy (vertical transmission); and living in areas of risk in the US. The presence of Chagas disease in other family members is also a strong indicator. Most adults with *Trypanosoma cruzi* infection are unaware of their diagnosis and history consistent with acute Chagas disease from years prior is rarely given.[128]

Chagas disease is a heterogeneous condition with a wide variation in clinical presentation. Approximately 60% to 70% of infected people remain asymptomatic throughout their life.[2] The condition has two phases: acute and chronic. The acute phase usually lasts for 3 to 8 weeks (up to 12 weeks in some cases). Patients may be asymptomatic, present with mild symptoms, or a non-specific febrile syndrome. Symptoms of the acute-phase may include fatigue, diarrhoea, headache, vomiting, myalgia, irritability (children), and anorexia; these may be more severe after infection via oral transmission or in immunosuppressed patients. After the acute phase, most patients develop a chronic indeterminate form of the disease in which they have no signs or symptoms. Chronic-phase disease develops if the acute phase is undiagnosed or untreated though symptoms may not occur until decades later.[13]

Patients with manifestations of acute myocarditis may have symptoms such as cough, dyspnoea, and atypical chest pain. Those who have ingested contaminated food or drink may have symptoms that include haematemesis, epigastric abdominal pain, melaena, and haematochezia. In children, the morbidity caused by the acute phase of Chagas disease is more pronounced than in adults.

In the chronic phase of Chagas disease, indeterminate forms do not exhibit any signs or symptoms consistent with cardiac or digestive issues. Additionally, ECGs and radiological examinations of the heart, oesophagus, and intestine show normal results. The gastrointestinal and cardiac manifestations of chronic disease usually become apparent years or decades after the infection, and occur almost exclusively in adults.[26] [129] [130] However, rarely patients can progress directly from acute infection to the chronic cardiac form.

Patients with cardiac forms of chronic-phase disease may present with symptoms that include palpitations, syncope, presyncope, dizziness, and even sudden death. Cardiomyopathy may cause

symptoms of congestive heart failure (e.g., dyspnoea, decreased exercise tolerance, peripheral oedema). Thromboembolic phenomena may present with stroke or pulmonary embolism due to emboli from an intracardiac thrombus.

Patients with gastrointestinal forms of chronic disease may present with symptoms of oesophagopathy (e.g., dysphagia, regurgitation, aspiration, odynophagia, substernal discomfort) and colonopathy (e.g., prolonged constipation, abdominal pain). Advanced cases of gastrointestinal disease may present with weight loss, acute abdominal pain, and evidence of complications (e.g., faecaloma, bowel obstruction, volvulus); these patients may also require surgical evaluation or treatment. Gastric dilation (with alterations of gastric motility and secretion) is a relatively rare manifestation.

Seizures and tremors may occur in patients with meningoencephalitis (acute or reactivation). Megaureter (with repeated urinary tract infections, back pain, nausea or vomiting) is a relatively rare manifestation.

Physical examination

Examination of patients with acute-phase disease may reveal prolonged fever, rash, swelling around the site of inoculation, splenomegaly, hepatomegaly, and/or enlarged lymph nodes. There may be a history of an obvious portal of entry (e.g., inoculation chagoma, Romaña's sign) in a small number of cases or the port of entry may be unknown. Chagoma (*T. cruzi* skin abscess) and Romaña's sign (unilateral conjunctivitis and painless swelling of the upper and lower eyelids) are pathognomonic, but only occur in a minority of patients, predominantly in children.[2] Patients with acute myocarditis may have tachycardia, hypotension, cardiomegaly, and/or signs of pericarditis. Jaundice may be present in patients who have ingested contaminated food or drink.

Examination of patients with indeterminate forms of chronic-phase disease will usually not reveal any specific signs. Patients with cardiac forms of chronic disease may have signs of congestive cardiac failure (jugular venous distension, cardiomegaly, lung rales or pleural effusion, oedema) or evidence of thromboembolic phenomena (e.g., signs suggestive of stroke).[4] [14] Gastrointestinal forms of chronic disease may reveal evidence of gastrointestinal complications (e.g., abdominal rebound tenderness, a sign of peritoneal irritation).

Patients with meningoencephalitis (acute or reactivation) may have specific clinical signs of meningeal irritation (predominant meningeal inflammation, Kernig's sign, Brudzinski's sign, nuchal rigidity, spinal rigidity), or clinical signs of cerebral mass lesions (mental status changes, seizures, focal motor or sensory abnormalities).

General laboratory investigations

Full blood count (FBC) and liver function tests (LFTs) are non-specific but are important for baseline profile as well as monitoring disease severity in the acute phase and adverse effects due to antiparasitic therapy. FBC is indicated to identify leukopenia or leukocytosis (mild or moderate), with a left shift. Lymphocytosis may be observed, but lymphocyte levels may also be normal or low. Hypochromic anaemia and low platelet counts are also observed. Abnormal LFTs in acute Chagas disease, especially with suspected ingestion of contaminated food or drink, suggest hepatic lesions.

Coagulation tests are important in cases with hepatic failure or haemorrhagic manifestations. Pregnancy testing in women is recommended prior to specific treatment. Urine sediment examination, with evidence of compromised urinary function and bleeding, is important in monitoring treatment. Lumbar puncture with cerebrospinal fluid (CSF) analysis is required in cases of neurological involvement.

Parasitological and serological evaluation

Diagnosis can be confirmed by parasitological evaluation (recommended for acute-phase disease and reactivation) or serological evaluation (recommended for chronic-phase disease).[13] [34] [131] [132] [133] [134] Diagnostic testing for Chagas disease is not widely available in the some countries.

Parasitological evaluation

- Direct methods are based on a search for the parasite in blood, CSF, or tissues (e.g., direct fresh test, stained smear). Indirect methods depend on the growth of the parasite in culture (haemoculture) to evaluate the life cycle in the vector after a blood meal on a patient (xenodiagnosis). Sensitivity depends on the level of parasitaemia. Molecular diagnosis (e.g., polymerase chain reaction [PCR]) can be used when available.
- Acute phase: direct examination of blood by microscopy of fresh preparations of anticoagulated blood is recommended. The trypomastigotes are translucent and are usually detected by the corresponding movement of red blood cells. Parasitic concentration methods (e.g., Strout's method; quantitative buffy coat [QBC] test; microhaematocrit) for evidence of trypomastigote forms are also used. Stained thin and thick blood smears may be examined for diagnosis; however, these have a lower sensitivity than other microscopy methods.[13] [24] PCR is also a highly sensitive test in acute infection, and may show rising parasite loads before the parasites are detectable by microscopy.[2]
- Chronic phase: although parasitological evaluation is not the first option for the diagnosis of chronic-phase disease, diagnosis can be confirmed by blood or CSF culture (low sensitivity, high specificity) or xenodiagnosis (low sensitivity, high specificity). A meta-analysis has suggested that PCR has a relatively low sensitivity but very high specificity in chronic disease; therefore, it is not recommended.[134]
- Reactivation phase: confirmed by direct examination of blood or CSF. This involves thick blood smear and applying parasitic concentration methods (e.g., Strout's method, QBC, microhaematocrit) for evidence of trypomastigote forms. Real-time PCR may also be used for early detection of reactivation in immunocompromised patients. Indirect parasitological methods and qualitative PCR are not valid to confirm reactivation.[2]

Serological evaluation

- Test of choice for chronic-phase disease. Based on the identification of IgM antibodies (acute phase) and IgG antibodies (chronic phase) to *T. cruzi* . IgM preparations are rarely available, even in endemic countries.
- Tests include enzyme-linked immunoassay (ELISA), indirect immunofluorescence antibody test, radioimmunoassay precipitation assay, indirect haemagglutination, and chemiluminescence which use whole or semi-purified extracts of the epimastigotes of *T. cruzi* A considerable variation in the reproducibility and reliability of the results is observed. Performance of ELISA tests is considered good.[134]
- For chronic-phase disease, at least two serological tests based on different antigens or techniques are used to increase the accuracy of diagnosis. When results are discordant, a third assay may be used to confirm or refute the diagnosis, or repeat sampling may be required.

Physiological cardiac tests

Assessment of cardiac disease is essential in all patients with confirmed *T. cruzi* infection in order to detect early cardiac disease, with ongoing routine monitoring. Patients with acute or chronic disease require cardiac evaluation by ECG. Indicators of ventricular dysfunction, such as non-sustained

or sustained ventricular tachycardia on resting ECG or ambulatory monitoring, severe sinus node dysfunction, and high-degree heart block, are major predictors of sudden death.[4] [14] [135] [136] [137] [138]

Resting 12-lead ECG with 30-second lead II rhythm strip

- Indicated in acute- and chronic-disease patients at the first evaluation, and then annually thereafter.
- The most frequent cardiac alterations in acute-phase disease are similar to other cases of acute myocarditis and include sinus tachycardia, low QRS voltage, prolonged PR and/or QT intervals, and primary alterations of the T wave. Ventricular extrasystoles, atrial fibrillation, or complete right bundle branch block (rare in this phase) indicate a fatal outcome.
- The most frequent cardiac alterations in chronic-phase disease are right bundle branch block; incomplete right bundle branch block; left anterior fascicular block; first-degree AV block; second-degree AV block (Mobitz type I or II); complete AV block; bradycardia; sinus node dysfunction; ventricular extrasystoles (often frequent, multifocal); or paired ventricular tachycardia (non-sustained or sustained). Less common, but clinically significant when present, are atrial fibrillation or flutter, left bundle branch block, low QRS voltage, primary alterations of repolarisation, and Q waves.

Ambulatory 24-hour ECG

- Indicated in patients with symptoms or ECG changes consistent with Chagas heart disease.
- Must be monitored to detect arrhythmias.

Exercise testing

- Indicated in patients with symptoms or ECG changes consistent with Chagas heart disease.
- Necessary for evaluation and identification of exercise-induced arrhythmias, and assessment of functional capacity and chronotropic response.

Imaging

Chest x-ray is indicated in all patients to define baseline status and to evaluate cardiac or pulmonary complications. It may demonstrate different stages of cardiomegaly and pleural effusion (and other congestive signs) in cases with cardiac failure. Echocardiography is indicated in patients with clinical, radiological, or ECG evidence of functional cardiac disturbance. This enables assessment of biventricular function, wall motion, and structure.[4] [14] [139] Cardiac magnetic resonance imaging (MRI) can be performed in select patients with Chagas cardiomyopathy to assess the extent of fibrosis. Nuclear medicine testing is an option to assess biventricular function when echocardiography is inadequate. Cardiac catheterisation and coronary angiography may be required in patients with disabling, angina-like symptoms to rule out concomitant coronary artery disease. Right cardiac catheterisation is necessary in patients with advanced heart failure to assess the feasibility of cardiac transplantation.[2]

Barium swallow or enema studies (oesophagography or colonography) are indicated in patients with gastrointestinal symptoms for diagnosis of achalasia or megacolon. Upper gastrointestinal endoscopy is not indicated for the diagnosis of mega-oesophagus; however, patients with impaired oesophageal motility are at increased risk of reflux oesophagitis and oesophageal carcinoma, and screening for these conditions may be necessary, especially if a change in symptoms has occurred.[107] Oesophageal manometry is employed to evaluate the extent and intensity of peristalsis impairment.

Cranial computed tomography or MRI are indicated in cases of suspected meningoencephalitis and in patients with acute or reactivation-phase disease and neurological symptoms. It may also be indicated

in patients with suspicion of cardioembolic stroke associated with chronic-phase disease with cardiac involvement.

Emerging investigations

Immunochromatography tests for Chagas disease, such as rapid diagnostic tests (RDTs) or lateral flow assays, are emerging investigations that have been developed and used for Chagas disease diagnosis.[140]

RDTs were developed as an easy-to-use alternative to conventional tests. Although they have high validity for diagnosing chronic Chagas disease, they are not yet used for this purpose.[141] RDT use is limited to diagnostic screening in the field. If the test is positive, confirmation with other serological tests is necessary.

Commercial PCR kits for the detection and quantification of *T. cruzi* in blood samples are available.[142] The kits may become a standard test for molecular diagnosis in endemic countries in the future.

History and exam

Key diagnostic factors

presence of risk factors (common)

- Includes history of exposure to *Triatoma* species; history of blood transfusion; history of organ transplantation; history of immunosuppression; healthcare or laboratory occupations; poverty; low education levels; travel to endemic areas; residence in endemic or high-risk areas; ingestion of contaminated food or drink; and positive family history (including mother with Chagas disease).

prolonged fever (common)

- May be present in acute-phase disease. A non-specific sign, characterised by prolonged (7-30 days) and constant febrile temperatures (usually 37.5°C to 38.5°C [99.5°F to 101°F]) with nocturnal elevation.
- In some cases of ingestion of contaminated food or drink, cases may have a short course with fever (usually <7 days).

palpitations (common)

- In the acute phase, this may be a sign of acute myocarditis.

syncope or presyncope (common)

- In the chronic phase, this may be a sign of cardiopathy (conduction system disease, or arrhythmias). Major predictor of sudden death.[135] [136] [137]

hepatosplenomegaly (common)

- Mild or moderate. Typically painless.

enlarged lymph nodes (common)

- Mild or moderate. Typically painless. Principal regions: auricular, cervical, sub-mandibular, axillary, and inguinal.

tachycardia (common)

- May be present in acute-phase disease as a sign of acute myocarditis.

hypotension (common)

- May be present in acute-phase disease as a sign of acute myocarditis.

cardiomegaly (common)

- May be present in acute-phase disease as a sign of acute myocarditis or pericardial effusion.
- May be present in chronic-phase disease as a sign of chronic heart failure, and is generally associated with systolic dysfunction.

dysphagia (uncommon)

- In the chronic phase, dysphagia for liquids and solids may be associated with gastrointestinal involvement.

regurgitation/aspiration (uncommon)

- In the chronic phase, this may be associated with gastrointestinal involvement.

odynophagia (uncommon)

- In the chronic phase, this may be associated with gastrointestinal involvement.

substernal discomfort (uncommon)

- In the chronic phase, this may be associated with gastrointestinal involvement.

prolonged constipation (uncommon)

- In the chronic phase, this may be associated with gastrointestinal involvement. Indicates intestinal occlusion, or sigmoid volvulus.

acute abdominal pain (uncommon)

- In the chronic phase, this may be associated with gastrointestinal involvement. This can be a gastrointestinal emergency (bowel ischaemia or volvulus). May also be associated with congestive hepatopathy in chronic-phase disease with cardiac involvement.

abdominal distension (uncommon)

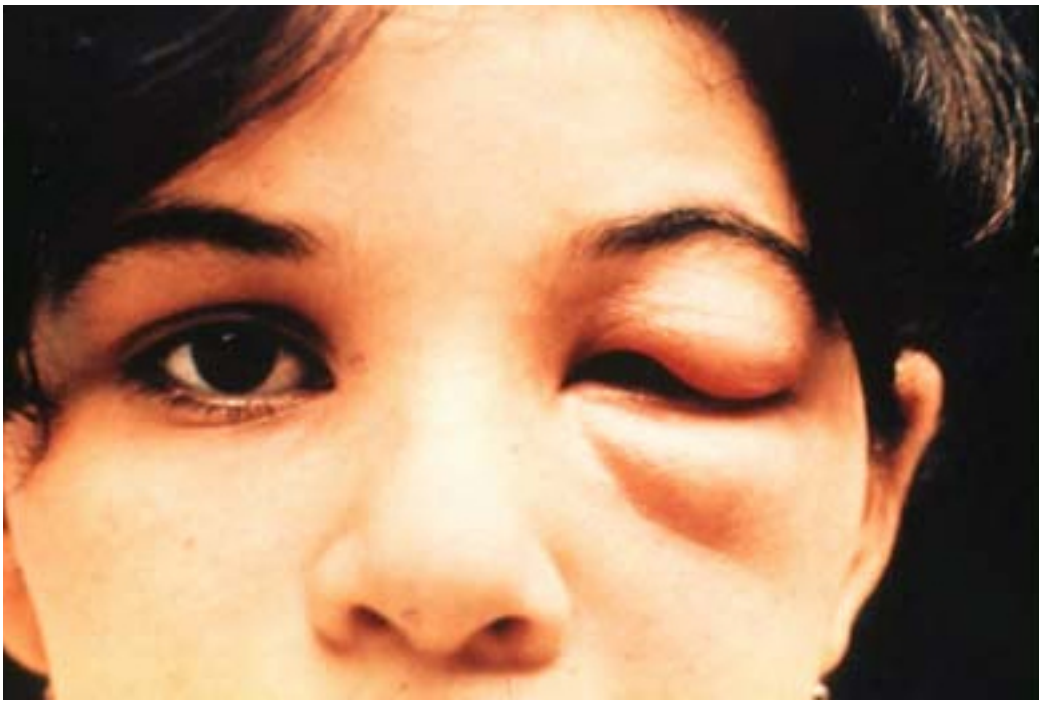
- In the chronic phase, gaseous or asymmetrical distension may be associated with gastrointestinal involvement. Sign of megacolon, intestinal occlusion, or sigmoid volvulus.

swelling around the site of inoculation (uncommon)

- Specific evidence of acute-phase disease. Related to vectorial transmission. Usually called inoculation chagoma. Represents an area where the parasite entered the skin or mucous membrane.
- Romaña's sign (ophthalmoganglionar complex) occurs when the inoculation site is the conjunctiva, with unilateral periocular oedema. This sign is associated with subcutaneous inflammatory nodule

or non-purulent unilateral palpebral oedema, and conjunctivitis with ipsilateral regional preauricular lymphadenopathy.

- Chagoma and Romaña's sign are pathognomonic, but only occur in a minority of patients.[2]



Child with an inoculation chagoma (Romaña's sign)

Grupo de Estudo em Correlalacao Anatomo-Clinica, Clínica Médica, Pontificia Universidade Catolica de Campinas, Sao Paulo, Brazil; used with permission

jaundice (uncommon)

- May be present in acute-phase disease after ingestion of contaminated food or drink.

abdominal rebound tenderness (uncommon)

- May be present in chronic-phase disease. Signals presence of a gastrointestinal emergency such as bowel ischaemia or volvulus.

clinical evidence of meningeal irritation (uncommon)

- Occurs in cases of meningoencephalitis (in acute phase, neonates, or reactivation).

clinical signs of a cerebral mass lesion (uncommon)

- Occurs in cases of meningoencephalitis (in acute phase, neonates, or reactivation), and is associated with cardioembolic stroke in patients with chronic-phase disease and cardiac involvement.

Other diagnostic factors

irritability (common)

- May be present in children with acute-phase disease.

anorexia or fatigue (common)

- May be present in acute-phase disease.

vomiting or diarrhoea (common)

- May be present in acute-phase disease.

headache (common)

- May be present in acute-phase disease.

myalgia (common)

- May be present in acute-phase disease.

reduced exercise tolerance (common)

- May be a symptom of congestive heart failure following Chagas-induced cardiac disease.

dizziness (common)

- In the chronic phase, this may be a sign of cardiopathy (conduction system disease, or arrhythmias).

thromboembolic phenomena (e.g., stroke, pulmonary embolism) (common)

- May be present in chronic-phase disease as a sign of cardiopathy.

dyspnoea (uncommon)

- May be a symptom of congestive heart failure following Chagas-induced cardiac disease.

cough (uncommon)

- May be present in acute-phase disease as a sign of acute myocarditis.

generalised oedema (uncommon)

- May be present as a sign of congestive heart failure.

pericarditis (uncommon)

- May be present in acute-phase disease as a sign of acute myocarditis.

epigastric pain and/or haematemesis (uncommon)

- In the acute phase, this may be associated with ingestion of contaminated food or drink.

melaena or haematochezia (uncommon)

- In the acute phase, this may be associated with ingestion of contaminated food or drink.

rash (uncommon)

- May be present in acute-phase disease. A non-specific sign characterised by rash with variable localisation, with or without pruritus.

seizures or tremors (uncommon)

- May occur with acute-phase meningoencephalitis. Indicates a poor prognosis.

Risk factors

Strong

living in endemic area

- Chagas disease is endemic in 21 Latin American countries and it is estimated that 6-7 million people worldwide are infected with *Trypanosoma cruzi* , including 300,000 people residing in the US and 80,000 in Spain.[11] [WHO: Chagas disease (American trypanosomiasis)] (https://www.who.int/news-room/fact-sheets/detail/chagas-disease-%28american-trypanosomiasis%29) Infected residents have also been reported in Switzerland, France, Italy, Canada, Australia, and Japan.[2]

exposure to Triatoma species

- Triatomines hide in the nests or resting places of wild animals. They feed on blood while the animal is sleeping (sylvatic cycle). Human activities sometimes may expose them to these insects. Some of these insect species have adapted to human dwellings where they hide in crevices, emerging at night for their blood meal (domestic cycle). The distribution of animal reservoirs (sylvatic or domesticated) in different habitats allows for evaluation of the probable place of transmission, indicating potential risk for vectorial and oral transmission.[12] [42] [43] [73]
- Classical transmission occurs by vectors that hide inside cracks in mud or adobe houses.[74] Studies have shown that vector populations are still abundant and highly prevalent in poor rural housing.[75] [76] Heterogeneous habitat conditions are expected to affect triatomine population parameters, dispersal, control, and infection with *Trypanosoma cruzi* . The presence of domestic animals increases colonisation of houses and makes control more difficult.[77] [78]

low socio-economic status

- Chagas disease is a preventable condition that affects mostly low-income populations or those previously living in rural areas of endemic regions. Like many other parasitic infections, it is classically associated with poverty and low educational level in both endemic and non-endemic areas.[31] [77] [79][80]

consumption of contaminated food or drink

- Accidental ingestion of triatome faeces or triatomine structures can occur with unhygienic food preparation. Some marsupial species (*Didelphis* species) can harbour and excrete *Trypanosoma cruzi* in their anal glands, leading to contamination of food and/or utensils. Some fruits (e.g., açaí, juçara, bacaba, and sugar cane) are commonly contaminated as vectors and sylvatic animals share this habitat. People become infected after drinking these juices.[9]

blood transfusion

- In most endemic Latin American countries, blood donors are routinely screened for Chagas disease.[27] [81] Massive migration from Latin America to US cities has, however, increased the number of infected individuals in the US.[82] The first reported case of transfusion-related transmission in the US was in 1987, but US screening for *Trypanosoma cruzi* in donated blood was not widely practised until 2007.[83] At least 2300 infected blood donors have been reported by blood banks across the US as of December 2017.[11] The risk of transmission varies between 12% and 44% for a single transfusion of 500 mL of infected blood.[84] [85] Risk depends on multiple factors, such as the degree of parasitaemia in the donor, the type of blood component transfused, and the parasite strain.[83] [86] [87]

organ transplantation

- Transplantation places the recipient at an additional risk for Chagas disease, due to induced immunosuppression. Infection has been described after heart, kidney, bone marrow, or liver

transplantation.[21] [88] [89] [90] [91] [92][93] In addition, acute disease may occur after bone marrow transplantation.[15] [94] [95] [96] [97] [98]

history of immunosuppression

- Patients with immunosuppression (acquired or induced), in association with chronic Chagas disease, may develop a typical syndrome of reactivation.

climate change

- Global climate changes are expected to affect populations of triatomines living in the surroundings of domestic dwellings much more than domestic bug populations.[78] [99] [100] [101] This will have an impact on the ecosystems that influence the dynamics of the sylvatic cycle: if their ecosystems are destroyed, the (sylvatic) insect vectors will search for alternative blood sources, and will consequently adapt to new environments close to human dwellings.[100]

deforestation

- Deforestation, and the associated loss of habitat and host diversity, in areas with a sylvatic cycle of *Trypanosoma cruzi* , may increase the frequency of *T. cruzi* infection rates in vectors and vector-human contact.[102] [103]

Weak

laboratory work occupations

- In laboratories, infection has been described via contaminated needles, exposure to the faeces of triatomine bugs, handling of infectious cultures, and possibly by inhalation.[104] The rate of recognised laboratory accidents per high-risk person-year has been estimated as 1 accident in 15 person-years, and infections per high-risk person-year as one infection per 46 person-years.[55] Depending on the nature of the accident, the individual risk may range from weak to strong.

travel to endemic areas

- Travel to rural areas in endemic regions poses an extremely low risk for acquisition of Chagas disease.[84] [105] [106] [107] [108] [109] [110][111] No cases of acquired infection during travel have been documented, however, travellers could be at risk if staying in poor-quality housing in recognised endemic areas.[84]

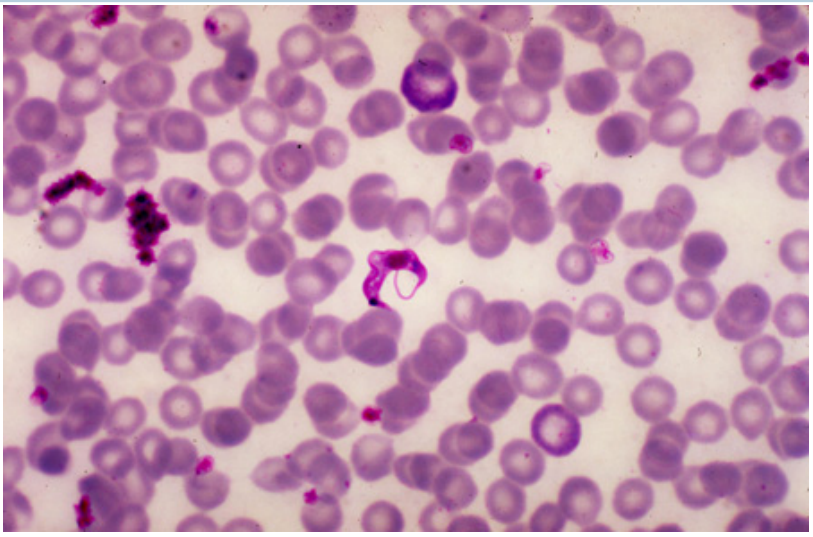
mother with Chagas disease

- Vertical (mother-to-child) transmission occurs mainly in the third month of pregnancy. The risk of transmission from infected mother to child ranges from 0% to 8%.[41] [112] [113] [114][115] [116] [117] Due to human migration, vertical transmission may also occur in non-endemic areas. Evidence suggests that approximately 0.3% of pregnant Latina women in Houston, Texas are seropositive.[118]

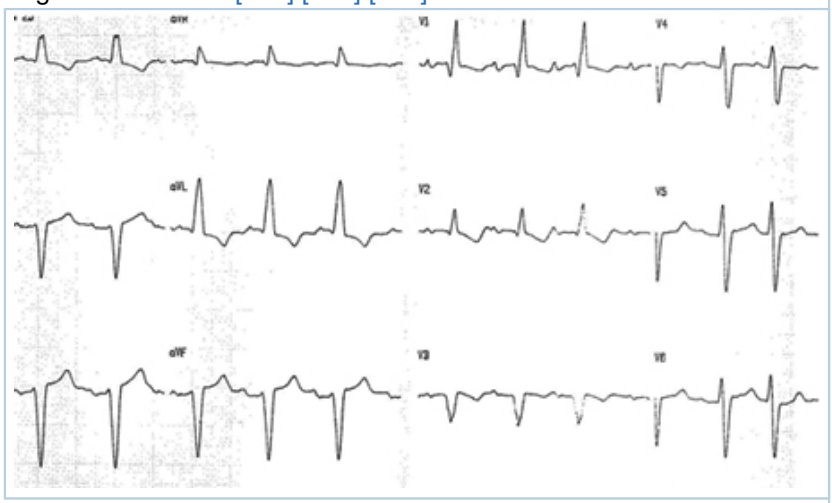
Investigations

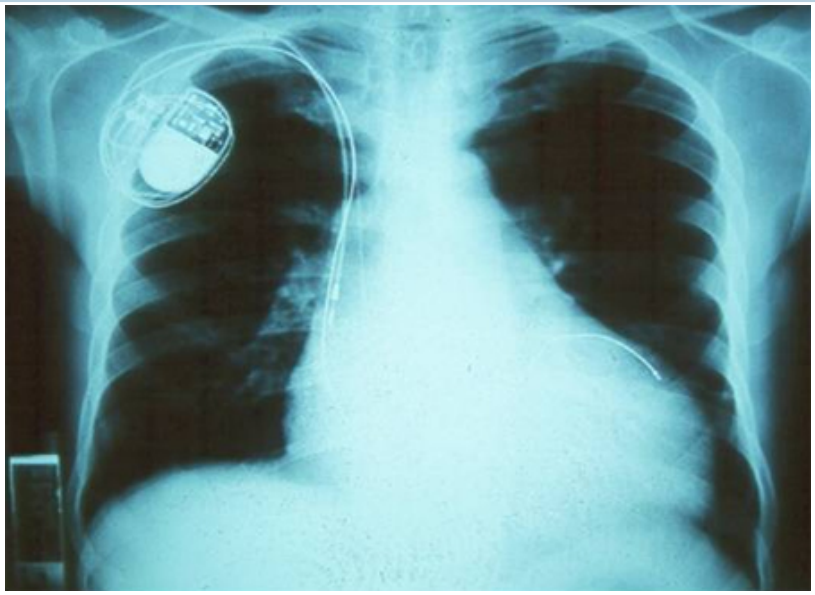
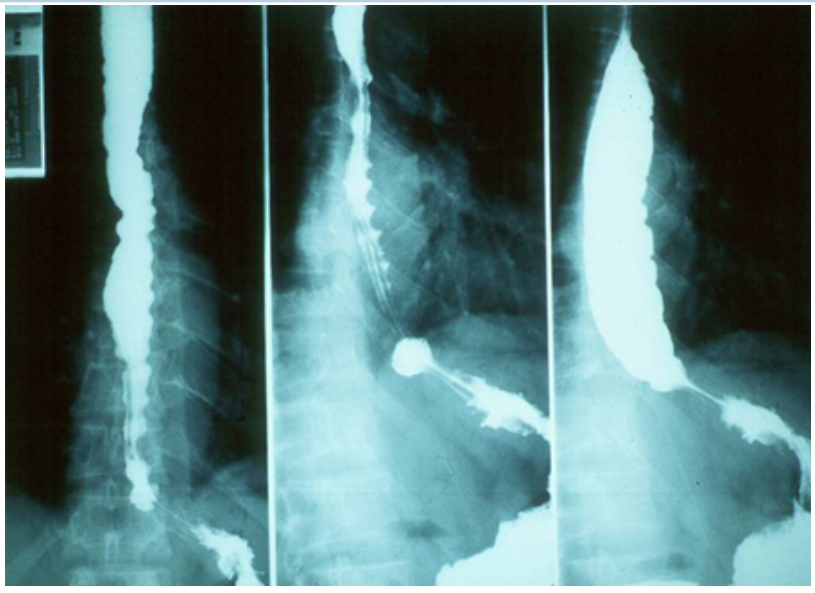
1st test to order

Test	Result
FBC • In acute Chagas disease, leukocytosis (mild or moderate) is common, but normal or low levels may be observed. Lymphocytosis with atypical lymphocytes is a significant marker.	**leukopenia or leukocytosis with a left shift and lymphocytosis; hypochromic anaemia; reduced platelets; low platelets**
LFTs • Helpful in acute Chagas disease (especially with suspected ingestion of contaminated food or drink) to assess for hepatic lesions. May be altered in some cases of chronic-phase disease with cardiac involvement due to congestive hepatopathy.	**elevated aspartate transaminase and alanine transaminase; elevated bilirubin**
serum electrolytes, urea nitrogen, and creatinine • Useful for assessing renal function. May be abnormal in acute Chagas disease and in some cases of complicated chronic-phase disease.	**normal or elevated sodium and potassium; normal or elevated urea nitrogen and creatinine**
microscopy: fresh blood • Useful in acute Chagas disease. • Detected by microscopy of fresh preparations of anticoagulated blood. The trypomastigotes are translucent, and are usually detected by the corresponding movement of red blood cells. A fast, simple, accurate test of low cost.[13] [24] Sensitivity is increased if the patient is febrile during blood collection. Parasitaemia decreases within 90 days of infection, even without treatment, and is undetectable by microscopy in the chronic phase.[34] • First-line diagnostic method in case of reactivation.	**mobile trypomastigotes**
microscopy: concentration methods applied to fresh blood • Useful in acute Chagas disease. • Parasites are detected by microscopy of fresh preparations of buffy coated blood (quantitative buffy coat test). Concentration methods (Strout's, microhaematocrit) are an alternative. The use of microhaematocrit tubes focuses the test for congenital Chagas disease in infants born to chronically infected mothers. • These tests are more sensitive (80% to 90%), but more complicated to perform.[13] [24] • The parasitaemia decreases within 90 days of infection, even without treatment, and parasites are undetectable by microscopy in the chronic phase. • First-line diagnostic method in case of reactivation.	**mobile trypomastigotes**

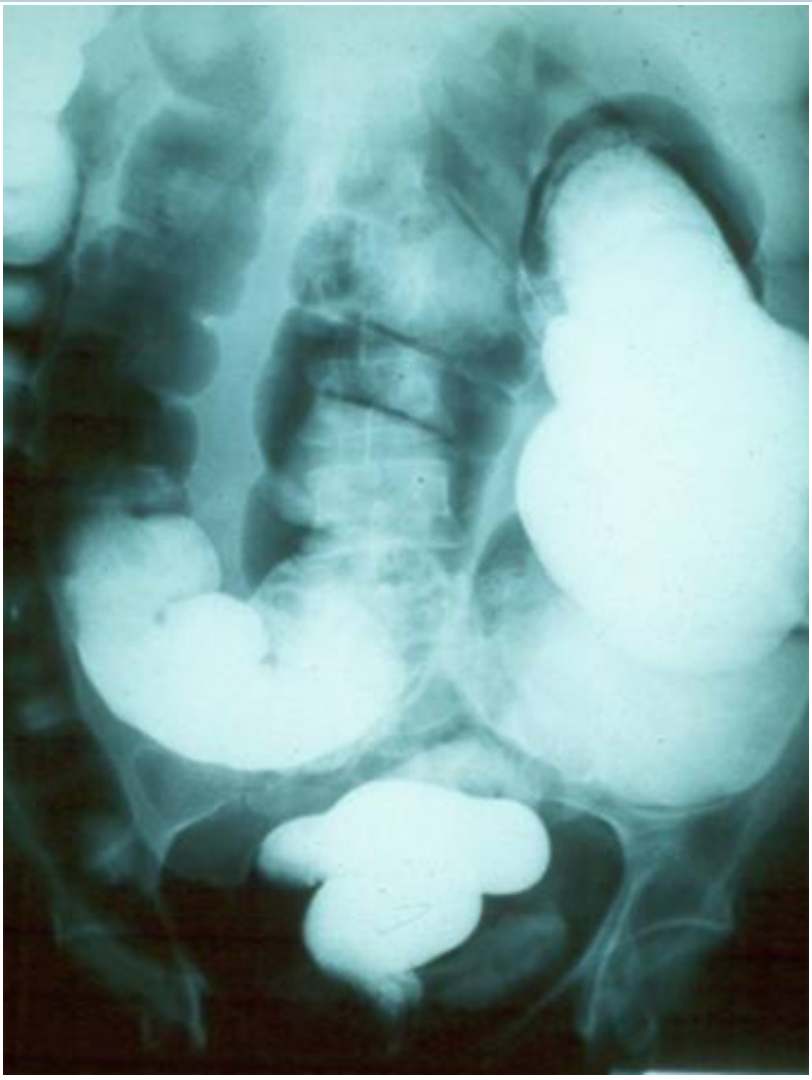
Test	Result
microscopy: thick blood smear • Useful in acute Chagas disease. • Stained thin and thick blood smears may be examined for diagnosis. However, these methods have lower sensitivity than other microscopy methods.[13] [24] • The parasitaemia decreases within 90 days of infection, even without treatment, and is undetectable by microscopy in the chronic phase.[34] • Commonly used in association with malaria control measures in malaria-endemic areas.[13] •  *Trypanosoma cruzi metacyclic trypomastigotes on a peripheral blood smear prepared with Giemsa stain* *Centers for Disease Control and Prevention, Atlanta, GA, USA: Public Health Image Library ID # 3013 (Dr Mae Melvin, 1977)*	**trypomastigote forms**
enzyme-linked immunosorbent assay based on parasite lysate • Used for chronic-phase disease. • This method has better sensitivity than conventional parasitological methods, due to low parasitaemia in chronic disease.[13] [24] • Serological methods detect almost 100% of cases.[13] [134] However, no single assay has sufficient sensitivity and specificity to be relied on alone. At least two subsequent tests based on different antigens or techniques are used in parallel, to increase the accuracy of diagnosis. When results are discordant, an additional assay may be used to confirm the diagnosis, or repeat sampling may be required.[34]	**antibody titre above locally validated threshold**
immunofluorescent antibody test • Used for chronic-phase disease. • No single assay has sufficient sensitivity and specificity to be relied on alone. At least two subsequent tests based on different methods or antigens must be used in association, to increase the accuracy of the laboratory diagnosis. • In cases of discordant results, a third assay may be used to confirm the diagnosis.[34]	**antibody titre above locally validated threshold**

Test	Result
indirect haemagglutination antibody test • Diagnostic option for chronic-phase disease. • No single assay has sufficient sensitivity and specificity to be relied on alone. At least two subsequent tests based on different methods or antigens must be used in association, to increase the accuracy of the laboratory diagnosis. • In cases of discordant results, a third assay may be used to confirm the diagnosis.[34]	**antibody titre above locally validated threshold**
chemiluminescence • Diagnostic option for chronic-phase disease. No single assay has sufficient sensitivity and specificity to be relied on alone. At least two subsequent tests based on different methods or antigens must be used in association, to increase the accuracy of the laboratory diagnosis.[143] • In cases of discordant results, a third assay may be used to confirm the diagnosis.	**antibody titre above locally validated threshold**
radio-immunoprecipitation assay • Serological screening option in the US to confirm reactive blood screening tests. Also used in the diagnosis of chronic-phase disease. No single assay has sufficient sensitivity and specificity to be relied on alone. At least two subsequent tests based on different methods or antigens must be used in association, to increase the accuracy of the laboratory diagnosis.[143] • In cases of discordant results, a third assay may be used to confirm the diagnosis.	**antibody titre above locally validated threshold**
western blot • Cross-reactivity between *T. cruzi* and Leishmania species in the serodiagnosis of Chagas disease is well known. Western blot assay, prepared with *T. cruzi* trypomastigote excreted-secreted antigens, is used as a reference test.[144] [145]	**positive for *Trypanosoma cruzi***
polymerase chain reaction (PCR) • PCR, when available, is a highly sensitive test in acute infection, and may show rising parasite loads before the parasites are detectable by microscopy. It is not recommended for diagnosis of chronic disease, but may be used for early detection of reactivation in immunocompromised patients.[2]	**evidence of *Trypanosoma cruzi* DNA**
urinalysis • In acute Chagas disease, urine sediment examination is useful to assess renal function.	**active sediment**
serum or urine beta-hCG • Pregnancy status determines the selection of antiparasitic drugs. All women of childbearing age should be tested prior to treatment.	**positive or negative**
ECG with a 30-second lead II rhythm strip • Acute-phase disease: sinus tachycardia, low QRS voltage, prolonged PR and/or QT intervals, and primary alterations of the T wave are common abnormalities. Ventricular extrasystoles, atrial fibrillation, or complete right bundle branch block may indicate a fatal outcome. • Chronic-phase disease: conduction disorders (especially right bundle branch block associated with left-anterior hemiblock), sinus bradycardia, primary and non-specific repolarisation alterations, Q	**abnormal**

Test	Result
waves, atrioventricular block, low QRS voltage, ventricular premature beats, and atrial fibrillation are common. • ECG normalises in some months with specific treatment or with disease progression, and may be normal for many years in the indeterminate form of the disease.[62] • In asymptomatic patients with non-specific ECG changes, further evaluation should be decided on an individual basis. • Major predictors of sudden death are ventricular dysfunction, non-sustained or sustained ventricular tachycardia on resting ECG or ambulatory monitoring, severe sinus node dysfunction, and high-degree heart block.[135] [136] [137]  *ECG with complete right bundle branch block and left anterior hemiblock* *Grupo de Estudo em Correlalacao Anatomo-Clinica, Clínica Médica, Pontificia Universidade Catolica de Campinas, Sao Paulo, Brazil; used with permission*	
chest x-ray • The cardiac area is normal in at least half of cases. Mild or moderate global increase of the cardiac area is common, as a result of cardiac involvement. The pleuro-pulmonary areas are generally clean, but pleural effusion can occur in cases of cardiac failure.	**enlargement of cardiac area, pleural effusion**

Test	Result
 *Chest x-ray: cardiomyopathy, heart enlargement* *Grupo de Estudo em Correlalacao Anatomo-Clinica, Clínica Médica, Pontificia Universidade Catolica de Campinas, Sao Paulo, Brazil; used with permission*	
barium swallow • Only indicated in cases with gastrointestinal symptoms. Following barium swallow, x-rays should be taken at 10 seconds, and at 5 and 10 minutes.[146] [147]  *Barium swallow showing dilation of oesophagus* *Grupo de Estudo em Correlalacao Anatomo-Clinica, Clínica Médica, Pontificia Universidade Catolica de Campinas, Sao Paulo, Brazil; used with permission*	**achalasia**
barium enema • Only indicated in cases with gastrointestinal symptoms.	**megacolon**

Test	Result



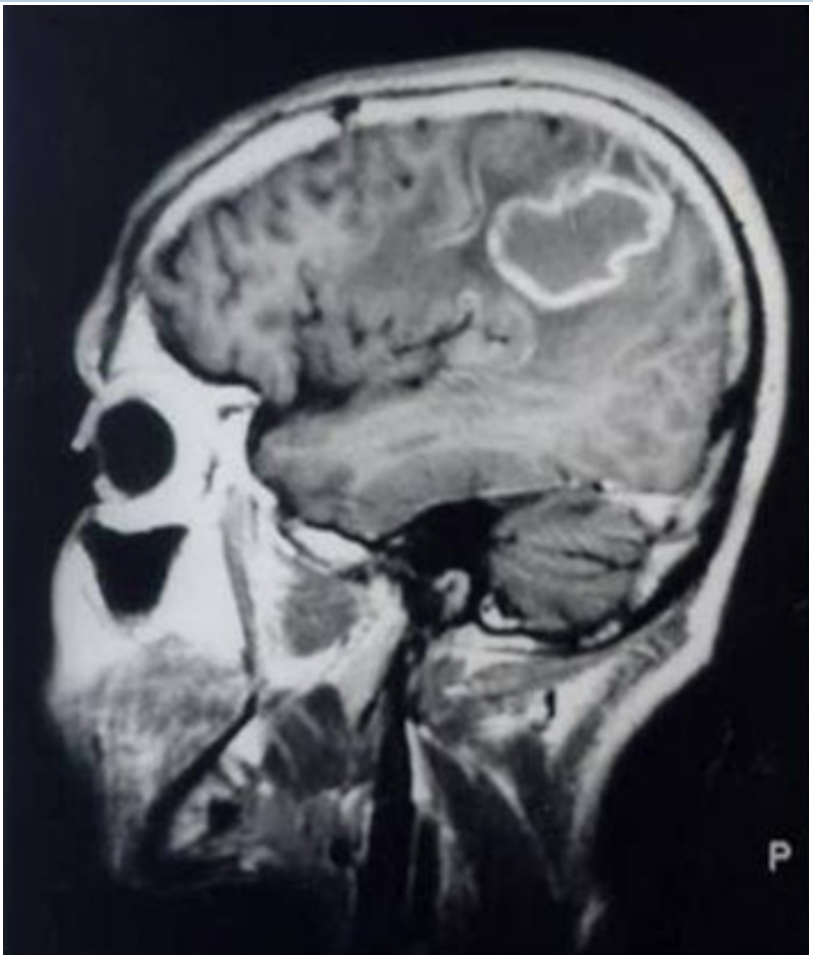
Barium enema showing excessive dilation of sigmoid colon
Grupo de Estudo em Correlalacao Anatomo-Clinica, Clínica Médica, Pontificia Universidade Catolica de Campinas, Sao Paulo, Brazil; used with permission

Other tests to consider

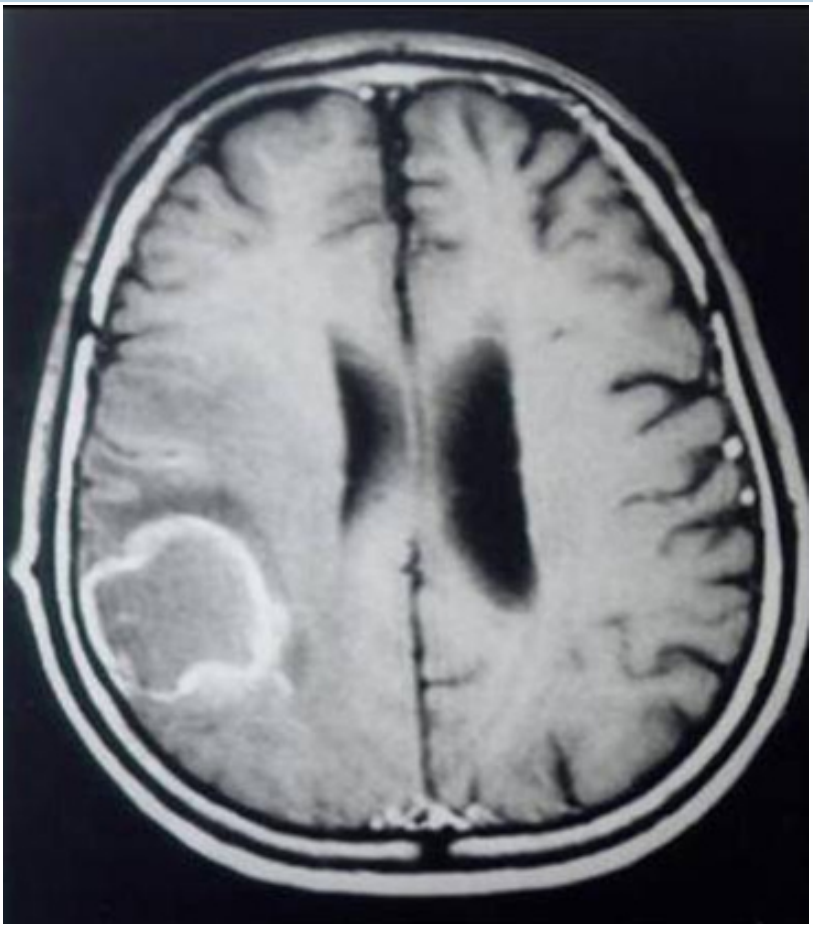
Test	Result
culture (blood and cerebrospinal fluid) • An indirect parasitological method. The sensitivity of this method is limited by the level of parasitaemia, and false negative results are common, but specificity is high. Involves the use of a specialised liquid culture medium that is not available commercially.	**epimastigote forms of *Trypanosoma cruzi***
xenodiagnosis • Indirect parasitological method. 30 to 40 laboratory-reared insects are allowed to feed directly (or indirectly) on the blood of a person suspected to have Chagas disease. After 1 month, the intestinal contents of the insects are extracted and examined microscopically for the presence of parasites. • The sensitivity of this method is limited by the level of parasitaemia, and false negative results are common, but specificity is high (up to 100%), and allows differentiation of *T. cruzi* from *T rangeli*. • Results are not available in time for short-term clinical management decisions.	**epimastigote forms of *Trypanosoma cruzi***
cerebrospinal fluid analysis • These results occur in cases of meningoencephalitis with no mass effect signs (reactivation).	**microbiological: motile trypomastigote forms of *Trypanosoma cruzi*; cytological/biochemical assay: elevated cells, normal levels of glucose and protein**
coagulation profile • Indicated in cases with hepatic failure or haemorrhagic manifestations.	**prolonged prothrombin time**
ambulatory 24-hour ECG • Patients with cardiac symptoms suggestive of arrhythmias (e.g., palpitations, presyncope, or syncope) or ECG changes consistent with heart disease must be monitored to detect arrhythmias. • Principal predictors of sudden death are indicators of ventricular dysfunction, ventricular tachycardia on resting ECG or on ambulatory monitoring, sinus node dysfunction, and high-degree heart block.[34] [148]	**bradyarrhythmias (atrioventricular block, sinoatrial block, sinus node dysfunction); tachyarrhythmias (non-sustained or sustained ventricular tachycardia, atrial fibrillation, or atrial flutter)**
exercise testing • Patients with cardiac symptoms or ECG changes consistent with heart disease must be monitored to identify exercise-induced arrhythmias and to assess functional capacity and chronotropic response. • Principal predictors of sudden death are indicators of ventricular dysfunction, ventricular tachycardia on resting ECG or on ambulatory monitoring, sinus node dysfunction, and high-degree heart block.[34] [148]	**acute phase: T wave alteration, prolonged PR interval, sinus tachycardia, low QRS voltage; chronic phase: bradycardia, sinus node dysfunction, paired ventricular tachycardia, atrial fibrillation, atrial flutter, left bundle branch block, low QRS voltage, Q waves, right bundle branch block**

Test	Result
echocardiography • Indicated in patients with clinical, radiological, or ECG evidence of functional cardiac disturbance. An important test considering the high frequency of pericardial effusion in patients with acute Chagas disease, and myocardial dysfunction in patients with chronic Chagas-related cardiomyopathy. • May show impaired biventricular function and abnormal wall motion and cardiac structures.[4] [14]	**acute phase: pericardial effusion and transitory myocardial dysfunction; chronic phase: biventricular dysfunction with diffuse or segmental pattern (more frequent), with characteristic aneurysm**
oesophageal manometry • Employed to evaluate the extent and intensity of peristalsis impairment. Detects more subtle changes, and may be indicated if results of contrast imaging are inconclusive.[149] [150] [151] [152] [153]	**impaired oesophageal motility**
upper gastrointestinal endoscopy • Used in cases with intense epigastric pain refractory to specific treatment. Also useful for investigation of haematemesis, persistent vomiting, dysphagia, or anaemia. Upper digestive endoscopy is not indicated for diagnosis of mega-oesophagus. • Patients with impaired oesophageal motility are at increased risk of reflux oesophagitis and oesophageal carcinoma, and screening for these conditions may be indicated, especially if a change of symptoms has occurred.[34]	**inflammation, bleeding**
cranial CT/MRI • Used in cases of suspected meningoencephalitis in severe acute-phase disease or reactivation disease in immunosuppressed patients. • May also be used to evaluate for cardioembolic ischaemic stroke in patients with chronic-phase disease with cardiac involvement.	**singular or multiple hypodensic pseudo tumour-like lesions (meningoencephalitis); hypodense lesions (cardioembolic ischaemic stroke)**

Test	Result



MRI brain in a patient with AIDS and reactivation of Chagas disease in CNS
Grupo de Estudos em Doenca de Chagas (GEDoCH), Departamento de Clínica Médica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Sao Paulo, Brazil; used with permission

Test	Result
 *MRI brain in a patient with AIDS and reactivation of Chagas disease in CNS* *Grupo de Estudos em Doenca de Chagas (GEDoCH), Departamento de Clínica Médica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Sao Paulo, Brazil; used with permission*	
cardiac MRI • Indicated in select patients with Chagas cardiomyopathy to assess the extent of fibrosis, if available.[2]	**fibrosis**
nuclear medicine testing • Indicated to assess biventricular function when echocardiography is inadequate if available, and when it is desirable to evaluate myocardial perfusion or sympathetic innervation.[2]	**myocardial dysfunction**
cardiac catheterisation and coronary angiography • May be required in patients with disabling, angina-like symptoms to rule out concomitant coronary artery disease. Right cardiac catheterisation must be performed in patients with advanced heart failure to assess the feasibility of cardiac transplantation.[2]	**coronary vessel anomalies**

Emerging tests

Test	Result
immunochromatography • Immunochromatography tests for Chagas disease, such as rapid diagnostic tests (RDTs) or lateral flow assays, are emerging investigations that have been developed and used for Chagas disease diagnosis.[140] • RDTs were developed as an easy-to-use alternative to conventional tests. Although they have high validity for diagnosing chronic Chagas disease, they are not yet used for this purpose.[141] RDT use is limited to diagnostic screening in the field. If the test is positive, confirmation with other serological tests is necessary.	**antibody titre above locally validated threshold**
commercial polymerase chain reaction (PCR) kits • Commercial PCR kits for the detection and quantification of *T. cruzi* in blood samples are available.[142] The kits may become a standard test for molecular diagnosis in endemic countries in the future.	**evidence of *Trypanosoma cruzi* DNA**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
CNS toxoplasmosis	• Exposure to cat faeces, consumption of undercooked or raw meat, focal neurological deficit, retinitis.	• Serum antitoxoplasma IgM and IgG: detectable with titre. • CT/MRI brain: ring-enhancing brain lesion(s), usually multiple, often involving the basal ganglia.
Non-Chagas-related cardiomyopathy	• Residence in Chagas non-endemic regions; history of infiltrative, storage, toxicity, endomyocardial, inflammatory, endocrine, cardiofacial, and neuromuscular/neurological causes; nutritional deficiencies; history of autoimmune or collagen diseases; history of electrolyte imbalance; history of cancer therapy.	• Differentiating tests vary depending on suspected underlying cause.
Toxic megacolon	• History of chronic use of drugs that could interfere with neuronal activity. Medication history of antacids (aluminium hydroxide and calcium carbonate), anticholinergics (pectin), antidiarrhoeals (casein), antiparkinsonians, antidepressives (tricyclics or lithium), antihypertensives or antiarrhythmics (calcium-channel blockers), metals (bismuth, iron, or heavy metals), opiates, laxatives, non-steroidal anti-inflammatory drugs, or sympathomimetics (pseudo-ephedrine).	• Microscopy: abnormalities vary depending on suspected underlying cause.
Non-toxic/non-Chagas megacolon	• History of schistosomiasis, lymphogranuloma venereum, Parkinson's disease, myotonic dystrophy, Fabry's disease (glycolipid accumulation), scleroderma, severe hypothyroidism, or amyloidosis.	• Microscopy: abnormalities vary depending on suspected underlying cause.

Condition	Differentiating signs / symptoms	Differentiating tests
Typhoid fever	• High fever, rose spots (blanching erythematous maculopapular lesions), history of travel to the Indian sub-continent.	• Serological and microbiological examinations (blood culture, faeces culture, bone marrow culture, urine culture, skin culture): positive for *Salmonella typhi* .
Visceral leishmaniasis	• History of travel to Mediterranean basin, Middle East, central Asia, sub-Saharan Africa (in particular, East Africa), northern India, southern Nepal, or northwest Bangladesh; high exposure to sand flies; ulcerative lesions; multiple, non-ulcerative skin nodules; skin darkening.	• FBC: pancytopenia. • Microscopic examination of spleen aspiration, bone marrow aspirate, or lymph node fluid: amastigote form of *Leishmania* species in macrophages or monocytes.
Acute intestinal schistosomiasis (Katayama fever)	• Travel to Africa, China, the Philippines, or the Caribbean; haematuria; bloody diarrhoea; genital ulcers.	• Parasitological examination of the faeces: visualisation of *Schistosoma* species eggs. • Rectal biopsy: granulomas surrounding eggs.
Infectious mononucleosis	• History of sexual activity and kissing; tender lymphadenopathy; pharyngitis.	• Heterophile antibodies: positive. • EBV-specific antibodies: positive viral capsid antigen (VCA)-IgM, VCA-IgG, early antigen (EA), Epstein-Barr nuclear antigen (EBNA).
Congenital syphilis infection	• Asymptomatic (60% to 90%). • Maternal syphilis infection; low birthweight; cutaneous lesions; periostitis; osteochondritis; pseudoparalysis; phinitis; nephrotic syndrome.	• Serology (mother and child): VDRL and FTAs positive.
Congenital toxoplasmosis	• Intellectual disability; blindness; epilepsy.	• Serology (mother and child): high toxoplasma-specific IgM and IgG antibody titre.
Hirschsprung's disease	• Mainly in young children in first year of life; vomiting; explosive passage of liquid and foul stools; delayed passage of meconium; abdominal distension.	• Rectal biopsy: absence of ganglion cells, and presence of an excess of non-myelinated nerves. • Contrast enema: contracted distal bowel and dilated proximal bowel, with demonstration of the location

Condition	Differentiating signs / symptoms	Differentiating tests
		of the transition zone in between.
Achalasia	• The most common presenting symptoms are dysphagia, regurgitation, and retrosternal pain. These can be slowly progressive over months to years.	• Upper gastrointestinal series shows a typical 'bird's beak' filling defect • Oesophageal manometry shows incomplete relaxation of the lower oesophageal sphincter.

Criteria

Introduction

There have been many attempts to define a classification system that allows patients to be placed into well-defined sub-groups in relation to prognosis; however, there has been no clear consensus on these systems, and it is important to recognise the diversity across diagnostic criteria in order to avoid a misleading diagnosis.

The nomenclature used across different classification systems is identical and uses the letters A, B, C, and D; however, the classification may refer specifically to chronic cardiac forms of the disease (as with the Brazilian consensus classification), or all patients with chronic disease, including the indeterminate form (as with the American College of Cardiology/American Heart Association, modified Los Andes, and modified Kuschnir classifications). Groups in each classification may correlate with groups in other classifications.

Chronic Chagas disease: American College of Cardiology/American Heart Association classification[2]

A: patients at risk for developing heart failure; positive serology for *Trypanosoma cruzi* ; neither structural cardiomyopathy or heart failure symptoms; normal ECG; no digestive changes (indeterminate form)

B1: patients with structural cardiomyopathy evidenced by electrocardiographic or echocardiographic changes, but with normal ventricular function and neither current or previous signs and symptoms of heart failure

B2: patients with structural cardiomyopathy characterised by global ventricular dysfunction and neither current or previous signs and symptoms of heart failure

C: patients with ventricular dysfunction and current or previous symptoms of heart failure (New York Heart Association functional class I, II, III, or IV)

D: patients with refractory symptoms of heart failure at rest despite optimised clinical treatment requiring specialised interventions.

Note: arrhythmias and conduction disease can occur from category B1 through to category D. Categories B1 to D are classified as Chagas cardiomyopathy, while categories B2 to D are also classified as Chagas dilated cardiomyopathy/heart failure.

Chagas cardiomyopathy: Brazilian consensus classification[13] [154]

Only used for patients with Chagas cardiomyopathy. Patients with the chronic indeterminate form are not present in this classification because they have an excellent prognosis, similar to people without Chagas disease.

A: abnormal ECG findings, normal echocardiogram findings, no signs of congestive heart failure (CHF)

B1: abnormal ECG findings, abnormal echocardiogram findings with left ventricular ejection fraction (LVEF) >45%, no signs of CHF

B2: abnormal ECG findings, abnormal echocardiogram findings with LVEF <45%, no signs of CHF

C: abnormal ECG findings, abnormal echocardiogram findings, compensated CHF

D: abnormal ECG findings, abnormal echocardiogram findings, refractory CHF.

Chagas cardiomyopathy: modified Los Andes classification[155]

In this system, group IA represents patients with the chronic indeterminate form of the disease. This classification differs to the others in that it contains a sub-group of patients with normal ECG, but with minimal changes in the echocardiogram. There is considerable overlapping of prognosis between some groups.

IA: normal ECG findings, normal echocardiogram findings, no signs of CHF

IB: normal ECG findings, abnormal echocardiogram findings, no signs of CHF

II: abnormal ECG findings, abnormal echocardiogram findings, no signs of CHF

III: abnormal ECG findings, abnormal echocardiogram findings, CHF.

Chronic Chagas disease: modified Kuschnir classification[156]

Similar to the American College of Cardiology/American Heart Association classification. An important limitation is the evaluation of heart size based on chest radiography, rather than echocardiogram.

0: normal ECG findings and normal heart size (usually based on chest radiography)

I: abnormal ECG findings and normal heart size (usually based on chest radiography)

II: left ventricular enlargement

III: congestive heart failure.

Screening

High-risk population screening

Screening asymptomatic people for *Trypanosoma cruzi* infection is a key strategy for Chagas disease control in many endemic countries and high-risk populations.[12][29] [33] [54] Conventional serological tests (parasite lysate enzyme-linked immunosorbent assays [ELISAs] or recombinant antigens, and immunofluorescent antibody [IFA] tests) are used for screening individuals with recognised risk (i.e., those living in endemic areas, travellers, immigrants).

In the US, screening is recommended in patients who were born in Latin America, who have spent >6 months in a rural area of Latin America, and/or who report exposure to triatomines.[33] In total, there are four commercial immunoassays available for clinical use: 3 ELISAs (Wiener Chagatest ELISA recombinante, Hemagen ELISA, and Ortho *T. cruzi* ELISA) and one rapid assay (InBios Chagas Detect Plus).[127]

Screening of blood and organ donors

Blood donors are screened by parasite lysate ELISA tests (sensitivity of 100% in patients with Chagas disease and a specificity of 99.997% among blood donors), according to US Food and Drug Administration-approved labelling.[157] Considering the large number of Latin American immigrant populations in non-endemic countries, screening of transplant donors has become increasingly important, and a multidisciplinary working group has published recommendations for screening and treatment of Chagas disease in organ transplant recipients.[158]

Familial screening

Family members of patients with similar histories of possible parasite exposure in endemic settings should be tested. Children of infected women should also be tested.

Antenatal screening

Mothers with recognised risk are screened using conventional serological tests (parasite lysate ELISA, or recombinant antigens and immunofluorescent antibody). Serological tests remain positive in the offspring for 6-9 months after birth.

Approach

Although there are differences regarding the cure rates in the treatment of Chagas disease, there is consensus about the utility of treatment, depending on several factors, such as the clinical phase and form of Chagas disease, age of the patient, and other associated clinical conditions.[34] [159] [160] Despite the public health importance of Chagas disease, few rigorous clinical trials have been conducted. The objectives of the clinical treatment for *Trypanosoma cruzi* infection are to eliminate the parasites in the human hosts with antiparasitic treatment, and to manage the clinical syndrome that results from the irreversible lesions associated with the disease. Surgical interventions may be necessary for the management of Chagas disease complications, mostly in advanced-stage disease (e.g., mega-oesophagus, volvulus, or cardiac function failure).

The phase of *T. cruzi* infection will determine the type of consultations (family medicine, internal medicine, infectious diseases, cardiology and cardiac surgery, gastroenterology, or general surgery) required. In all cases, a multi-professional approach is needed.

Antiparasitic treatment: general principles

Antiparasitic drugs should be given as soon as possible after infection in order to achieve the best chance of cure.[127] At present, there are only two antiparasitic drugs available with established efficacy for the treatment of Chagas disease: benznidazole and nifurtimox.[34] [131] [161] [162] [163] The same treatments are recommended in patients with HIV.[7] Benznidazole is recommended as the first-line treatment as it is more widely available, is better tolerated, and has more efficacy data available. Nifurtimox may be used if the patient is unable to tolerate benznidazole, or if it is not available.[2] [127]

Adverse effects are common with both drugs and tend to be more frequent and severe with increasing age. Benznidazole is associated with allergic dermatitis, peripheral neuropathy, weight loss, and insomnia. Leukopenia can occur; therefore, a complete blood count is recommended approximately 21 days after starting treatment. Mild-to-moderate dermatitis can be controlled with the use of an oral corticosteroid. Nifurtimox is associated with polyneuropathy, nausea/vomiting, headache, dizziness/vertigo, and weight loss.[2] [CDC: Chagas disease: antiparasitic treatment] (https://www.cdc.gov/parasites/chagas/health_professionals/tx.html) Treatment may need to be stopped temporarily and re-introduced, stopped permanently, or the dose reduced and then uptitrated according to tolerance if the patient reports adverse effects, depending on the severity of the effects.

Antiparasitic drugs are not recommended in pregnancy or in patients with severe renal or hepatic impairment; however, they may be used after birth or if the hepatic/renal impairment is corrected. A negative pregnancy test result is required before starting treatment in women of childbearing potential.[2] Breastfeeding is generally not contraindicated in women with chronic disease; however, it is not recommended in the acute phase or reactivated disease, or if the mother has perimamillar fissures or bleeding mamillae.[164]

Availability of these drugs varies across different countries and a local formulary should be consulted. In the US, benznidazole is approved for use in children 2-12 years of age and is commercially available from the manufacturer after completing a fast access order. [Exeltis: benznidazole tablets] (https://www.benznidazoletablets.com/en) Nifurtimox is now also commercially available in the US, and no longer needs to be obtained from the US Centers for Disease Control and Prevention (CDC).[165] In other countries, the drugs are available from local health regulatory agencies such as the World Health Organization.[166]

Antiparasitic treatment: indications for treatment

Parasite elimination and cure is achieved in 60% to 90% of patients with acute infection, and more than 90% of infants treated during the first year of life achieve cure.[2] According to recent studies, the cure rate for the aetiological treatment of acute Chagas disease is lower in cases of oral transmission with contaminated food compared to traditional vector transmission.[167] Therefore, antiparasitic treatment is indicated in the following patient groups once the diagnosis has been confirmed, provided there are no contraindications:[2] [127] [168]

- Acute phase of infection (regardless of mode of transmission)
- Infants with congenital infection
- Women of childbearing age (to prevent vertical transmission)
- All cases of reactivation in immunocompromised patients
- Accidental high-risk contaminations (e.g., contact with living parasites or cultures through skin breaks or mucosal membranes in laboratory/clinical/necroscopy settings).

Treatment is not recommended in low-risk exposures (e.g., contact with the blood of a chronically infected patient); however, serological monitoring is recommended. Monitoring is also recommended in patients with high-risk exposures who cannot take antiparasitic drugs.

The role of antiparasitic therapy in the chronic phase of disease is less certain.[127]

- Paediatric patients: treatment is recommended in all paediatric patients <18 years of age.[2] [159] [169]
- Adults: treatment may be considered in patients >18 years of age with indeterminate disease (i.e., positive serology with no evidence of end-organ damage), mild-to-moderate cardiomyopathy (i.e., without congestive cardiac failure), and gastrointestinal disease.[2] [34] [170] [171] [172] The CDC strongly recommend treatment in adults ≤50 years of age who do not have advanced Chagas cardiomyopathy, but due to the increased risk of drug toxicity they only recommend treatment in adults >50 years after weighing the risks and benefits of treatment, taking into consideration factors such as age, clinical status, overall health, and patient preference. [CDC: Chagas disease: antiparasitic treatment] (https://www.cdc.gov/parasites/chagas/health_professionals/tx.html)
- Women of childbearing potential: treatment should generally be offered (once pregnancy has been excluded) in order to reduce the risk of vertical transmission.[173]

In a study with long-term follow-up, benznidazole was associated with reduced occurrence of progression from the indeterminate form to the cardiac form and was also linked to a decreased risk of cardiovascular events, compared with no treatment.[174] However, data show that treatment is unlikely to change clinical outcomes in patients with established cardiac disease.[127] [175] Therefore, antiparasitic treatment is not recommended in patients with established dilated cardiomyopathy. It is also not recommended in patients with advanced gastrointestinal disease (e.g., mega-oesophagus or megacolon).[34]

There is insufficient evidence to support the efficacy of both benznidazole and nifurtimox for late-stage symptomatic disease.[176]

Supportive treatment

Supportive therapy is indicated for all patients with acute, chronic, or reactivated forms of the disease. Supportive therapy is the only treatment indicated in patients who cannot take antiparasitic treatment (e.g., pregnant and breastfeeding women, severe hepatic/renal insufficiency) or in those with advanced disease.

Patients with cardiac manifestations require obesity correction and maintenance at optimal weight, control of salt consumption, water intake restriction (for the most severe cases), elimination of complicating factors, avoidance of alcohol, individualised physical activity programme (in accordance with cardiopathy grade and patient age), influenza and pneumococcal vaccination (if cardiopathy is advanced). It may be necessary to limit professional, school, or sport activities.

Patients with oesophageal manifestations should be advised to chew food well; ingest liquid and semi-solid food if necessary; avoid food consumption before sleep; and avoid ingestion of tablets at night. Patients with colonic manifestations require habitual diet; restriction of constipating foods (e.g., banana, guava, jaboticaba); abundant ingestion of water (≥2 L/day if there is no heart failure); increased ingestion of food that favours intestinal transit (e.g., pawpaw, plum, orange, high-fibre food); systematic attention to the wish to evacuate; osmotic laxatives or mineral oil (avoid administration at night, due to risk of aspiration); enemas twice a week; avoidance of constipating medications (e.g., opioids, diuretics, antidepressants, antihistamines, anticonvulsants, antacids with aluminium hydroxide) if possible.

Exercise is an important aspect of cardiovascular rehabilitation because it increases both functional capacity and quality of life; however, there are few trials regarding this subject in the literature.[177] Individualised cardiovascular rehabilitation based on simple, supervised aerobic training can be safely performed in patients with chronic Chagas disease.[178] [179] [180] [181]

Pharmacological treatment of heart failure

Recommendations for the medical management of Chagas cardiomyopathy are based on extrapolated data from other forms of heart failure, and the safety and efficacy of these drugs in patients with Chagas disease has not been established. Drugs such as ACE inhibitors or angiotensin-II receptor antagonists, beta-blockers, aldosterone receptor antagonists, diuretics, digoxin, anticoagulants, antiplatelet agents, and amiodarone are recommended depending on the presentation (e.g., heart failure, arrhythmias, stroke). Detailed discussion of the medical management of Chagas cardiomyopathy is beyond the scope of this topic.[2] One Cochrane review found very low quality evidence for the use of pharmacological interventions, such as rosuvastatin and carvedilol, in patients with Chagas disease and heart failure.[182]

Surgical intervention

Patients with cardiopathy may require pacemaker placement for atrial and ventricular rhythm disturbances; ablation procedures for tachyarrhythmias; implanted defibrillators; resection of left ventricular apical aneurysms, or heart transplant.[4][26][136] [137] [169] [183]

Patients with mega-oesophagus may require oesophagocardiomyectomy of the anterior gastro-oesophageal junction (combined with valvuloplasty) to reduce reflux in cases with no response to oesophageal dilation; laparoscopic myotomy to manage severe mega-oesophagus; or partial oesophageal resection with reconstruction by oesophagogastroplasty, in severe cases. Patients with megacolon may require the Duhamel-Haddad operation, and patients with sigmoid volvulus may require anterior sigmoidostomy with resection of the necrosed segment.[4][26] [151]

End-stage organ failure

Patients with Chagasic end-stage organ failure may require organ transplantation.[184] [185] [186] [187] [188] In these situations, the serological status of donor and receiver should be checked, as the risk of infection transmission and Chagas reactivation needs to be considered for both.[13] [90] [158] [169] [189] The surgical transplant team will be able to decide which parties require antiparasitic pharmacotherapy.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial			(summary)
accidental exposure and infection: non-pregnant without severe renal/ hepatic insufficiency			
■	**high risk**	**1st**	**antiparasitic treatment**
■	**low risk**	**1st**	**serological monitoring**
accidental exposure and infection: pregnant or with severe renal/hepatic disease			
		1st	**serological monitoring**

Acute (summary)

acute infection		
non-pregnant without severe renal/hepatic insufficiency	**1st**	**antiparasitic treatment**
	plus	**supportive therapy**
	adjunct	**medical management of cardiac disease and/or surgical intervention**
pregnant or with severe renal/hepatic insufficiency	**1st**	**supportive therapy**
	adjunct	**medical management of cardiac disease and/or surgical intervention**
reactivated disease		
non-pregnant without severe renal/hepatic insufficiency	**1st**	**antiparasitic treatment**
	plus	**supportive therapy**
	adjunct	**medical management of cardiac disease and/or surgical intervention**
pregnant or with severe renal/hepatic insufficiency	**1st**	**supportive therapy**
	adjunct	**medical management of cardiac disease and/or surgical intervention**

Ongoing		(summary)
chronic infection: indeterminate disease or mild to moderate symptoms: children		
	1st	antiparasitic treatment
	plus	supportive therapy
chronic infection: indeterminate disease or mild to moderate symptoms: adults		
	1st	antiparasitic treatment
	plus	supportive therapy
	adjunct	medical management of cardiac disease and/or surgical intervention
chronic infection: advanced disease: children and adults		
	1st	supportive therapy
	adjunct	medical management of cardiac disease and/or surgical intervention
end-stage organ failure		
	1st	organ transplantation

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial

accidental exposure and infection: non-pregnant without severe renal/ hepatic insufficiency

high risk — **1st** — **antiparasitic treatment**

Primary options

» benznidazole: children <2 years of age: consult specialist for guidance on dose; children 2-12 years of age: 5-8 mg/kg/day orally given in 2 divided doses; children >12 years of age and adults: 5-7 mg/kg/day orally given in 2 divided doses

Secondary options

» nifurtimox: children <1 year of age: consult specialist for guidance on dose; children 1-10 years of age: 15-20 mg/kg/day orally given in 3-4 divided doses; children 11-16 years of age: 12.5 to 15 mg/kg/day orally given in 3-4 divided doses; children ≥17 years of age and adults: 8-10 mg/kg/day orally given in 3-4 divided doses

» Recommended in all patients with accidental high-risk contaminations (e.g., contact with living parasites or cultures through skin breaks or mucosal membranes in laboratory/clinical/ necroscopy settings).[2]

» Benznidazole is the recommended first-line treatment as it is more widely available, is better tolerated, and has more efficacy data. Nifurtimox is an alternative option.[2]

» Both drugs are contraindicated in pregnancy and severe hepatic/renal impairment. A negative pregnancy test is required before starting treatment in women of childbearing potential.

» Adverse effects are more frequent and severe with increasing age and include: allergic dermatitis, peripheral neuropathy, weight loss, insomnia, leukopenia (benznidazole); polyneuropathy, nausea/vomiting, headache, dizziness/vertigo, and weight loss (nifurtimox). A complete blood count is recommended 21 days after starting treatment with benznidazole to monitor for leukopenia.[2]

Initial

		[CDC: Chagas disease: antiparasitic treatment] (https://www.cdc.gov/parasites/chagas/health_professionals/tx.html) » Availability varies across countries. In the US, benznidazole is approved in children 2 to 12 years of age and is available here: [Exeltis: benznidazole tablets] (https://www.benznidazoletablets.com/en) Nifurtimox is now also commercially available in the US, and no longer needs to be obtained from the US Centers for Disease Control and Prevention.[165] In other countries, the drugs are available from local health regulatory agencies such as the World Health Organization.[166] » Treatment course: 60 days (benznidazole); 60-90 days (nifurtimox).
low risk	**1st**	**serological monitoring** » Antiparasitic treatment is not recommended in low-risk exposures (e.g., contact with the blood of a chronically infected patient); however, serological monitoring is recommended.
accidental exposure and infection: pregnant or with severe renal/hepatic disease		
	1st	**serological monitoring** » Antiparasitic therapy is contraindicated in pregnant women or patients with severe hepatic/renal impairment. Therefore, serological monitoring is recommended in these patients, regardless of exposure risk. Antiparasitic treatment may be started in pregnant women after birth, or in patients with severe hepatic/renal impairment if their organ function improves.

Acute

acute infection

non-pregnant without severe renal/hepatic insufficiency

1st **antiparasitic treatment**

Primary options

» benznidazole: children <2 years of age: consult specialist for guidance on dose; children 2-12 years of age: 5-8 mg/kg/day orally given in 2 divided doses; children >12 years of age and adults: 5-7 mg/kg/day orally given in 2 divided doses

Secondary options

» nifurtimox: children <1 year of age: consult specialist for guidance on dose; children 1-10 years of age: 15-20 mg/kg/day orally given in 3-4 divided doses; children 11-16 years of age: 12.5 to 15 mg/kg/day orally given in 3-4 divided doses; children ≥17 years of age and adults: 8-10 mg/kg/day orally given in 3-4 divided doses

» Recommended in all patients with acute phase of infection (including congenital infection), regardless of mode of transmission.[2]

» Benznidazole is the recommended first-line treatment as it is more widely available, is better tolerated, and has more efficacy data. Nifurtimox is an alternative option.[2]

» Both drugs are contraindicated in pregnancy and severe hepatic/renal impairment. A negative pregnancy test is required before starting treatment in women of childbearing potential.

» Adverse effects are more frequent and severe with increasing age and include: allergic dermatitis, peripheral neuropathy, weight loss, insomnia, leukopenia (benznidazole); polyneuropathy, nausea/vomiting, headache, dizziness/vertigo, and weight loss (nifurtimox). A complete blood count is recommended 21 days after starting treatment with benznidazole to monitor for leukopenia.[2] [CDC: Chagas disease: antiparasitic treatment] (https://www.cdc.gov/parasites/chagas/health_professionals/tx.html)

» Availability varies across countries. In the US, benznidazole is approved in children 2 to 12 years of age and is available here: [Exeltis: benznidazole tablets] (https://www.benznidazoletablets.com/en) Nifurtimox is now also commercially available in the

Acute

US, and no longer needs to be obtained from the US Centers for Disease Control and Prevention.[165] In other countries, the drugs are available from local health regulatory agencies such as the World Health Organization.[166]

» Treatment course: 60 days (benznidazole); 60-90 days (nifurtimox).

plus **supportive therapy**

Treatment recommended for ALL patients in selected patient group

» Supportive treatment should be targeted at the presenting symptoms.

» Cardiac manifestations may be treated with weight control; salt intake control; water intake control; alcohol avoidance; influenza/pneumococcal vaccination; and limiting sporting activity.

adjunct **medical management of cardiac disease and/or surgical intervention**

Treatment recommended for SOME patients in selected patient group

» Patients with cardiopathy may require pacemaker placement for atrial and ventricular rhythm disturbances; ablation procedures for tachyarrhythmias; implanted defibrillators; or resection of left ventricular apical aneurysms (not defined).[4][26][136] [137] [169] [183] Drugs such as ACE inhibitors or angiotensin-II receptor antagonists, beta-blockers, aldosterone receptor antagonists, diuretics, digoxin, anticoagulants, antiplatelet agents, and amiodarone are recommended depending on the presentation (e.g., heart failure, arrhythmias, stroke).[2]

pregnant or with severe renal/hepatic insufficiency

1st **supportive therapy**

» Supportive treatment should be targeted at the presenting symptoms.

» Cardiac manifestations may be treated with weight control; salt intake control; water intake control; alcohol avoidance; influenza/pneumococcal vaccination; and limiting sporting activity.

» Breastfeeding is not recommended in mothers in the acute phase of the disease.[164]

adjunct **medical management of cardiac disease and/or surgical intervention**

Treatment recommended for SOME patients in selected patient group

Acute

» Patients with cardiopathy may require pacemaker placement for atrial and ventricular rhythm disturbances; ablation procedures for tachyarrhythmias; implanted defibrillators; or resection of left ventricular apical aneurysms.[4] [26][136] [137] [169] [183] Drugs such as ACE inhibitors or angiotensin-II receptor antagonists, beta-blockers, aldosterone receptor antagonists, diuretics, digoxin, anticoagulants, antiplatelet agents, and amiodarone are recommended depending on the presentation (e.g., heart failure, arrhythmias, stroke).[2]

reactivated disease

non-pregnant without severe renal/hepatic insufficiency

1st

antiparasitic treatment

Primary options

» benznidazole: children <2 years of age: consult specialist for guidance on dose; children 2-12 years of age: 5-8 mg/kg/day orally given in 2 divided doses; children >12 years of age and adults: 5-7 mg/kg/day orally given in 2 divided doses

Secondary options

» nifurtimox: children <1 year of age: consult specialist for guidance on dose; children 1-10 years of age: 15-20 mg/kg/day orally given in 3-4 divided doses; children 11-16 years of age: 12.5 to 15 mg/kg/day orally given in 3-4 divided doses; children ≥17 years of age and adults: 8-10 mg/kg/day orally given in 3-4 divided doses

» Recommended in all patients with disease reactivation.[2] Reactivation risk varies considerably, depending on the degree of immunosuppression.[88] [96] [190]

» Benznidazole is the recommended first-line treatment as it is more widely available, is better tolerated, and has more efficacy data. Nifurtimox is an alternative option.[2]

» Both drugs are contraindicated in pregnancy and severe hepatic/renal impairment. A negative pregnancy test is required before starting treatment in women of childbearing potential.

» Adverse effects are more frequent and severe with increasing age and include: allergic dermatitis, peripheral neuropathy, weight loss, insomnia, leukopenia (benznidazole); polyneuropathy, nausea/vomiting, headache, dizziness/vertigo, and weight loss (nifurtimox).

Acute

A complete blood count is recommended 21 days after starting treatment with benznidazole to monitor for leukopenia.[2] [CDC: Chagas disease: antiparasitic treatment] (https://www.cdc.gov/parasites/chagas/health_professionals/tx.html)

» Availability varies across countries. In the US, benznidazole is approved in children 2 to 12 years of age and is available here: [Exeltis: benznidazole tablets] (https://www.benznidazoletablets.com/en) Nifurtimox is now also commercially available in the US, and no longer needs to be obtained from the US Centers for Disease Control and Prevention.[165] In other countries, the drugs are available from local health regulatory agencies such as the World Health Organization.[166]

» Treatment course: 60 days (benznidazole); 60-90 days (nifurtimox).

plus **supportive therapy**

Treatment recommended for ALL patients in selected patient group

» Supportive treatment should be targeted at the presenting symptoms.

» Cardiac manifestations: weight control; salt intake control; water intake control; alcohol avoidance; influenza/pneumococcal vaccination; and limiting sporting activity.

» Oesophageal manifestations: advise to chew food well and consume liquid or semi-solid food; avoid eating food or taking tablets before sleep.

» Colonic manifestations: dietary advice (avoid constipating foods, drink plenty of water, consume high-fibre foods to speed up transit times); advise to defecate regularly and use osmotic laxatives, mineral oil, or enemas if necessary; advise avoidance of constipating medications if possible.

adjunct **medical management of cardiac disease and/or surgical intervention**

Treatment recommended for SOME patients in selected patient group

» Patients with cardiopathy may require pacemaker placement for atrial and ventricular rhythm disturbances; ablation procedures for tachyarrhythmias; implanted defibrillators; or resection of left ventricular apical aneurysms.[4] [26][136] [137] [169] [183] Drugs such as ACE inhibitors or angiotensin-II receptor antagonists, beta-blockers, aldosterone receptor antagonists,

Acute

diuretics, digoxin, anticoagulants, antiplatelet agents, and amiodarone are recommended depending on the presentation (e.g., heart failure, arrhythmias, stroke).[2]

» Patients with mega-oesophagus may require oesophagocardiomyectomy of the anterior gastro-oesophageal junction (combined with valvuloplasty), to reduce reflux in cases with no response to oesophageal dilation; laparoscopic myotomy, to manage severe mega-oesophagus; or partial oesophageal resection with reconstruction by oesophagogastroplasty, in severe cases.[4][26] [151]

» Patients with megacolon may require the Duhamel-Haddad operation, and patients with sigmoid volvulus may require anterior sigmoidostomy with resection of the necrosed segment.[4][26]

pregnant or with severe renal/hepatic insufficiency

1st **supportive therapy**

» Supportive treatment should be targeted at the presenting symptoms.

» Cardiac manifestations: weight control; salt intake control; water intake control; alcohol avoidance; influenza/pneumococcal vaccination; and limiting sporting activity.

» Oesophageal manifestations: advise to chew food well and consume liquid or semi-solid food; avoid eating food or taking tablets before sleep.

» Colonic manifestations: dietary advice (avoid constipating foods, drink plenty of water, consume high-fibre foods to speed up transit times); advise to defecate regularly and use osmotic laxatives, mineral oil, or enemas if necessary; advise avoidance of constipating medications if possible.

» Pregnancy is rare in this group of patients. Clinical monitoring is indicated, and maternal immune status should be improved. High levels of parasitaemia, as found in HIV-infected patients, may favour higher rates of vertical transmission of Chagas disease. Ideally, children born to HIV-infected mothers should not be breastfed. Antiparasitic drugs should be withheld until after the birth, or until the renal/hepatic impairment has improved.

adjunct **medical management of cardiac disease and/or surgical intervention**

Treatment recommended for SOME patients in selected patient group

Acute

» Patients with cardiopathy may require pacemaker placement for atrial and ventricular rhythm disturbances; ablation procedures for tachyarrhythmias; implanted defibrillators; or resection of left ventricular apical aneurysms (not defined).[4][26][136] [137] [169] [183]
Drugs such as ACE inhibitors or angiotensin-II receptor antagonists, beta-blockers, aldosterone receptor antagonists, diuretics, digoxin, anticoagulants, antiplatelet agents, and amiodarone are recommended depending on the presentation (e.g., heart failure, arrhythmias, stroke).[2]

» Patients with mega-oesophagus may require oesophagocardiomyectomy of the anterior gastro-oesophageal junction (combined with valvuloplasty), to reduce reflux in cases with no response to oesophageal dilation; laparoscopic myotomy, to manage severe mega-oesophagus; or partial oesophageal resection with reconstruction by oesophagogastroplasty, in severe cases.[4][26] [151]

» Patients with megacolon may require the Duhamel-Haddad operation, and patients with sigmoid volvulus may require anterior sigmoidostomy with resection of the necrosed segment.[4][26]

Ongoing

chronic infection: indeterminate disease or mild to moderate symptoms: children

1st antiparasitic treatment

Primary options

» benznidazole: children <2 years of age: consult specialist for guidance on dose; children 2-12 years of age: 5-8 mg/kg/day orally given in 2 divided doses; children >12 years of age: 5-7 mg/kg/day orally given in 2 divided doses

Secondary options

» nifurtimox: children <1 year of age: consult specialist for guidance on dose; children 1-10 years of age: 15-20 mg/kg/day orally given in 3-4 divided doses; children 11-16 years of age: 12.5 to 15 mg/kg/day orally given in 3-4 divided doses; children ≥17 years of age: 8-10 mg/kg/day orally given in 3-4 divided doses

» Treatment is recommended all paediatric patients <18 years of age.[2][159] [169]

» Benznidazole is the recommended first-line treatment as it is more widely available, is better tolerated, and has more efficacy data. Nifurtimox is an alternative option.[2]

» Both drugs are contraindicated in pregnancy and severe hepatic/renal impairment. A negative pregnancy test is required before starting treatment in women of childbearing potential.

» Adverse effects are more frequent and severe with increasing age and include: allergic dermatitis, peripheral neuropathy, weight loss, insomnia, leukopenia (benznidazole); polyneuropathy, nausea/vomiting, headache, dizziness/vertigo, and weight loss (nifurtimox). A complete blood count is recommended 21 days after starting treatment with benznidazole to monitor for leukopenia.[2] [CDC: Chagas disease: antiparasitic treatment] (https://www.cdc.gov/parasites/chagas/health_professionals/tx.html)

» Availability varies across countries. In the US, benznidazole is approved in children 2 to 12 years of age and is available here: [Exeltis: benznidazole tablets] (https://www.benznidazoletablets.com/en) Nifurtimox is now also commercially available in the

Ongoing

US, and no longer needs to be obtained from the US Centers for Disease Control and Prevention.[165] In other countries, the drugs are available from local health regulatory agencies such as the World Health Organization.[166]

» Treatment course: 60 days (benznidazole); 60-90 days (nifurtimox).

plus **supportive therapy**

Treatment recommended for ALL patients in selected patient group

» Supportive treatment should be targeted at the presenting symptoms.

» Cardiac manifestations: weight control; salt intake control; water intake control; alcohol avoidance; influenza/pneumococcal vaccination; and limiting sporting activity.

» Oesophageal manifestations: advise to chew food well and consume liquid or semi-solid food; avoid food consumption or taking tablets before sleep.

» Colonic manifestations: dietary advice (avoid constipating foods, drink plenty of water, consume high-fibre foods to speed up transit times); advise to defecate regularly and use osmotic laxatives, mineral oil, or enemas if necessary; advise avoidance of constipating medications if possible.

chronic infection: indeterminate disease or mild to moderate symptoms: adults

1st **antiparasitic treatment**

Primary options

» benznidazole: adults: 5-7 mg/kg/day orally given in 2 divided doses

OR

» nifurtimox: adults: 8-10 mg/kg/day orally given in 3-4 divided doses

» Treatment may be considered in patients >18 years of age with indeterminate disease (i.e., positive serology with no evidence of end-organ damage), mild-to-moderate cardiomyopathy (i.e., without congestive cardiac failure), and gastrointestinal disease.[2] [34] [170] [171] [172]

» The US Centers for Disease Control and Prevention (CDC) strongly recommend treatment

Ongoing

in adults ≤50 years of age who do not have advanced Chagas cardiomyopathy. Due to the increased risk of drug toxicity, the CDC only recommend treatment in adults >50 years after weighing the risks and benefits of treatment, taking into consideration factors such as age, clinical status, overall health, and patient preference. [CDC: Chagas disease: antiparasitic treatment] (https://www.cdc.gov/parasites/chagas/health_professionals/tx.html)

» Benznidazole is the recommended first-line treatment as it is more widely available, is better tolerated, and has more efficacy data. Nifurtimox is an alternative option.[2]

» Both drugs are contraindicated in pregnancy and severe hepatic/renal impairment. A negative pregnancy test is required before starting treatment in women of childbearing potential.

» Adverse effects are more frequent and severe with increasing age and include: allergic dermatitis, peripheral neuropathy, weight loss, insomnia, leukopenia (benznidazole); polyneuropathy, nausea/vomiting, headache, dizziness/vertigo, and weight loss (nifurtimox). A complete blood count is recommended 21 days after starting treatment with benznidazole to monitor for leukopenia.[2] [CDC: Chagas disease: antiparasitic treatment] (https://www.cdc.gov/parasites/chagas/health_professionals/tx.html)

» Availability varies across countries. In the US, benznidazole is available here: [Exeltis: benznidazole tablets] (https://www.benznidazoletablets.com/en) Nifurtimox is now also commercially available in the US, and no longer needs to be obtained from the US Centers for Disease Control and Prevention.[165] In other countries, the drugs are available from local health regulatory agencies such as the World Health Organization.[166]

» Treatment course: 60 days (benznidazole); 60-90 days (nifurtimox).

plus **supportive therapy**

Treatment recommended for ALL patients in selected patient group

» Supportive treatment should be targeted at the presenting symptoms.

» Cardiac manifestations: weight control; salt intake control; water intake control; alcohol avoidance; influenza/pneumococcal vaccination;

MANAGEMENT

Ongoing

and limiting sporting activity. Individualised cardiovascular rehabilitation based on simple, supervised aerobic training can be safely performed in patients with chronic Chagas disease.[178] [179] [180] [181]

» Oesophageal manifestations: advise to chew food well and consume liquid or semi-solid food; avoid eating food or taking tablets before sleep.

» Colonic manifestations: dietary advice (avoid constipating foods, drink plenty of water, consume high-fibre foods to speed up transit times); advise to defecate regularly and use osmotic laxatives, mineral oil, or enemas if necessary; advise avoidance of constipating medications if possible.

adjunct **medical management of cardiac disease and/or surgical intervention**

Treatment recommended for SOME patients in selected patient group

» Patients with cardiopathy may require pacemaker placement for atrial and ventricular rhythm disturbances; ablation procedures for tachyarrhythmias; implanted defibrillators; or heart transplant.[4][26][136] [137] [169] [183] Drugs such as ACE inhibitors or angiotensin-II receptor antagonists, beta-blockers, aldosterone receptor antagonists, diuretics, digoxin, anticoagulants, antiplatelet agents, and amiodarone are recommended depending on the presentation (e.g., heart failure, arrhythmias, stroke).[2]

» Patients with mega-oesophagus may require oesophagocardiomyectomy of the anterior gastro-oesophageal junction (combined with valvuloplasty), to reduce reflux in cases with no response to oesophageal dilation; laparoscopic myotomy, to manage severe mega-oesophagus; or partial oesophageal resection with reconstruction by oesophagogastroplasty, in severe cases.[4][26] [151]

» Patients with megacolon may require the Duhamel-Haddad operation, and patients with sigmoid volvulus may require anterior sigmoidostomy with resection of the necrosed segment.[4][26]

chronic infection: advanced disease: children and adults

1st **supportive therapy**

» Antiparasitic treatment is not indicated in cases of advanced disease, such as Chagasic

Ongoing

cardiomyopathy with congestive heart failure (Kuschnir grade III), mega-oesophagus, or megacolon.[34] The focus is on supportive therapy, since regression of inflammatory and fibrotic lesions, as observed in experimental studies, has not yet been confirmed clinically.[13] [34] [157]

» Supportive treatment should be targeted at the presenting symptoms.

» Cardiac manifestations: weight control; salt intake control; water intake control; alcohol avoidance; influenza/pneumococcal vaccination; and limiting sporting activity. Individualised cardiovascular rehabilitation based on simple, supervised aerobic training can be safely performed in patients with chronic Chagas disease.[178] [179] [180] [181]

» Esophageal manifestations: advice to chew food well and consume liquid or semi-solid food; avoidance of food consumption or taking tablets before sleep.

» Colonic manifestations: dietary advice (avoid constipating foods, drink plenty of water, consume high-fibre foods to speed up transit times); advise to defecate regularly and use osmotic laxatives, mineral oil, or enemas if necessary; advise avoidance of constipating medications if possible.

adjunct **medical management of cardiac disease and/or surgical intervention**

Treatment recommended for SOME patients in selected patient group

» Patients with cardiopathy may require pacemaker placement for atrial and ventricular rhythm disturbances; ablation procedures for tachyarrhythmias; implanted defibrillators; or heart transplant.[4][26][136] [137] [169] [183] Drugs such as ACE inhibitors or angiotensin-II receptor antagonists, beta-blockers, aldosterone receptor antagonists, diuretics, digoxin, anticoagulants, antiplatelet agents, and amiodarone are recommended depending on the presentation (e.g., heart failure, arrhythmias, stroke).[2]

» Patients with mega-oesophagus may require oesophagocardiomyectomy of the anterior gastro-oesophageal junction (combined with valvuloplasty), to reduce reflux in cases with no response to oesophageal dilation; laparoscopic myotomy, to manage severe mega-oesophagus; or partial oesophageal resection

Ongoing

		with reconstruction by oesophagogastroplasty, in severe cases.[4][26] [151] » Patients with megacolon may require the Duhamel-Haddad operation, and patients with sigmoid volvulus may require anterior sigmoidostomy with resection of the necrosed segment.[4][26]
end-stage organ failure		
	1st	**organ transplantation** » Patients with Chagasic end-stage organ failure may require organ transplantation. In these situations, the serological status of donor and receiver should be checked, as the risk of infection transmission and Chagas reactivation needs to be considered for both.[13] [90] [158] [169] [189] The surgical transplant team will be able to decide which parties require antiparasitic treatment.

Emerging

Drug development for Chagas disease

Drugs that are more effective than benznidazole or nifurtimox are not likely to be available in the near future. However, trials investigating adapted dose regimens for benznidazole are underway, in order to improve compliance and decrease adverse effects while maintaining efficacy. Pharmacokinetic studies of trypanocidal drugs used in clinical practice play a vital role in comprehending the factors associated with adverse events.[191] Research on new drugs and optimised treatment regimens (including combination therapies) are lacking and should be a priority in future trials.[163] [192] [193] Recent studies show that translational research in Chagas disease, addressing drug combinations and repositioning, is an alternative in improving intolerance to benznidazole and/or nifurtimox, as well as increasing the effectiveness of these drugs.[194] The Drugs for Neglected Diseases Initiative (DNDi) is a non-profit organisation that develops new treatments for Chagas disease, as well as other global infectious diseases. [DNDi: Chagas] (http://www.dndi.org/diseases-projects/diseases/chagas.html)

Fexinidazole

One phase 2 clinical trial assessed the efficacy and safety of fexinidazole, an antiprotozoal agent targeting *Trypanosoma cruzi* , in patients with indeterminate chronic Chagas disease. The findings highlight the necessity for further research to determine the optimal dose of fexinidazole and its risk-benefit ratio. The results indicate promising potential for treatment regimens lasting less than 10 days.[195]

Isosorbide dinitrate and nifedipine

Isosorbide dinitrate and nifedipine are effective in reducing oesophageal symptoms. Isosorbide dinitrate appears to be more effective, and its use is supported by a larger number of studies; however, nifedipine appears to have a better tolerability profile.[196]

Amiodarone

Amiodarone has been widely used for the treatment of arrhythmias in Chagas disease but data are lacking to support its use in Chagas disease specifically. A systematic review found that amiodarone is effective in reducing the incidence of ventricular arrhythmias in patients with Chagas disease; however, there is no evidence for an improvement in clinically relevant outcomes such as hospitality and mortality.[197] Amiodarone is being tested in a phase III trial to see whether treatment for at least 6 months has a trypanocidal effect in patients with mild-to-moderate chronic Chagas cardiomyopathy, and whether there are any clinical benefits from this treatment.[198]

Biomarkers

Studies are ongoing to identify biomarkers which can be used to assess therapeutic accuracy and help to determine which patients are at risk of progression to chronic disease. Various biomarker types have been investigated but none have demonstrated effectiveness in assessing the therapeutic response to trypanocidal treatment.[199]

Stem cell therapy

Cell transplantation with bone marrow stem cells has been suggested as an alternative for heart transplantation in patients with chronic Chagasic cardiomyopathy.[200] [201] [202] [203] The aim of this therapy is not to kill the parasite, but to improve chronic heart disease.[204] In fact, in mice with chronic Chagas infections, bone marrow mononuclear cells from normal donors reduced cardiac inflammation and fibrosis, and prevented right ventricular dilation.[205] [206] There is limited evidence demonstrating slight improvement 6 months after autologous bone marrow cell transplantation,[207] although other studies show no such benefit.[208]

Vaccination

For decades, there have been many attempts to develop a Chagas vaccine, but in general, results have not been very promising. Development of an effective vaccine in the near future is not likely.[209] [210] There are, however, several candidate proteins of *T. cruzi* that have been considered for vaccine development (e.g., cruzipain, trans-sialidase, amastigote surface protein).[210] [211] [212] [213] [214] Studies have identified more than 30 gene fragments that may be future targets for immunisation.[215] [216] [217] [218]

Primary prevention

Despite the success of vaccines against several infectious diseases, there are no available vaccines for Chagas disease mainly due to the weak immune response of the host against *T. cruzi* and the strategies developed by the parasite to escape the host immune system.[119]

The World Health Organization has included Chagas disease in their 2021 - 2030 road map for neglected tropical diseases which lists key targets for the prevention, control, elimination, and eradication of the disease by the end of the decade.[120] Primary prevention strategies are based on the control of human population exposure to *Trypanosoma cruzi* . The complex interaction between triatomines, animal reservoirs, and human populations must be evaluated. While control of both vectorial and blood transfusion transmission of *T. cruzi* has been successful in many regions of Latin America and the US, some ecosystem approaches to control are under-utilised. These include: reservoir studies and surveillance; environmental education and surveillance; traveller orientation; and strong policies in favour of sustainable development and decreasing social inequalities. Health education of at-risk people living in endemic active areas is very important to reduce the incidence of the disease.[121] [122] [123]

Depending on the geographical area, preventative and control measures include:

- Reduction of triatomine colonies inside dwellings (e.g., by using mosquito nettings on windows)
- Residual insecticide spraying of houses and surrounding areas
- House improvements and house cleanliness to prevent vector infestation
- Use of repellents and clothes with long sleeves during activities at night in the forest (hunting, fishing, camping), as well as the use of bed nets.
- Avoiding consumption of raw homemade products and other possibly contaminated products in endemic areas; high-risk food should be pasteurised
- Screening of blood donors
- Testing of organ, tissue, or cell donors and receivers
- Screening of newborns and other children of infected mothers to provide early diagnosis and treatment.

An increased number of cases due to oral transmission have been observed, including familial micro-epidemics in Latin American countries, principally Brazil.[9] This demonstrates the need for better food safety practices in endemic regions.

As vector control has led to great advances in many endemic countries, screening of blood and organs for donation has become crucial to control transmission.[12] [29] [124] In the US, screening for *T. cruzi* in donated blood was not widely practised until 2007. Blood donations that are found to be reactive by blood screening tests are then tested using radio-immunoprecipitation assay (RIPA). This is the standard serological screening test in the US although other serological screening tests may be used in different countries. Donors who are positive in the screening test are excluded from blood donation, regardless of their RIPA results.

Sylvatic populations of triatomines represent a new challenge in vector control transmission.[48] [125] [126] Owing to ecological changes, contacts of humans and domestic animals with sylvatic populations have been increasing. A co-ordinated multi-country programme, targeting the reduction of transmission by vectors and via blood transfusion in the Southern Cone, Andean, Amazonian, and Central American countries, has succeeded in significantly reducing the transmission of Chagas disease.

Secondary prevention

Chagas disease is a reportable condition in some countries.

Primary chemoprophylaxis in uninfected people who plan to visit endemic regions is not recommended, considering the extremely low risk of the infection, and the risks of adverse events with the use of the specific treatment.

Effective approaches for eliminating vector-borne transmission of *Trypanosoma cruzi* to humans include health education for people at risk for acquiring the infection; improvement in socio-economic conditions; and triatomine control by the use of residual insecticides.

Patients must be counselled not to donate blood or solid organs. People who are diagnosed with indeterminate Chagas disease are typically identified by screening processes before these procedures.

If the patient has family members with a similar history of possible exposure to the parasite in endemic settings, they should be tested. Children of infected women should also be tested for the disease. In pregnant women or infants with acute Chagas disease, breastfeeding must be evaluated, to assess the possibility of transmission by bleeding nipple fissures. No other approaches for reducing this risk of vertical transmission have been defined. There are no sexual restrictions for patients with Chagas disease.

Laboratory personnel and researchers who work with or manipulate *T. cruzi* or infected triatomines should always take protective measures.

People who travel to endemic areas should take general measures to protect themselves from the disease.

Patient discussions

Patients with cardiac manifestations require: obesity correction and maintenance at optimal weight; control of salt consumption; water intake restriction (for the most severe cases); elimination of complicating factors; prevention of alcohol use; individualised physical activity programmes (in accordance with the cardiopathy grade and the patient age); and influenza and pneumococcal vaccination (in cases of advanced cardiopathy).

Patients with oesophageal manifestations should be advised to: chew food well; consume liquid and semi-solid food if necessary; avoid food consumption before sleep; and avoid taking tablets at night.

Patients with colonic manifestations require: habitual diet; restriction of constipating foods (e.g., banana, guava, jaboticaba); abundant ingestion of water (at least 2 L/day if there is no heart failure); increased consumption of food that favours intestinal transit (e.g., pawpaw, plum, orange, high-fibre food, other foods known to the patient that favour reflex evacuation); systematic attention to the wish to evacuate; osmotic laxatives or mineral oil (avoid administration at night due to risk of aspiration); enemas twice a week; and avoidance of constipating medications (e.g., opioids, diuretics, antidepressants, antihistamines, anticonvulsants, antacids with aluminium hydroxide) if possible.

Patients should be advised to report the following symptoms to their physicians: cutaneous erythema with pruritus; pain and paraesthesia in the plantar and palmar regions; dysgeusia; anaemia; or gastrointestinal symptoms.

Patients with indeterminate Chagas disease may carry on their normal lives, and there is no need to exclude them from work or other daily activities. This recommendation is very important to avoid stigmatisation.[72] A positive serological result for *Trypanosoma cruzi* antibodies does not require

termination of employment in most professions; however, many experts recognise it could be an issue for pilots or drivers who are responsible for transporting many people, or for people who operate heavy machinery or equipment, due to the risk of cardiac arrhythmias or sudden cardiac arrest. Generally, working does not worsen the patient's condition, regardless of the clinical form. Rarely, people with acute infection may temporarily be unable to work due to treatment.[13]

Patients should be counselled not to donate blood.

Patient fact sheets are available from the US Centers for Disease Control and Prevention and the World Health Organization:

[CDC: Parasites - American trypanosomiasis (also known as Chagas disease)] (http://www.cdc.gov/parasites/chagas)

[WHO: Chagas disease (American trypanosomiasis)] (https://www.who.int/news-room/fact-sheets/detail/chagas-disease-%28american-trypanosomiasis%29)

FOLLOW UP

Monitoring

Monitoring

Asymptomatic patients with normal ECG findings have a good prognosis, and follow-up should rely on annual history, physical examination, and ECG findings.

Full blood count (FBC) should be repeated every 2 to 3 weeks during aetiological treatment, and patients should be monitored for dermatitis beginning 9 to 10 days after initiation of treatment. Patients receiving benznidazole should be weighed and monitored for symptoms and signs of peripheral neuropathy fortnightly, especially during the second and third months of treatment.

The level of follow-up care depends mostly on the clinical condition of the patient. Patients who present with acute-phase disease require follow-up for many years.

Monitoring involves the following measures:

- At diagnosis: baseline evaluations before onset of treatment (full blood count [FBC], liver function tests [LFTs], coagulation tests, ECG, echocardiogram if indicated, and upper digestive endoscopy in case of epigastralgia)
- Days 0 to 89 of treatment: fortnightly evaluation with FBC, LFTs, coagulation tests, ECG, blood urea nitrogen, serum creatinine
- Days 60 to 90: blood culture for *Trypanosoma cruzi* , polymerase chain reaction (PCR) of buffy coated blood, serology (IgM/IgG)
- Day 90: barium contrast x-ray (oesophagus, stomach, duodenum), abdominal ultrasound
- Day 90 to month 6: monthly evaluation with FBC, ECG, echocardiogram if indicated, and chest x-ray
- Month 6: blood culture for *T. cruzi* ; PCR of buffy coated blood; barium contrast x-ray (oesophagus, stomach, duodenum); abdominal ultrasound; upper digestive endoscopy (in case of previous or recent epigastralgia); enema (in case of symptoms)
- Month 9: chest x-ray, ECG, echocardiogram, barium contrast x-ray (oesophagus, stomach, duodenum), abdominal ultrasound
- Month 12: FBC, ECG, echocardiogram, chest x-ray, serology (IgM/IgG), blood culture for *T. cruzi* , PCR of buffy coated blood, barium contrast x-ray (oesophagus, stomach, duodenum), abdominal ultrasound, upper digestive endoscopy (in cases of previous or recent epigastralgia), enema (if indicated by symptoms)
- Month 13: initiate 6-monthly ECG and chest x-ray; also 12-monthly serology (IgM/IgG), blood culture for *T. cruzi* , PCR of buffy coated blood, barium contrast x-ray (oesophagus, stomach, duodenum), abdominal ultrasound, enema (if indicated by symptoms), exercise test.

There are no clinical criteria that accurately define cure from acute Chagas disease. Using a serological criterion, cure is based on negativation of serology (in most cases, up to 5 years after treatment). The performance of conventional serological tests (IgG) is recommended every 6 months or annually, for 5 years. The follow-up can be discontinued when two successive examinations are negative.

In the offspring of Chagasic mothers, serological titres of IgG for *T. cruzi* may be positive for up to 9 months. By the 6th month, most children will have negative serology. In rare cases of persisting positive serological results, a final test after 9 months will be sufficient. If this test is positive, congenital Chagas disease is diagnosed, and the child should undergo specific treatment.[168]

Children born of mothers with acute Chagas disease, or with *T cruzi* -HIV co-infection, should be investigated thoroughly in the first two months after birth (direct parasitological methods, xenodiagnosis, blood culture).[7]

Complications

Complications	Timeframe	Likelihood
severe acute myocarditis	**short term**	**low**
Although cardiac manifestations in the acute phase of Chagas disease are common, severe cases are rare clinical events. The intense process of inflammation and cell destruction (myocytes and autonomic nervous system) causes associated pericarditis and endocarditis. In the follow-up period, diagnosis should be made promptly, and treatment started as soon as possible. Treatment should include supportive measures and specific antiparasitic treatment.		
severe acute meningoencephalitis	**short term**	**low**
Observed in neonates with congenital disease or the acute phase of Chagas disease. Occurs in association with myocarditis. Prognosis is poor. Treated with specific antiparasitic treatment and supportive measures.		
oesophageal rupture	**short term**	**low**
Occurs as a consequence of chronic gastrointestinal disease involving the oesophagus. May progress to bowel ischaemia and sepsis. Surgical treatment is required.		
aspiration pneumonia	**short term**	**low**
Occurs as a consequence of chronic gastrointestinal disease involving the oesophagus. Patients with severe mega-oesophagus who do not receive medical attention can die of malnutrition and/or of chronic aspiration pneumonitis, which is caused by regurgitation and aspiration of food, particularly during sleep.		
chronic cardiomyopathy	**long term**	**low**
Mortality is high in patients with chronic *Trypanosoma cruzi* infection due to rhythm disturbances and congestive heart failure.		
pulmonary embolism	**long term**	**low**
Frequently associated with chronic cardiopathy as a consequence of thromboembolism.		
stroke	**long term**	**low**
Frequently associated with chronic cardiopathy as a consequence of thromboembolism.		
oesophageal fistula	**long term**	**low**
Occurs as a consequence of chronic gastrointestinal disease involving the oesophagus. Surgical treatment is required.		

FOLLOW UP

Complications	Timeframe	Likelihood
erosive oesophagitis	**long term**	**low**
Occurs as a consequence of chronic gastrointestinal disease involving the oesophagus. There is an increased risk of oesophageal rupture or cancer.		
oesophageal adenocarcinoma	**long term**	**low**
Occurs as a consequence of chronic gastrointestinal disease involving the oesophagus. There is a higher occurrence in patients with Chagas disease than in the general population. Radiotherapy or chemotherapy is required.		
cachexia	**long term**	**low**
Weight loss and cachexia occurs as a consequence of severe chronic gastrointestinal disease of the oesophagus.		
sigmoid volvulus	**long term**	**low**
Occurs as a consequence of chronic gastrointestinal disease of the colon. May progress to bowel ischaemia and sepsis. Surgical treatment is required. Megacolon can result in death, usually when sigmoid volvulus occurs and is not resolved surgically.		
faecolith	**long term**	**low**
Occurs as a consequence of chronic gastrointestinal disease of the colon.		

Prognosis

The number of deaths related to Chagas disease is estimated at 10,000 to 12,500 per year.[27] [28][29] [219] There are an estimated 546,000 to 806,000 disability-adjusted life years lost.[220] [221] [222]

Antiparasitic treatment is almost 100% effective in curing the disease but only if it is administered as soon as possible after infection at the onset of the acute phase. Efficacy diminishes the longer a person has been infected. Morbidity and mortality rates in patients with oral transmission are higher than in acute cases caused by other modes of transmission.[9]

The overall prognosis among patients with the indeterminate phase is excellent.[72][127] From 10-20 years after the acute phase, the indeterminate form progresses to cardiomyopathy at an annual rate of 1.9%.[223] Patients who have experienced acute symptomatic Chagas disease but have not received trypanocidal treatment face a higher risk of developing the cardiac form, with an estimated annual progression rate of 4.6%.[2] [223]

Cardiomyopathy is the leading cause of death in patients with the cardiac form of chronic disease, due to heart failure, cardioembolic stroke, or sudden death.[4] [13] [14] [224]

The case fatality rate in patients with reactivation is high, especially if diagnosis is delayed.[6] [8] [225] Diagnosis should be made quickly, as the early administration of specific treatment increases prognosis considerably.[4][8]

The criteria for cure are based on achieving negative serology. The time to reach negative serology varies depending on the phase of disease: from 3-5 years in acute Chagas disease; about 1 year for congenital infection; 5-10 years for recent chronic-phase disease; and ≥20 years for long-term chronic-phase disease.[168] [226] In the chronic phase, a sustainable and progressive decline of serological titres (≥3 dilutions in serological titres) may occur, suggesting future negative serology. At any stage of disease evolution, positive parasitological testing indicates failure of treatment. Spontaneous cure in chronic cases of Chagas disease is usually not observed, although some cases have been registered in Costa Rica, Uruguay, and Brazil.[227] [228] [229]

Diagnostic guidelines

United Kingdom

Chagas disease: migrant health guide (https://www.gov.uk/guidance/chagas-disease-migrant-health-guide)

Published by: Public Health England **Last published:** 2021

North America

Chagas cardiomyopathy: an update of current clinical knowledge and management (https://professional.heart.org/professional/GuidelinesStatements/UCM_316885_Guidelines-Statements.jsp)

Published by: American Heart Association **Last published:** 2018

Screening and treatment of Chagas disease in organ transplant recipients in the United States (https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-6143.2011.03444.x)

Published by: Chagas in Transplant Working Group **Last published:** 2011

Evaluation and treatment of Chagas disease in the United States (https://www.cdc.gov/parasites/chagas/health_professionals/index.html)

Published by: Centers for Disease Control and Prevention **Last published:** 2019

Treatment guidelines

United Kingdom

Chagas disease: migrant health guide (https://www.gov.uk/guidance/chagas-disease-migrant-health-guide)

Published by: Public Health England **Last published:** 2021

North America

Prevention and treatment of opportunistic infections in adults and adolescents with HIV: Chagas disease (https://clinicalinfo.hiv.gov/en/guidelines)

Published by: National Institutes of Health **Last published:** 2023

Chagas cardiomyopathy: an update of current clinical knowledge and management (https://professional.heart.org/professional/GuidelinesStatements/UCM_316885_Guidelines-Statements.jsp)

Published by: American Heart Association **Last published:** 2018

CDC Yellow Book: health information for international travel - American trypanosomiasis (Chagas disease) (https://wwwnc.cdc.gov/travel/page/yellowbook-home)

Published by: Centers for Disease Control and Prevention **Last published:** 2023

Screening and treatment of Chagas disease in organ transplant recipients in the United States (https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-6143.2011.03444.x)

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Evaluation and treatment of Chagas disease in the United States (http://www.cdc.gov/parasites/chagas/health_professionals/index.html)

Published by: Centers for Disease Control and Prevention **Last published:** 2019

Latin America

Diagnosis and treatment of Chagas disease (https://iris.paho.org/handle/10665.2/49653)

Published by: Pan American Health Organization **Last published:** 2019

Online resources

1. WHO: Chagas disease (American trypanosomiasis) (https://www.who.int/news-room/fact-sheets/detail/chagas-disease-%28american-trypanosomiasis%29) *(external link)*

2. CDC: Chagas disease: antiparasitic treatment (https://www.cdc.gov/parasites/chagas/health_professionals/tx.html) *(external link)*

3. Exeltis: benznidazole tablets (https://www.benznidazoletablets.com/en) *(external link)*

4. DNDi: Chagas (http://www.dndi.org/diseases-projects/diseases/chagas.html) *(external link)*

5. CDC: Parasites - American trypanosomiasis (also known as Chagas disease) (http://www.cdc.gov/parasites/chagas) *(external link)*

Key articles

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- Dias JC, Ramos AN Jr, Gontijo ED, et al. 2 nd Brazilian Consensus on Chagas disease, 2015. Rev Soc Bras Med Trop. 2016 Dec;49Suppl 1(Suppl 1):3-60. Full text (https://www.scielo.br/j/rsbmt/a/mNgRbrGjpwwc9dSF73PdMHt/?lang=en) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27982292?tool=bestpractice.bmj.com)
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Images

Figure 1: Triatoma sanguisuga : vector species with wide distribution in the US

Cleber Galvao, PhD, Laboratório Nacional e Internacional de Referência em Taxonomia de Triatomíneos, Instituto Oswaldo Cruz, Rio de Janeiro, Brazil; used with permission

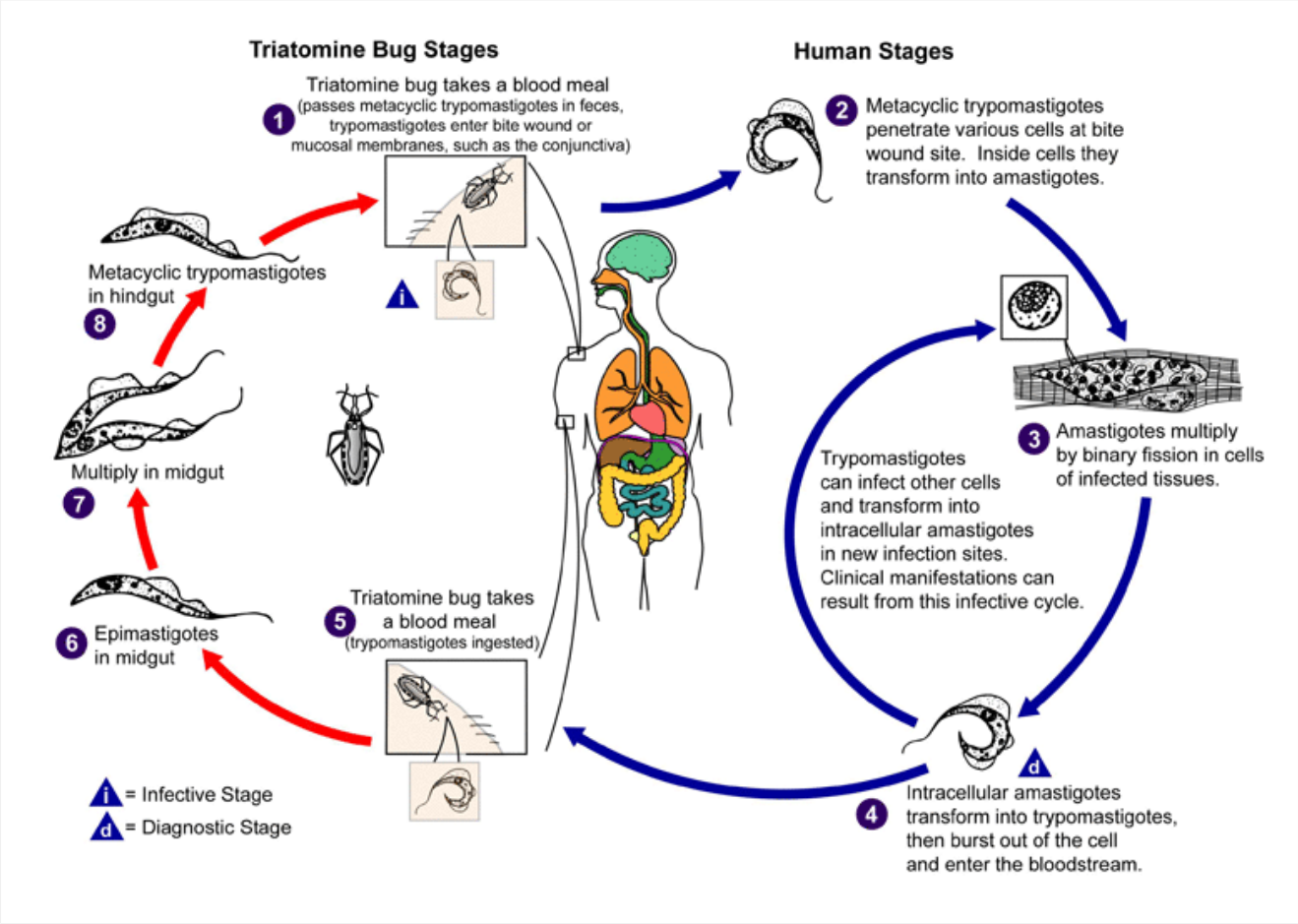

Figure 2: Life cycle of Trypanosoma cruzi , the causative parasite of Chagas disease

Centers for Disease Control and Prevention, Atlanta, GA, USA: Public Health Image Library ID # 3384 (Alexander J. da Silva, PhD/Melanie Moser, 2002)

IMAGES

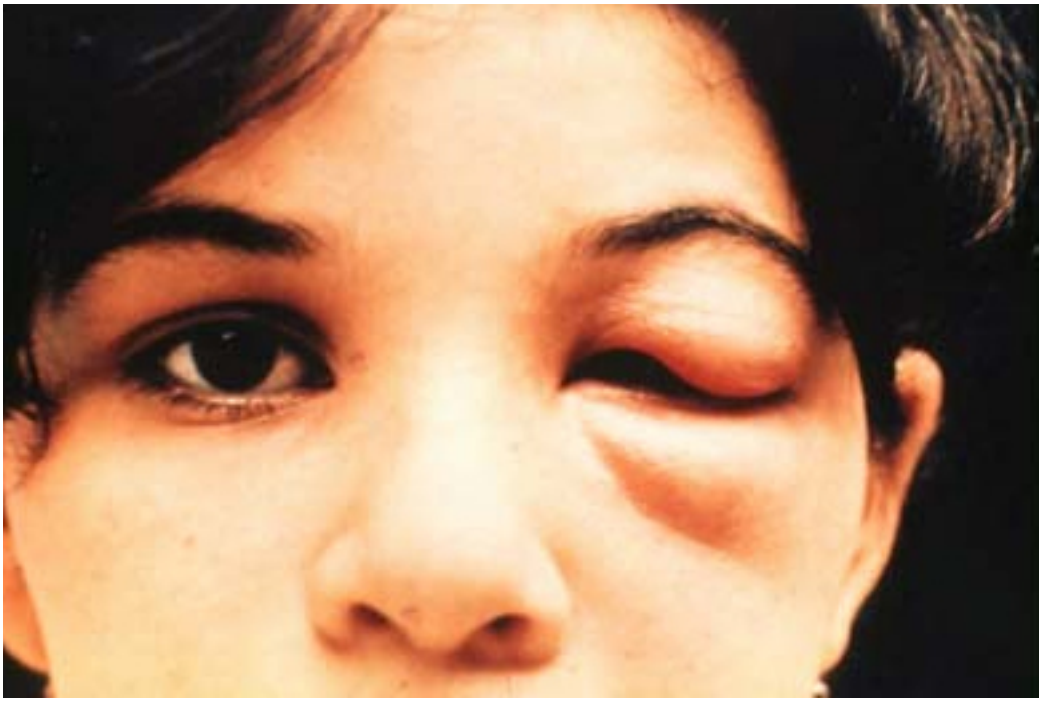

Figure 3: Child with an inoculation chagoma (Romaña's sign)

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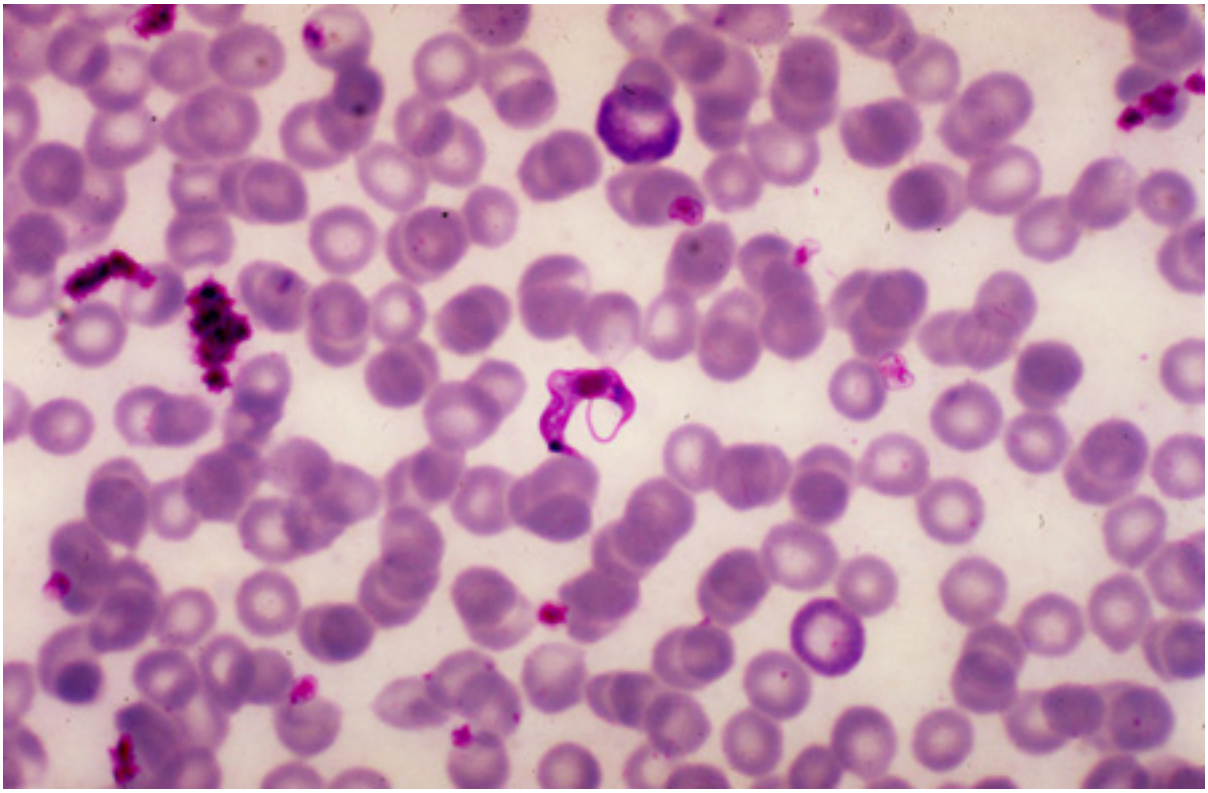

Figure 4: Trypanosoma cruzi metacyclic trypomastigotes on a peripheral blood smear prepared with Giemsa stain

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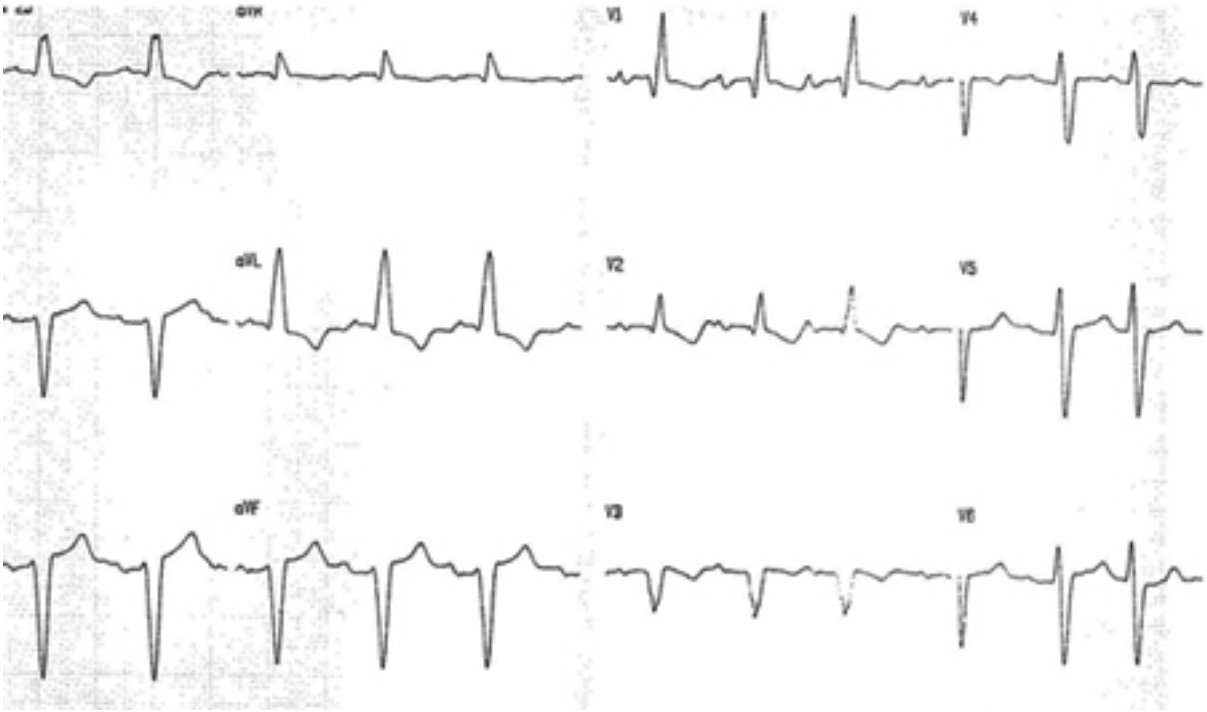

Figure 5: ECG with complete right bundle branch block and left anterior hemiblock

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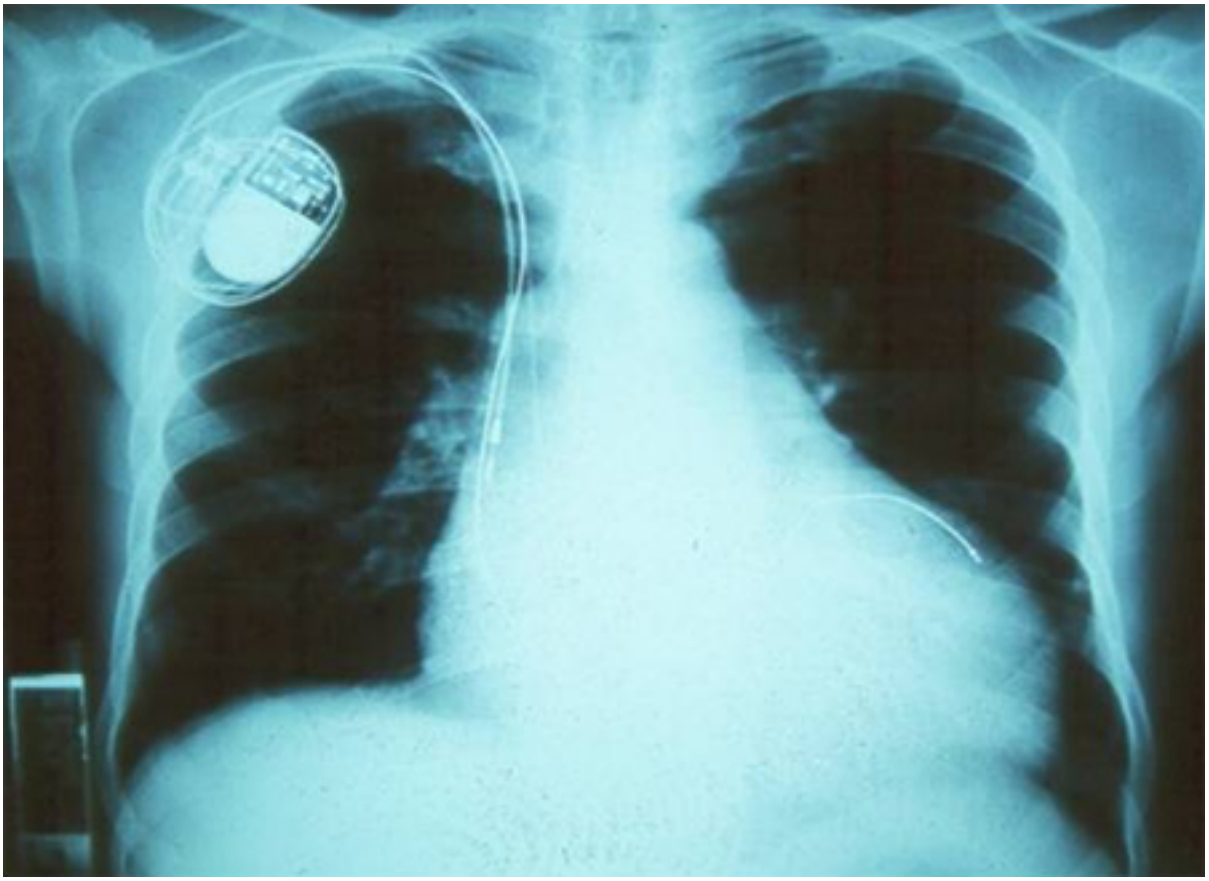

Figure 6: Chest x-ray: cardiomyopathy, heart enlargement

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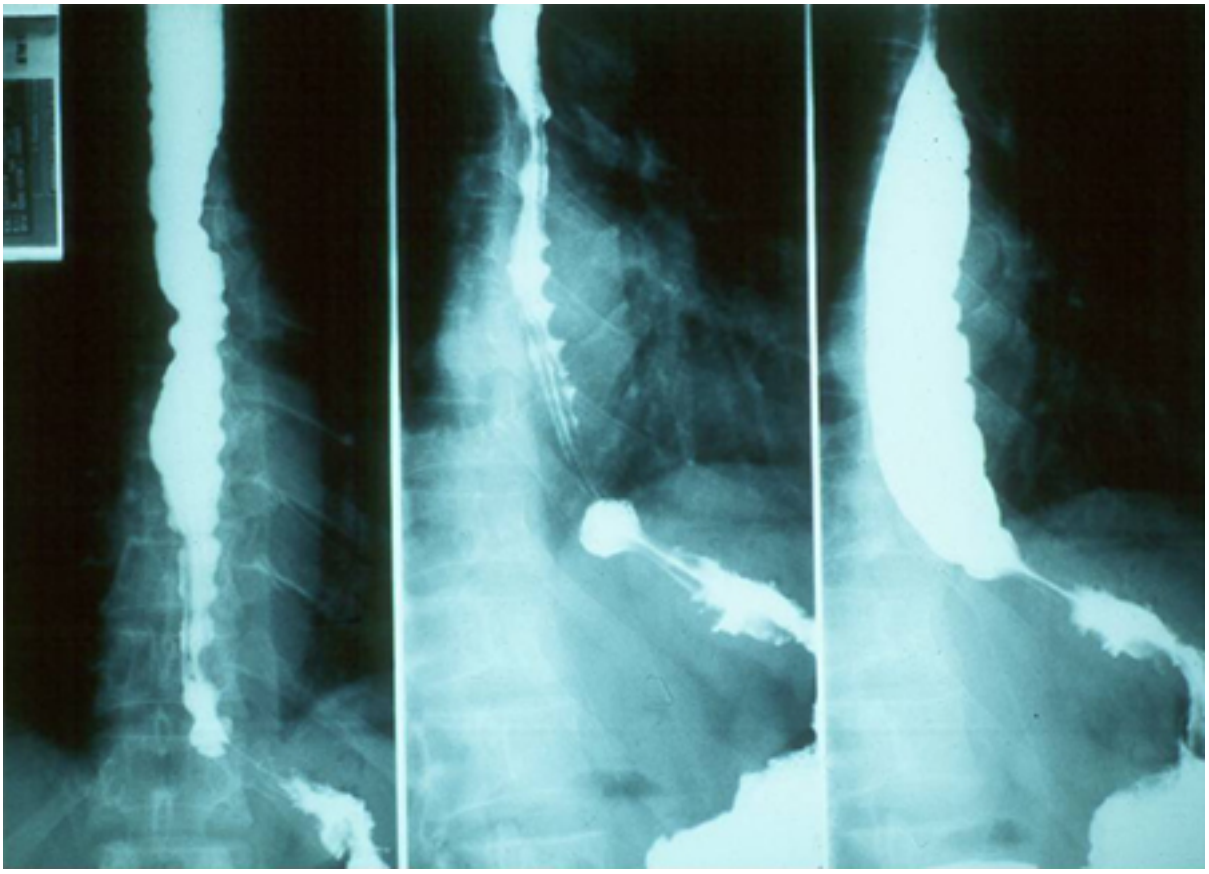

Figure 7: Barium swallow showing dilation of oesophagus

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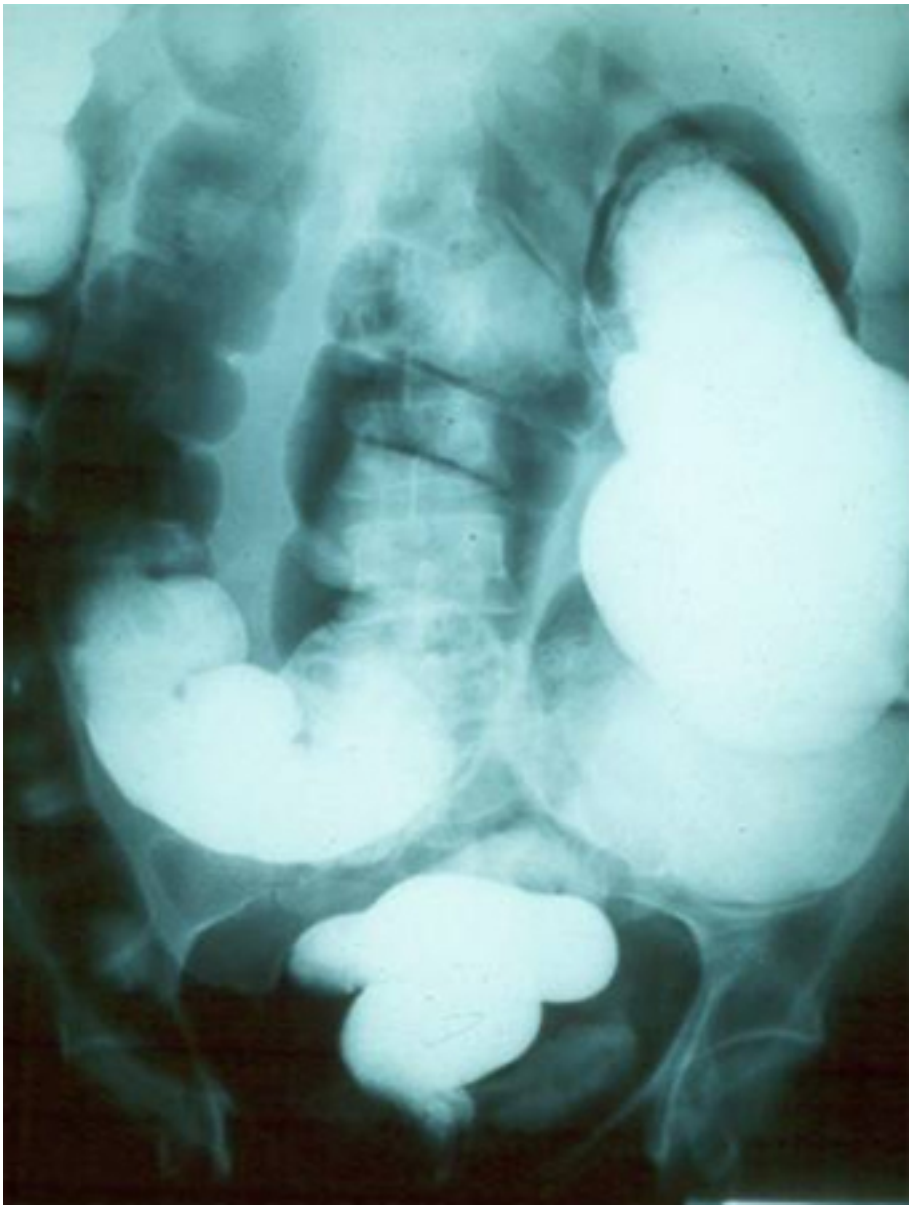

Figure 8: Barium enema showing excessive dilation of sigmoid colon

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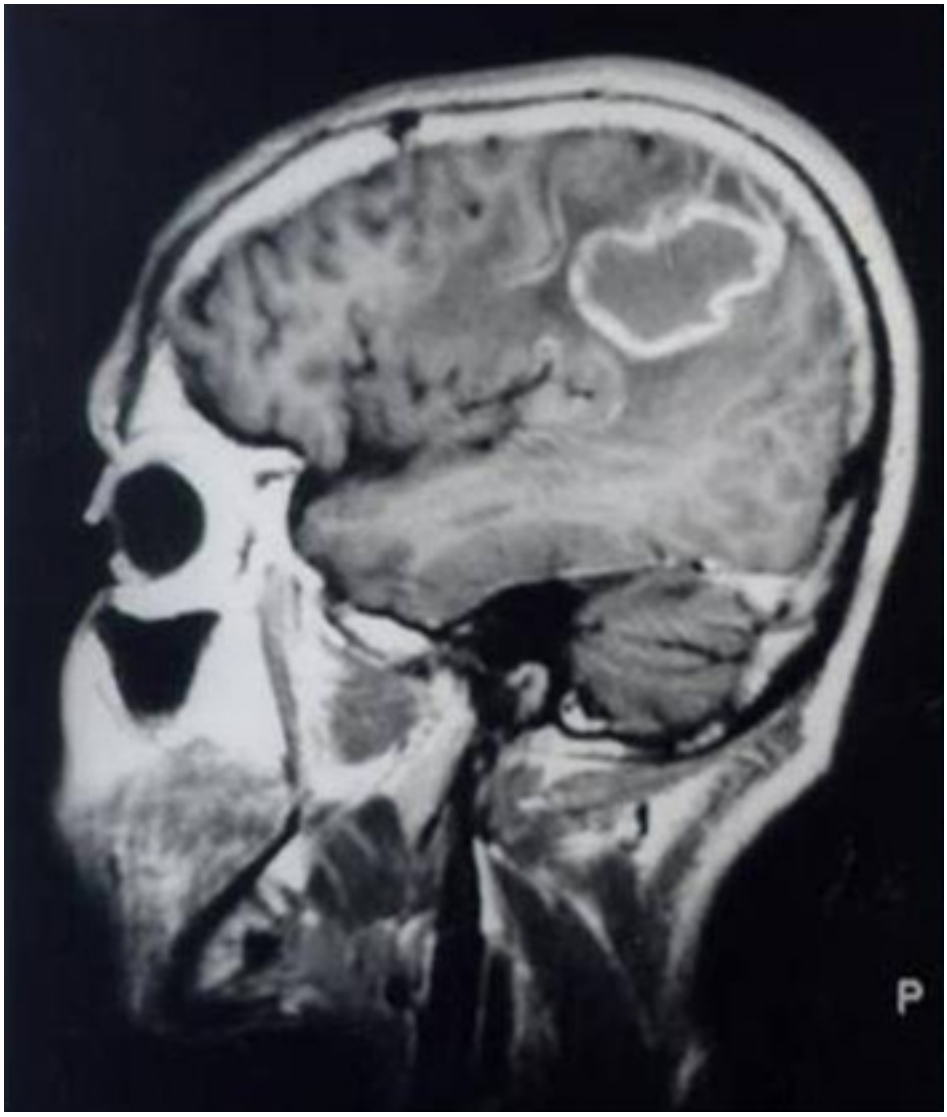

Figure 9: MRI brain in a patient with AIDS and reactivation of Chagas disease in CNS

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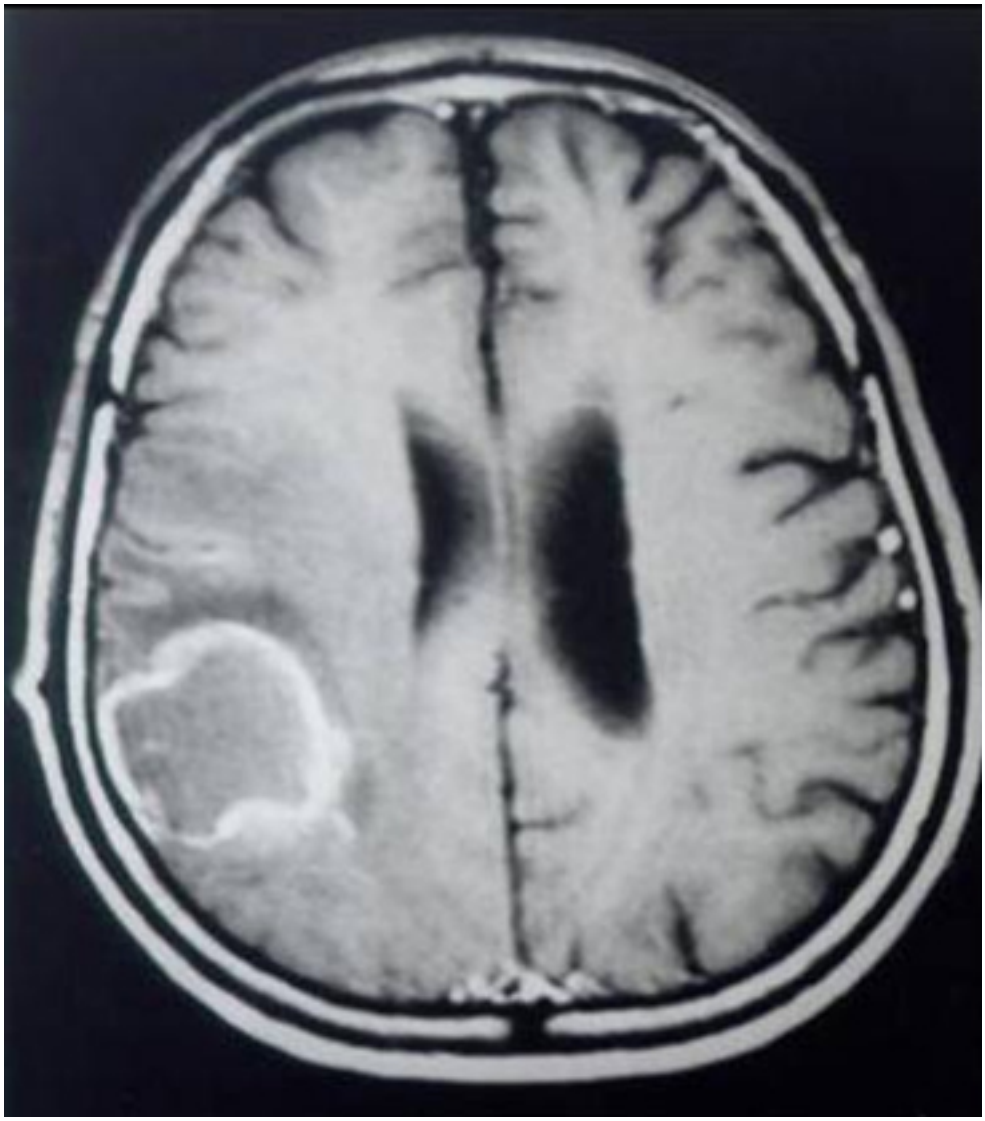

Figure 10: MRI brain in a patient with AIDS and reactivation of Chagas disease in CNS

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

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numerals < 1: 0.25

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