Toxoplasmosis and the Heart

Zier Zhou, BSc[1],
Hector Isaac Alejandro Ortiz Lopez, MD[2],
Gonzalo Emanuel Pérez, MD, FSIAC[3],
Lucrecia Maria Burgos, MD[4], Juan María Farina, MD[3],
Clara Saldarriaga, MD[5], Ricardo Lopez-Santi, MD[6],
Juan Ignacio Cotella, MD[7],
Ana Laura Sauce Pérez, MD[8], and
Adrian Baranchuk, MD, FACC, FRCPC, FCCS[1,*]

From the [1] Division of Cardiology, Kingston Health Sciences Centre, Queen's University, Kingston, Ontario, Canada, [2] Division of Cardiology, Hospital Herrera Llerandi, Guatemala City, Guatemala, [3] Division of Cardiology, Clínica Olivos, Buenos Aires, Argentina, [4] Department of Heart Failure, Pulmonary Hypertension and Heart Transplant, Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina, [5] Department of Cardiology and Heart Failure Clinic, Cardiovascular Clinic Santa Maria, University of Antioquia, Medellín, Colombia, [6] Division of Cardiology, Hospital Italiano de La Plata, Buenos Aires, Argentina, [7] Division of Cardiology, Centro Privado de Cardiología San Miguel de Tucumán, Tucumán, Argentina and [8] Division of Cardiology, Centro Médico Nacional Siglo XXI, Mexico City, Mexico.

Abstract: Toxoplasmosis is a common disease caused by *Toxoplasma gondii*, a parasite with high prevalence in tropical regions. Most infections show minimal symptoms, but immunocompromised patients tend to have a poor prognosis. Cardiovascular manifestations in toxoplasmosis are rare and reported in a limited number of patients. As part of the "Neglected Tropical Diseases and Other Infectious Diseases Affecting the Heart" (NET-Heart) project, this paper aims to systematically review all available information regarding the cardiovascular implications of toxoplasmosis. Relevant studies were identified in the MEDLINE and/or PubMed database, and 48 articles were ultimately included. This was completed according to the Preferred Reporting Items for Systematic Reviews and

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Meta-analyses guidelines. Cardiac compromise in toxoplasmosis mainly involves myocarditis, and complications vary widely in severity. Toxoplasmic myocarditis is challenging to diagnose, as endomyocardial biopsy is usually required. This article provides a summary of cardiac toxoplasmosis, including an original algorithm facilitating diagnosis and treatment. (Curr Probl Cardiol 2021;46:100741.)

Introduction

Toxoplasmosis is a communicable disease that commonly occurs in tropical and subtropical developing countries around the world.[1] An increased prevalence is seen in rural areas and populations with low socioeconomic status.[2] Since relatively little attention has been paid to its surveillance and management, toxoplasmosis is classified as 1 of 5 neglected parasitic infections in the United States (US).[3] The disease is currently targeted for public health action, given its high prevalence, its potential severity, and the ability for treatment.[3]

Toxoplasmosis is caused by *Toxoplasma (T) gondii*, a protozoan parasite that spends most of its life cycle inside cats.[4] It spreads easily to humans, either by consumption of undercooked meat, by contaminated water, or by contact with feline feces.[4] Toxoplasmosis is not transmitted from person-to-person, except in instances of congenital transmission[5] and organ transplantation.[6,7]

While mild forms of toxoplasmosis in immunocompetent hosts tend to be self-resolving, more advanced presentations can lead to detrimental effects in immunocompromised patients.[8] This is a significant problem for patients with human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) or other immunosuppressive conditions.[1,9]

T gondii microorganisms can spread and infect the brain, heart, lungs, liver, lymph nodes, and skeletal muscle.[10,11] In immunocompromised individuals, the central nervous system is the most frequently affected site.[9] Severe cases are known to present as encephalitis, chorioretinitis, pneumonitis, or multiorgan damage with respiratory failure and hemodynamic instability.[9]

In contrast, cardiovascular (CV) involvement in toxoplasmosis is rare and often asymptomatic or obscured by neurological deterioration.[12,13] Likely for these reasons, the effects of toxoplasmosis on the heart have not been widely discussed in existing literature.[4] Case studies comprise

the majority of published papers discussing cardiac toxoplasmosis and its clinical characteristics.

This article is part of the "Neglected Tropical Diseases and Other Infectious Diseases Affecting the Heart" (NET-Heart) project, conducted by the Emerging Leaders program of the Inter-American Society of Cardiology.[14,15] It aims to systematically review all available evidence regarding CV involvement in toxoplasmosis and to propose diagnostic and therapeutic strategies for managing this condition.

Methods

This review process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] A literature search was conducted in the MEDLINE/PubMed database to select publications detailing CV involvement of toxoplasmosis. The following MESH terms were used: "Toxoplasmosis," "heart," "heart diseases," "arrhythmias," "myocarditis," "pericarditis," and "endocarditis." Additional articles were identified by manually searching the references of included studies.

Inclusion criteria were: (1) all original studies and reviews providing insight into the epidemiology, physiopathology, symptoms, diagnosis, and treatment of cardiac toxoplasmosis; (2) publications issued from 1990 to 2020; (3) English articles; (4) human studies. Articles were excluded when full-text versions were unavailable or when connections between toxoplasmosis and the heart could not be confirmed.

Two investigators (ZZ and HO) independently reviewed titles and abstracts of retrieved articles. Kappa interobserver was determined, and disagreements were resolved by consensus. The remaining articles were assessed for eligibility.

This systematic review was completed according to the methods and design outlined in the NET-Heart project.[14] Primary outcomes of this article are: (1) to synthesize knowledge about CV involvement in toxoplasmosis and (2) to develop an algorithm towards its clinical diagnosis and management.

Results

Our initial electronic search returned 132 results. Manual searching of reference lists identified another 16 sources. After screening, 68 articles were evaluated according to eligibility criteria. Interrater reliability was substantial ($\kappa = 0.638$, 95%CI: 0.527-0.749). In total, 48 articles were deemed relevant and included in this systematic review. The selection

consists of 22 case reports, 3 case series, 7 retrospective studies, 5 cross-sectional studies, 8 reviews, 1 seminar paper, 1 textbook chapter, and 1 report from a professional association (Fig 1).

Table 1 summarizes each study discussing cardiac manifestations and clinical outcomes in toxoplasmosis patients. It comprises the following data: (1) first author's last name and publication year, (2) number of cases, (3) age, (4) gender, (5) CV involvement, and (6) clinical outcomes.

Epidemiology

Toxoplasmosis affects approximately one-third of the world's population.[9,17] Prevalence varies by geographical region, and infections occur more often in tropical countries.[1] Seroprevalence in most of Canada and the US is relatively low at 10%-20%, while areas with prevalence over 60% are found in Latin America, the Middle East, parts of Southeast Asia, and Africa.[2] Global distribution of *T gondii* infection is presented in Figure 2.

This extensive distribution of toxoplasmosis can be attributed to the global abundance of cats as definitive hosts, a large number of intermediate hosts, and diverse methods of parasite transmission.[18] Large-scale studies have also detected *T gondii* presence in domestic and wild cats outside human endemic areas.[19] As seroprevalence is correlated with specific disease burden based on age-standardized disability-adjusted life years or mortality, it has been proposed that latent toxoplasmosis may be responsible for the development of various clinical pathologies.[20]

Epidemiology in North America. Although toxoplasmosis is considered to be a neglected parasitic infection in the US, *T gondii* is estimated to exist in more than 40 million Americans.[3] Over the past few decades, seroprevalence has been steadily falling.[9] This is likely due to improved hygiene and food consumption habits and greater awareness regarding the risks of undercooked meat.[1] While the trend towards lower seroprevalence has similarly been observed in Mexico, rates in the southern region remain relatively high and resemble those in the rest of Latin America.[2]

Available information on toxoplasmosis in Canada is limited, as the infection tends to be underreported and underdiagnosed.[21] Annual incidence of severe toxoplasmosis requiring hospitalization was 0.257 cases per 100,000 Canadians, and the ratio of serious to mild cases was approximately 1:74.[21] Recent population data from Toronto reported seropositivity to be 16.8%-18.6%.[2] The region with the highest seroprevalence nationally is Nunavik in Northern Québec, where outbreaks of clinical

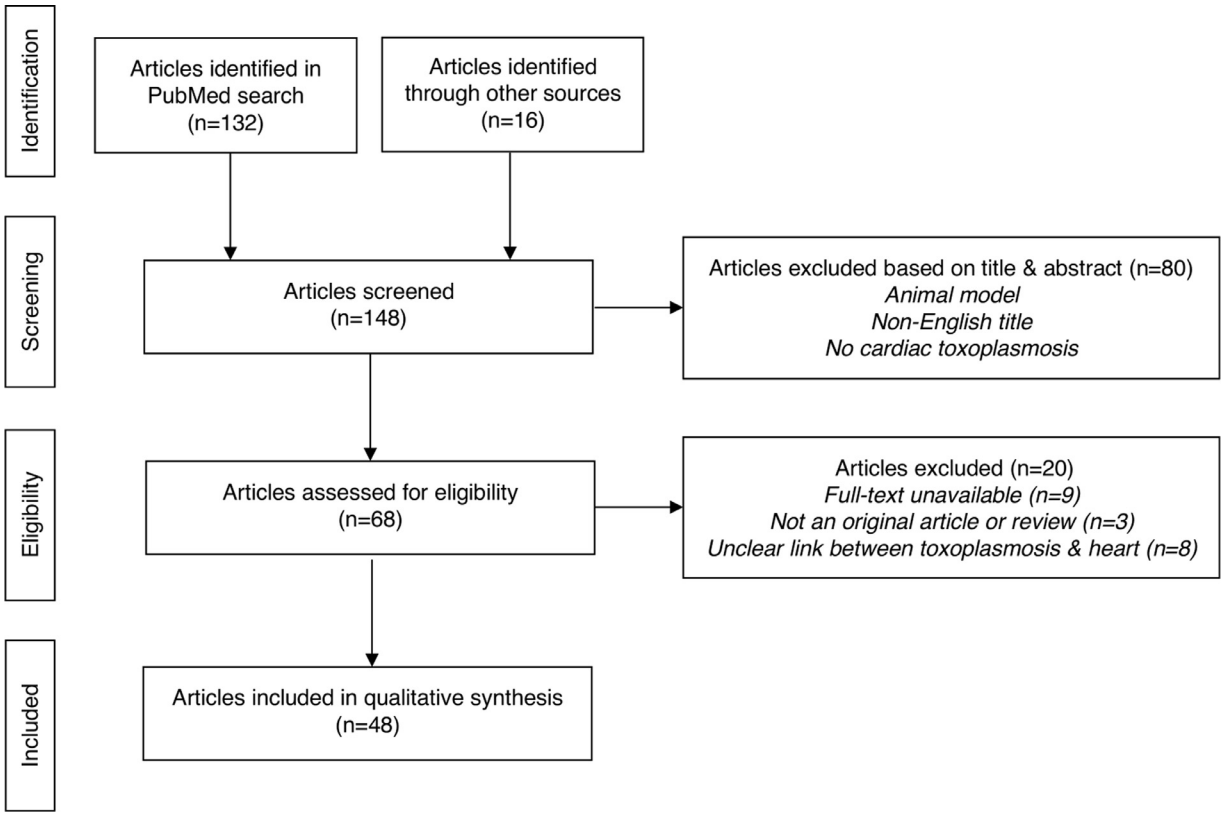

FIG 1. Flow of studies through the review process.

Table 1. Summary of studies mentioning cardiac complications and clinical outcomes of toxoplasmosis

Literature	Study design	No. of cases	Age	Sex	Immune status	Cardiovascular involvement	Clinical outcomes
Albrecht et al (1994)	Case report	1	45	M	Immunocompromised (HIV)	Myocarditis, tachycardia, atrial fibrillation, *Toxoplasma gondii* microorganisms	Recovery after sulfadiazine + pyrimethamine + clindamycin
Bal et al (2014)	Case report	1	44	M	Immunocompromised (HIV)	Myocarditis, tachycardia, dilated heart, *T gondii* tachyzoites, necrosis, edema, mixed infiltrate	Sudden death due to refractory shock
Bousquet et al (2016)	Case report	1	20	M	Immunocompetent	Myocarditis, incomplete right bundle branch block, myocardial edema	Recovery with sulfamethoxazole + trimethoprim
Capell et al (1992)	Case report	1	28	M	Immunocompromised (AIDS)	Myocarditis, bradycardia, atrial premature contractions, *T gondii* microorganisms	Death due to pneumonia & respiratory failure
Chandenier et al (2000)	Case series	2	21 9	F F	Immunocompetent	Myocarditis, heart failure, tachycardia	Recovery without treatment (1), recovery with sulfadiazine + pyrimethamine (1)
Chapman et al (1995)	Case report	1	86	M	Immunocompromised (chronic bronchitis)	Myocarditis, left bundle branch block, cardiomegaly, heart failure, *T gondii* cysts	Death due to deteriorating condition

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Table 1. (*continued*)

Literature	Study design	No. of cases	Age	Sex	Immune status	Cardiovascular involvement	Clinical outcomes
Chimenti et al (2007)	Case report	1	45	F	Immunocompromised (HIV)	Myocarditis, atrial fibrillation, heart dilation, *T gondii* cysts	Death due to cardiac arrest
Cuervo et al (2016)	Case report	1	32	M	Immunocompromised (HIV)	Myocarditis, tachycardia, left ventricular failure, circulatory collapse	Recovery with pyrimethamine + sulfadiazine
Duband et al (2008)	Case report	1	59	M	Immunocompromised (stem cell transplant)	*T gondii* cysts in myocardium, pericardial effusion, heart failure	Death due to disseminated infection & heart failure
Duffield et al (1996)	Case report	1	25	F	Immunocompetent	Myocarditis, atrioventricular block, hypotension, left ventricular dysfunction	Recovery with pyrimethamine + spiramycin + pacemaker implant
Eza and Lucas (2006)	Case series	1	55	M	Immunocompromised (HIV)	Myocarditis, left ventricular hypertrophy, pericardial effusion, *T gondii* tachyzoites	Death due to cardiac & multiorgan failure
Grange et al (1990)	Case report	1	58	M	Immunocompromised (AIDS)	Myocarditis, cardiomegaly, atrial fibrillation, heart failure	Recovery with pyrimethamine & clindamycin
Guerot et al (1995)	Case report	1	28	M	Immunocompromised (AIDS)	Pericarditis, pericardial effusions, tachycardia	Death due to pneumonia with hypoxemia & shock
Hadem et al (2006)	Case report	1	41	F	Immunocompromised (stem cell transplant)	Myocarditis, ventricular fibrillation, hypotension	Death due to hypoxemia & multiorgan failure

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Table 1. (*continued*)

Literature	Study design	No. of cases	Age	Sex	Immune status	Cardiovascular involvement	Clinical outcomes
Hermanns et al (2001)	Case report	1	64	M	Immunocompromised (heart transplant)	Myocarditis, dilated ventricles, *T gondii* microorganisms	Death due to toxoplasmosis & respiratory failure
Hofman et al (1993)	Retro-spective study	21	Mean: 33.6 (range: 25-52)	F: 38% M: 62%	Immunocompromised (AIDS)	Myocarditis (14), *T gondii* cysts (4), cardiac lesions (3)	Death due to heart disease (6), nervous system lesions (12), pulmonary failure (2), gastrointestinal bleeding (1)
Holliman et al (1990)	Case report	1	58	M	Immunocompromised (heart transplant)	*T gondii* cysts, inflammatory infiltrate, thickened ventricles	Sudden death due to toxoplasmosis
Jautzke et al (1993)	Retro-spective study	12	N/A	N/A	Immunocompromised (AIDS)	*T gondii* pseudocysts or tachyzoites (8), necrosis & mixed infiltrate (4)	Death due to AIDS in all cases
Lanjewar et al (2006)	Case report	1	35	M	Immunocompromised (AIDS)	Myocarditis, necrosis, inflammatory infiltrate, *T gondii* pseudocysts	Sudden death due to cardiac arrest
Lévêque et al (2019)	Case report	1	23	M	Immunocompetent	Myopericarditis, necrosis	Recovery without treatment
Mariani et al (2006)	Case report	1	19	M	Immunocompetent	Myocarditis, atrioventricular block	Recovery with co-trimoxazole + pacemaker implant
Montoya et al (1997)	Case report	1	43	F	Uncertain (past lymphoma, melanoma)	Myocarditis, heart failure, atrioventricular block, *T gondii* cysts, mixed infiltrate	Condition improved with corticosteroid therapy
Pergola et al (2010)	Case report	1	32	M	Immunocompetent	Myocarditis, pericarditis, pericardial effusion	Recovery without specific treatment

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Table 1. (*continued*)

Literature	Study design	No. of cases	Age	Sex	Immune status	Cardiovascular involvement	Clinical outcomes
Petty et al (2015)	Case report	1	30	M	Immunocompromised (heart transplant)	Asymptomatic, *T gondii* cyst	Condition likely improved without therapy
Robert-Gangneux et al (2000)	Case series	2	46 67	M M	Immunocompromised (heart transplant)	Asymptomatic (1), myocarditis with *T gondii* microorganisms, necrosis, edema (2)	Recovery without treatment (1), death due to deteriorating condition (1)
Rostoff et al (2008)	Case report	1	67	F	Uncertain (past heart disease, hypertension)	Perimyocarditis, pericardial effusions, acute heart failure	Recovery with spiramycin therapy
Schmidt et al (1995)	Case report	1	74	F	Immunocompromised (kidney transplant)	Myocarditis, cardiomegaly, heart failure, *T gondii* cysts	Death due to severe pulmonary edema

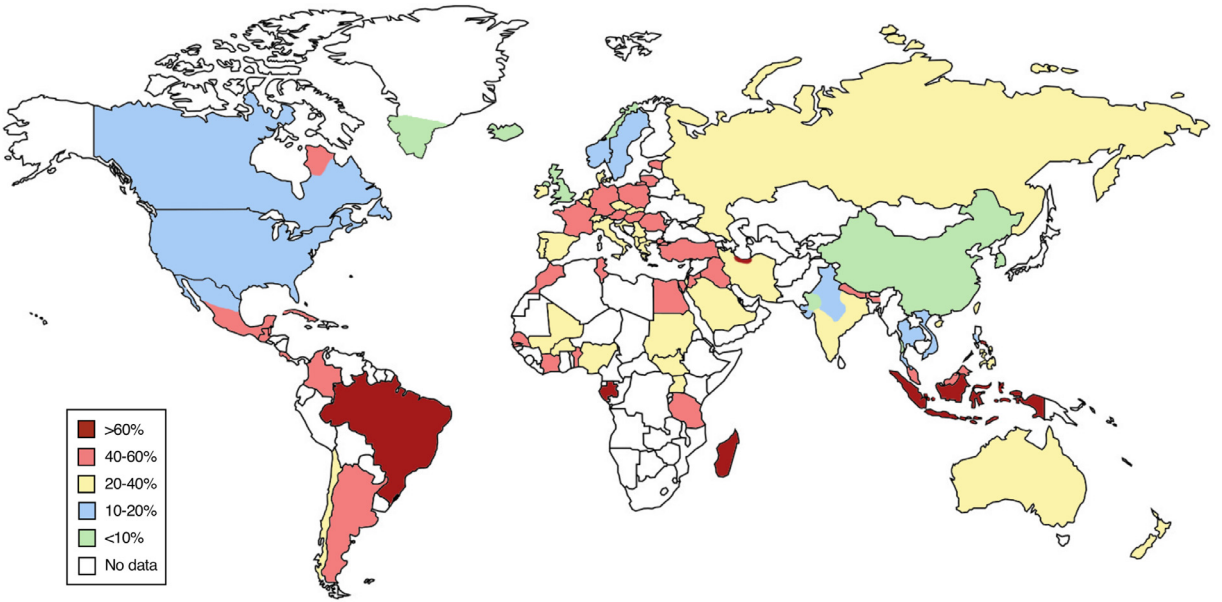

FIG 2. Global status of *Toxoplasma gondii* seroprevalence. Modified from multiple epidemiological studies.[2,17,51]

toxoplasmosis have occurred.[21] Seroprevalence among Inuit people in Nunavik was determined to be 59.8%, which may be related to their consumption of seal and caribou meat.[2]

At-risk Populations. Toxoplasmosis is common in tropical regions with hot, humid climates and lower altitudes, as these environments are more optimal for *T gondii* oocyst survival.[3] Travelers residing in or returning from tropical countries, especially in South America, are also at risk of developing serious infection with pulmonary involvement.[1]

High-risk groups for severe toxoplasmosis include infants born to mothers newly exposed to *T gondii* during pregnancy and individuals with weakened immune systems, such as HIV/AIDS patients and organ transplant recipients.[3] Toxoplasmosis is the most popular nonviral cause of myocarditis in patients with AIDS.[22] and the most frequently reported parasitic disease arising after cardiac transplantation.[13]

Patients with history of heart disease represent another risk group, particularly for chronic *T gondii* infection.[18,23] Recent studies in Mexico and Iran demonstrated significantly higher seroprevalence in CV patients compared to age- and sex-matched controls.[18,23]

Physiopathology

T gondii mainly exists in three forms: oocysts, tachyzoites, and bradyzoites.[9] Oocysts are only produced in members of the family Felidae, known as definitive hosts.[24] When humans or other intermediate hosts are infected, oocysts develop into tachyzoites.[1] These tachyzoites divide rapidly within intestinal epithelial cells following ingestion and disperse throughout the body via lymphatics, often localizing in muscle and neural tissues.[1] Once the host mounts an effective immune response, tachyzoites are converted into bradyzoites, which reside in tissue cysts.[9] Key stages in the *T gondii* life cycle are depicted in Figure 3**.**

Although latent infections can persist in the long term, damage caused by the parasite is usually avoided in immunocompetent people.[1] An immune response is initiated when *T gondii* is detected by innate immune cells including macrophages and dendritic cells via pattern recognition receptors, leading to the production of pro-inflammatory cytokines and chemokines such as tumor necrosis factor-α, interleukin-6, and interleukin-12.[25] This process results in the activation of acquired immunity involving CD4 helper T cells and CD8 cytotoxic T cells and the production of abundant levels of interferon-gamma, a cytokine which induces cell-autonomous immunity in infected cells.[25]

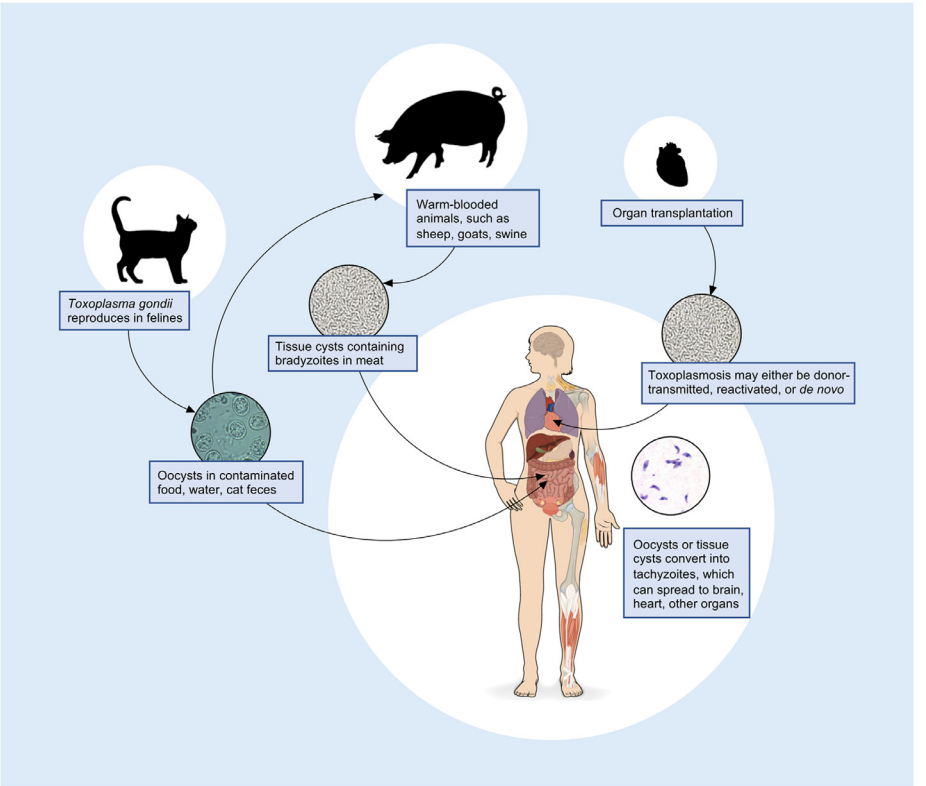

FIG 3. Life cycle of *Toxoplasma gondii* parasite. Modified from: Montoya JG, Liesenfeld O: Toxoplasmosis. The Lancet 363:1965-1976, 2004.

Cardiovascular Involvement. While uncommon in toxoplasmosis, CV involvement mainly features myocarditis, which is characterized by inflammatory cellular infiltrate with or without myocyte necrosis.[12] Parasite invasion is driven by actin-based motility, establishing intracellular vacuoles derived from the plasma membrane of cardiomyocytes.[13] Heart tissue damage depends on the intensity of inflammatory reactions and the intramyocytic presence of *T gondii* tachyzoites.[12] Pericarditis is a less common manifestation of cardiac toxoplasmosis that can appear either alongside.[8,26,27] or separately.[28] from myocarditis.

Although toxoplasmic myocarditis is often subclinical, it may be associated with progressive cardiac dysfunction.[29] CV conditions such as arrhythmias and congestive heart failure are likely complications of myocarditis and thus less frequent.[4,13,29] Sinus tachycardia may be a classical warning sign of infectious myocarditis.[30] Atrial fibrillation,[31-33] atrioventricular blocks,[11,34,35] and bundle branch blocks[36,37] were also described in a number of cases. These abnormalities may lead to hemodynamic compromise and congestive heart failure under specific circumstances.[11,30,33,37]

Physiopathology in Immunocompromised Patients. Immunocompromised patients tend to experience reactivated toxoplasmosis, where tissue cysts rupture and dormant bradyzoites revert to disease-causing tachyzoites.[4] These individuals often fail to generate an adequate antibody response and have an abnormal cytokine profile and an impaired T cell functionality.[38] As a consequence, *T gondii* infection can spread out of control and cause serious illness. Autopsies of adults with disseminated toxoplasmosis may demonstrate interstitial pneumonia, focal hepatitis, myocarditis, myositis, and encephalitis.[4]

In AIDS patients with toxoplasmosis, the heart is the second most commonly affected organ after the brain.[29] One retrospective study found CV involvement in 12 of 74 extracerebral toxoplasmosis cases, and necrotic tissue plus inflammatory infiltrate materialized in 8 of these cases.[10] In rare instances, toxoplasmosis can occur without clinical evidence of cerebral involvement.[10,22] In another study, 21 of 182 HIV patients were diagnosed with cardiac toxoplasmosis, presenting with myocarditis, tissue cysts, and cardiac lesions that were not discovered until necropsy.[12]

Toxoplasmic myocarditis may also arise in transplant patients, either due to infection from a seropositive donor to a seronegative recipient, reactivation of latent toxoplasmosis in the previously infected recipient, or de novo infection after transplantation.[39] Patients receiving hearts from seropositive donors are at considerable risk of undergoing serological reactivation and developing cardiac toxoplasmosis.[7] However,

T gondii serostatus does not seem to have a statistically significant effect on post-heart transplant mortality.[40] In cases of kidney and bone marrow transplantation, disseminated toxoplasmosis with myocarditis tends to result in multiorgan failure and fatal outcomes.[41-43]

Some clinical consequences of CV involvement have been observed in both HIV/AIDS and organ transplant groups. In addition to arrhythmias, dilated cardiomyopathy was detected in multiple immunocompromised adults with cardiac toxoplasmosis.[6,22,32] Certain patients have even experienced sudden death due to serious complications.[22,44,45]

Symptoms

In individuals with normal immune defenses, around 90% of acute *T gondii* infections are asymptomatic, and the rest may experience constitutional symptoms ranging from mild to moderate.[11] Fever is often the earliest manifestation,[41] while other key symptoms include fatigue, headache, and lymphadenopathy.[46]

Cardiovascular Involvement. While the majority of symptoms in toxoplasmic myocarditis are constitutional, those more often associated with CV involvement are chest pain, palpitations, and shortness of breath.[30,31,47] The latter may also be related to pulmonary problems.[37,43] These symptoms result from cellular and humoral autoimmune reactions against *T gondii*-induced myocardial antigens.[30] Myocarditis may either be classified as mild and self-limiting or fulminant with severe left ventricular dysfunction requiring hemodynamic support.[42,48]

Clinical expression of heart symptoms varies among cases of toxoplasmic myocarditis. Despite significant histopathological changes, cardiac lesions caused by *T gondii* can be asymptomatic.[47] or have nonspecific symptoms.[49] However, as described in Table 2, most patients with cardiac toxoplasmosis present with multiple signs and symptoms. These presentations are usually a consequence of the disease's general implications and specific CV involvement.

Symptoms in Immunocompromised Patients: In contrast, symptoms tend to be more common and severe in immunocompromised patients with HIV infections or organ transplants.[1] Apart from acute infection, activation of chronic toxoplasmosis can lead to encephalitis, pneumonitis, myocarditis, and other inflammatory conditions.[22,31] Focal neurological disease or encephalitis is a frequent manifestation in HIV patients with low CD4 counts ($<$100 cells/μL).[4]

Table 2. Key signs and symptoms in selected cases of cardiac toxoplasmosis

Symptom	No. of cases
Fever	16
Dyspnea	12
Chest pain	9
Lymphadenopathy	6
Myalgia	5
Malaise/weakness	5
Headaches	4
Fatigue/lethargy	3
Cough	3
Diarrhea	3
Anorexia/weight loss	2
Edema	2
Seizure	2
Nausea/vomiting	1
Palpitations	1

Diagnostic Tests

Serologic testing is typically used for diagnosing toxoplasmosis. IgG antibodies emerge within 1-2 weeks, peak within 1-2 months, and then decline to levels that persist for life.[36] Meanwhile, IgM antibodies appear within the first few days following infection and can be detected over a year later.[36] Presence of IgG antibodies only confirms past infection, whereas IgM can estimate the time of infection.[13] Diagnosis is marked by rising antibody titers measured in serially collected blood specimens. Interpretations of these results are displayed in Supplementary Table 1.

Most reported cases of myocarditis occur in patients with systemic toxoplasmosis and are not confirmed until the heart tissue is microscopically examined.[22] Endomyocardial biopsy is the gold standard for diagnosis,[8,36] which relies on a compatible clinical syndrome and the exclusion of other known causes.[11] However, biopsies are not regularly performed because cardiac involvement tends to be clinically silent.[29,36] As a consequence, isolation of *T gondii* tachyzoites in the myocardium is mostly made post-mortem.[29,31]

Polymerase chain reaction (PCR) testing is another technique to diagnose toxoplasmosis. One patient with myopericarditis was determined to be acutely infected when *T gondii* DNA in peripheral blood was detected by PCR.[27] This happened during the symptomatic phase when serological tests were negative, which was likely due to the delayed synthesis of specific antibodies.[27] In transplant settings, PCR has been reported to diagnose toxoplasmosis more frequently than histological analysis of cardiac biopsy samples.[13]

When toxoplasmosis affects the heart, initial diagnostic evaluation involves undergoing an electrocardiogram (ECG), chest radiograph, and echocardiogram (echo).[26,30,47] Laboratory test results should also be considered because elevated levels of cardiac troponin, creatine kinase, and nonspecific inflammatory biomarkers are indicative of CV involvement.[8,22] Cardiac magnetic resonance imaging scans provide additional evidence of myocardial compromise such as edema.[36,48] An algorithm to guide the diagnosis of cardiac toxoplasmosis is demonstrated in Figure 4.

Treatment

Standard management of toxoplasmosis consists of pyrimethamine plus sulfadiazine and folinic acid.[1,9,13] Folinic acid is responsible for reducing bone marrow suppression due to pyrimethamine.[9] Some cases of cardiac toxoplasmosis have been successfully treated with this combination.[30,31,48] However, current drugs are only active against *T gondii* tachyzoites and do not entirely eliminate the infection.[1]

Acquired toxoplasmosis in immunocompetent patients with mild symptoms usually does not demand specific treatment.[1,11] In contrast, therapy should be initiated when symptoms are severe and organs are impacted, which is often seen in immunosuppressed individuals with acute or reactivated infection.[1,11] Recommended toxoplasmosis treatments for different patient types are summarized in Table 3. Key CV manifestations including myocarditis and pericarditis have been reported to respond to these medications.[4]

For those who do not respond or develop adverse reactions to first-line therapy, sulfadiazine can be replaced with clindamycin, which has been effective in the treatment of toxoplasmic myocarditis.[33] Spiramycin is another option for treating heart failure related to *T gondii* infection when sulfonamides are contraindicated.[34] Antibiotic therapy with trimethoprim-sulfamethoxazole (TMP-SMX) was also shown to relieve symptoms in cardiac toxoplasmosis.[35,36]

Serological screening of organ donors and recipients before transplantation is necessary for identifying high-risk patients and providing prophylaxis to counteract the harmful effects of disseminated disease.[29] According to the International Society of Heart and Lung Transplantation guidelines, TMP-SMX is preferred for preventing toxoplasmosis.[50] Although minimal data for alternative agents are available, atovaquone may be an effective option. Atovaquone prophylaxis was administered to a reported case of cardiac toxoplasmosis with TMP-SMX intolerance.[50]

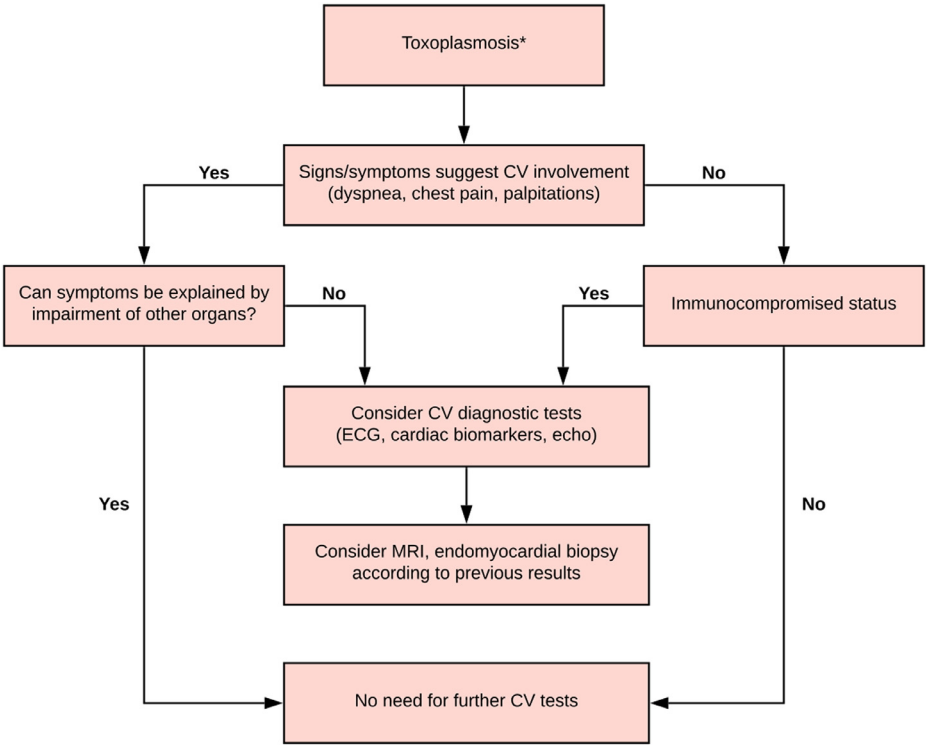

FIG 4. Diagnostic procedure for cardiac toxoplasmosis. *Toxoplasmosis diagnosis may rely on serologic tests for IgG and IgM antibodies, PCR techniques to identify *Toxoplasma gondii* DNA, or direct observations of the parasite in biopsy specimens. CV, cardiovascular; ECG, electrocardiogram; Echo, echocardiogram; MRI, magnetic resonance imaging.

Table 3. Recommended treatments for cardiac toxoplasmosis

Patient	Recommended treatment
Immunocompetent (mild or no symptoms)	Not required
Immunocompetent (severe or persistent illness)[1]	Pyrimethamine (200 mg loading dose for 1 day, then 50-75 mg/d) + folinic acid (5-10 mg/d) + sulfadiazine (1-1.5 g, 4 times daily) OR clindamycin (600 mg, 4 times daily) for duration of 2-4 wk
Immunocompromised (HIV/AIDS)[1]	Same treatment as severely affected immunocompetent patients but administered for minimum of 6 wk Maintenance therapy for duration of immunosuppression: pyrimethamine 20-50 mg/d + sulfadiazine 2-4 g/d + folinic acid 5 mg/kg daily
Immunocompromised (post-transplant)[1,4]	Prophylaxis with trimethoprim-sulfamethoxazole (160 mg/800 mg daily) OR pyrimethamine (25 mg/d) Same treatment as severely affected immunocompetent patients but administered for minimum of 6 wk

Severe myocarditis following *T gondii* exposure has been found to improve with antiprotozoal therapy plus corticosteroids, which are indicated when arrhythmias and conduction defects are present.[11] In patients with atrioventricular block resulting from toxoplasmic myocarditis, the implantation of a dual-chamber pacemaker can be necessary.[34,35] In the event of fulminant myocarditis causing cardiogenic shock and hemodynamic instability, the implementation of an extracorporeal membrane oxygenation device or a left ventricular assist device may be required.[42]

Discussion

Toxoplasmosis is a widespread infection caused by the *T gondii* parasite, which is prevalent in tropical and subtropical climates. Given that the majority of infected individuals are immunocompetent and asymptomatic,[13] disease burden is not considered to be particularly high. HIV and transplant patients are especially vulnerable because of their immunocompromised state and the possible reactivation of past infection.[4] Patients with history of CV disease may also be more prone to chronic *T gondii* infection.[18] While CV involvement in toxoplasmosis is unusual, it is primarily characterized by myocarditis, and complications can result in arrhythmias, heart failure, cardiomyopathies, and cardiac arrest.[12,22]

Challenges in diagnosing toxoplasmosis are generally attributed to its nonspecific and often asymptomatic patterns of presentation. CV

symptoms such as chest pain and shortness of breath may occur before *T gondii* seroconversion. As serological tests for toxoplasmosis are not always reliable and sometimes negative during the symptomatic phase, PCR should be considered as a sensitive alternative.[27] Cardiac biopsy is critical for confirming toxoplasmic myocarditis.[44] However, patchy or focal infiltration of the myocardium can lead to false-negative results, and multiple biopsies may be needed to improve sensitivity.[31] More accessible and less invasive assessments include ECG, echo, magnetic resonance imaging, and cardiac biomarker testing. While these are useful for diagnosing CV compromise, its specific etiology may still be challenging to determine through these methods alone.

Regarding the cases selected for our review, all immunocompetent patients survived, whereas most HIV/AIDS patients and all transplant patients died. This supports the fact that host immune status influences disease severity and clinical outcome, as immunocompromised recipients are at greater risk of serious infection. In patients with cardiac toxoplasmosis, continuous monitoring for adverse events and routine follow-up appointments with ECG and echo testing is essential. Future experiments and clinical trials should focus on increasing drug efficacy, reducing adverse effects, shortening treatment duration, and eradicating chronic toxoplasmosis.

The study is subject to certain limitations. In terms of epidemiology, determining the actual global prevalence of cardiac toxoplasmosis is difficult due to the high number of underreported cases and various diagnostic barriers. Sample size is another limitation because the majority of currently available studies are case reports or case series. Despite these shortcomings, key findings were largely consistent across different populations in different periods.

As for next steps, it is important to enhance the strength and availability of evidence surrounding toxoplasmosis and the heart. Increased surveillance and monitoring would enable greater accuracy in estimating toxoplasmosis disease burden and risk factors. Healthcare professionals should continue to report relevant cases, and these results can eventually be confirmed in larger cohorts of patients and prospective studies. More research is also required to clarify diagnostic criteria for toxoplasmic myocarditis and to develop better treatments for eliminating the infection. Improving access to antiparasitic therapies, along with spreading awareness about food safety and sanitation, can further contribute to the management and prevention of toxoplasmosis.

Conclusions

Toxoplasmosis is a widespread parasitic disease with variable clinical presentations based on patients' immune status. As cardiac toxoplasmosis prevalence is low and thus not a major public health problem, routine screening in immunocompetent individuals is unwarranted. However, CV involvement can be fatal, especially in immunocompromised patients. People in endemic regions should be well-informed about this condition and take necessary precautions to avoid infection.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2020.100741.

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