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## Cardiovascular manifestations of Lyme disease - a literature review

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### **Abstract**

Lyme disease is an infectious zoonosis transmitted by ticks infected with *Borrelia* spirochetes. Condition affects multiple organ systems and typically has a protracted course.

Although Lyme carditis is a comparatively rare symptom of Lyme borreliosis, it can cause major cardiac conditions, including death, if left untreated. Atrioventricular block of various degrees is the hallmark of cardiac involvement, although other manifestations of the disease are increasingly describe such as ventricular and supraventricular arrhythmias, pericarditis, acute coronary syndrome, mild heart failure, cardiac tamponade or individual cases of cardiomyopathy, degenerative valvular lesions and vasculitis.

Cardiovascular conduction disorders have a good prognosis despite their abrupt onset and completely resolve after a few days of antibiotic therapy. Therefore, a wait-and-see attitude should be maintained. However, a temporary or permanent pacemaker may be required if the patient's clinical condition necessitates prompt intervention. Nevertheless, current recommendations suggest avoiding temporary stimulation wherever possible and limiting its use to the shortest treatment time possible.

### **Aim of the study**

The following paper aims to present a review of the current possible complications of Lyme carditis described in the literature and to discuss the treatment.

### **Materials and methods**

The following English keywords and its Polish equivalents were used to search Google Scholar's medical databases: lyme carditis, lyme disease, tick-borne disease. The articles most pertinent to the subject have been chosen.

**Keywords:** Lyme disease; Lyme carditis; borreliosis; tick-borne disease; ticks

## Introduction

Lyme borreliosis (LB) is an endemic zoonosis of the northern hemisphere and the most common tick-borne disease in Europe. Clinical manifestations concern mainly skin, joints, nervous system and heart.

Lyme carditis (LC) is a relatively rare manifestation - occurs in 4-10% of all cases of LB patients after usually 3 weeks to 3 months after infection, and is typically present in the disseminated phase. It is still perceived as one of the significant causes of mortality in this disease entity, especially untreated infection [1,2]. Cardiovascular manifestation is typically characterized by atrioventricular block of various degrees, though other clinical forms such as ventricular and supraventricular arrhythmias, pericarditis, myocarditis, cardiomyopathy and degenerative valvular lesions have also been reported. However, compared to the typical conduction system defects, such conditions have not been recorded as frequently [3].

Carditis is usually self-limited or can be treated successfully in the majority of cases with standard antibiotic regimens. Up to one-third of patients may require temporary cardiac pacing, and the majority of patients (more than 90%) recover fully. Lyme carditis has a fairly good prognosis overall, albeit recovery may be delayed and there may be late sequelae like dilated cardiomyopathy [4].

## What is Lyme disease?

Lyme disease is a multisystem disease caused by Gram-negative spirochaetes of the genus *Borrelia*. The most usually infectious and pathogenic for humans are categorized as the collective species *B. burgdorferi sensu lato* (Bb). The role of the vector for Bb plays *Ixodes ricinus*, which is a common tick in biopsies of moderately moist mixed forests, in gardens, meadows, and city parks. The prerequisite for infection is the tick's transmission of *Borrelia* spirochetes during its feeding in the skin through saliva or vomit while in any of its maturation phases (larva, nymph, mature form). The tick's presence in the skin for two to three days causes infection. Therefore, early identification of a tick and its removal from the skin within 48 hours is the greatest form of protection [5].

Since many years ago, there has been an upsurge in the prevalence of tick-borne illnesses in Europe due to climate change and the growth of tourism [6]. Each year, over 85,000 cases of LB are reported in Europe. Poland is one of several nations where *I. ricinus* ticks are infected with *B. burgdorferi* spirochetes at a medium to high prevalence [5].

The most typical division of Lyme disease is into three stages (Table 1). Erythema migrans (EM) is the most common and most pathognomonic symptom of LB which affects 30–60% of infected people. The lesion can be characterized as a macule or papule, frequently with a central clearing at the site of the tick bite after 3–30 days and accompanying flu-like symptoms. EM must be identified in clinical practice because early antibiotic treatment prevents the development of late manifestations, such as Lyme carditis [7].

**Table 1. Stages of Lyme disease**

Stage 1 - early Lyme disease	
Early, acute localized infection = phase 1	- Erythema migrans - Borrelial lymphoma - flu-like symptoms - fatigue, fever, muscle pain
Early disseminated infection = phase 2	- multiple erythema migrans - Bannwarth syndrome (meningoradiculitis), encephalitis, meningitidis, neuropathy - acute, recurrent Lyme arthritis - Lyme carditis
Stage 2 - late disseminated Lyme disease = phase 3	
- Acrodermatitis chronica atrophicans - encephalomyelitis, meningoencephalitis, peripheral neuropathies, polyneuropathy, memory loss - chronic inflammation of joints and periarticular structures - chronic fatigue	

Since Lyme vaccine production was halted in 2002, avoiding tick bites remains the mainstay of Lyme disease prevention [8]. Strategies have necessarily focused on the use of insect repellents on exposed skin and permethrin on outdoor clothing and the adoption of behaviors, which include conducting a full-body check, removing ticks with fingers or tweezers, showering within two hours of exposure and drying clothes at a high temperature setting [9,10,11,12,13].

### **Lyme carditis (LC)**

#### **Epidemiology**

Cardiovascular borreliosis is not a prevalent type of this disease and may occur in approximately one out of every hundred Lyme disease cases reported to CDC due to the fact that it is recognized more quickly and treated more successfully [14]. Approximately 11% of Lyme disease patients admitted to hospitals are diagnosed with carditis, most

commonly in the form of cardiac conduction system dysfunction [15]. LC has a strong male predominance (approximately 3:1) [16].

Involvement of the cardiovascular system usually occurs within a few days to several weeks after being bitten by an infected tick (an average of 21 days from erythema), but it can also occur many months after infection. It is most often observed in the second stage of the disease [1]. Although both conduction dysfunction and dilated cardiomyopathy might develop years after the pathogen entered the body [17].

### **Symptomatology**

The hallmark of cardiac involvement is the acute onset of the disease, particularly in previously healthy young individuals. Cardiac complaints might appear alone or in conjunction with other infection symptoms, such as erythema migrans or neuroborreliosis. Shortness of breath, reduced exercise tolerance, palpitations, chest pain and syncope are reported by 4–10% of patients, however infection may be asymptomatic in 50% of cases [5]. On physical examination, bradycardia is observed in 35% of patients, but tachycardia may develop in 15% [18].

### **Atrioventricular block**

90% of patients with Lyme disease of the heart and arteries experience symptoms related to the heart's conduction system. The most frequent is **atrioventricular block (AVB)** of variable severity, with a tendency to abrupt progression to block of the higher degree.

Data on the incidence of different degrees of block are inconsistent. There is evidence that 49% of patients experienced third-degree block, 16% second-degree block and 12% first-degree block, while other authors report that AV blocks are present in almost all patients and more advanced blocks in 40-50% of the subjects.

The prevalent view is that asymptomatic AVBs are more common. However, it is crucial to note that the type of AVB can change from the first to the complete block within a few minutes, especially when the PQ interval is more than 300 ms.

However, symptomatic complete blocks with concomitant haemodynamic disturbances and MAS syndromes, in which permanent cardiac pacing was necessary despite antibiotic therapy, have been described. Unfavorable prognostic factors were determined: the appearance of complete block with escape rhythm and wide QRS complexes, brief episodes of asystole, alternating bundle branch blocks [1,2,3].

### **Less frequent manifestations**

A rare manifestation of Lyme carditis are **sinoatrial conduction disorders** or **His bundle branch block**. Lyme infection may also manifest itself with cardiac arrhythmias such as **atrial fibrillation**, **ventricular and supraventricular extrasystoles** and **transient supraventricular tachycardia**. A case of a 26-year-old male have been described with non-prodromal syncope, multifocal annular rashes, and antecedent inflammatory knee pain and effusion was diagnosed with 2-tier Lyme disease after presenting to the emergency room. His ECG demonstrated an AV block with a right bundle branch. His rhythm eventually swiftly quickly deteriorated into polymorphic ventricular tachycardia leading to cardiac arrest [1,19,20].

Spirochete invasion can also result in **myocarditis**, **pericarditis**, or **pancarditis**, all of which are typically mild and occasionally include pericardial effusion. In Polish literature, a case of pancarditis imitating **acute coronary syndrome** has been reported. On the ECG, the patient had generalized ST segment elevation and a large rise in troponin I. The patient complained of a strong, burning pain behind the sternum. On the ECG diffuse ST segment elevation and a significant increase in Troponin I. Following coronary angiography, the patient's healthy coronary arteries were identified [1,21].

In a small percentage of cases, the myocardium suffers chronic damage as a result of the spirochetes' prolonged residence in the heart and blood arteries, leading to **dilated cardiomyopathy**. The involvement of Bb infection has been firmly proven in several cases of progressive dilated cardiomyopathy. An orthotopic heart transplant was necessary in one of these situations for a woman with end-stage heart failure.

Anti-Lyme antibodies have been found by some authors in as much as 32.7% of people with chronic heart failure and in 11% of people awaiting heart transplants. 4-8% of patients with untreated Lyme disease have mild heart failure [1,22].

Due to LB patients can experience severe manifestations, including **cardiac tamponade**. A 61-year-old woman with no previous cardiac history experienced generalized weakness and dyspnea on exertion for over 4 weeks. In the emergency room were discovered a large pericardial effusion and diastolic RV collapse concerning impending tamponade. She shortly became severely hypotensive and urgently performed pericardiocentesis where 500cc of fluid was removed. Upon further investigation, she reported visiting a family member's cabin a few months prior and noted a single erythematous lesion on her arm which resolved after 1 week. She also reported unilateral right 6th and 7th nerve palsy which also resolved [23].

There have been documented single incidences of **cardiac valvular apparatus damage** reported in the literature. A 20-year-old lady was diagnosed with acute mitral regurgitation, which was proven to be caused by *Bb*-infected myocarditis and required urgent valve replacement. Another case is a 59-year-old patient who developed aortic stenosis as a result of Lyme endocarditis [24,25].

The heart's tissues are not the only ones affected by Lyme disease. There are verified instances of **vasculitis** during the Lyme disease course, particularly of the arteries of the central nervous system, even resulting in stroke. According to animal studies, infections may affect other arteries, even big ones like the aorta [5].

## Diagnosis

Lyme carditis still causes diagnostic difficulties, especially since patients often do not recall contact with a tick. It is crucial to consider Lyme disease in the differential diagnosis of unexplained cardiac ailments or ECG abnormalities, particularly in young patients, as it is a potentially reversible cause. Prompt implementation of treatment will prevent the needless pacemaker placement.

Several factors should be considered during the diagnostic process:

- typical clinical presentation of the illness;
- history of contact with a tick, presence of *Erythema migrans*, staying in an endemic area or being exposed to bites due to their profession;
- two-tier serological diagnostics: ELISA and Western blot;
- response to antibiotic therapy
- differential diagnosis

Evaluation by ELISA of the presence of IgG and IgM antibodies against *Borrelia* spirochetes is a good screening method, although imperfect. In the early stages of the disease, these tests can give negative results and are characterized by low specificity and a significant probability of false positive results (for instance in patients with rheumatoid factor or autoimmune diseases). It should also be remembered that a positive titer of antibodies may persist for years after the disease. Therefore, in order to verify positive or questionable results, it is recommended to perform a two-stage diagnosis using verification tests based on the Western blot method [5]. In cases with clinical suspicion of the illness and negative serology, Lyme disease cannot be eliminated hence testing should be done after roughly 6 weeks [1].

Additional methods are sometimes used to assess the myocardium in the course of Lyme disease. **Cardiac magnetic resonance** using the late gadolinium enhancement allows to detect foci of necrosis, scars, inflammation of the myocardium, and thus indirectly diagnose the disease. The literature has recently placed a strong emphasis on the correlation between the degree of AVB in the course of LC and the picture of inflammatory changes in CMR, as well as the potential importance of this test in determining whether to administer antibiotics [26].

Tests detecting genetic material of bacteria (PCR and real time PCR) have only limited use to search for spirochetes in skin lesions, from cerebrospinal fluid or synovial fluid, especially in the early phase of infection. Therefore, it is not always possible to perform this test, because these symptoms should occur simultaneously with cardiac involvement to prove the link between the disease and the infection. This may be possible by examining the myocardial material obtained by endomyocardial biopsy, but is not routine practice due to its invasive nature [5].

## **Treatment**

The foundation of Lyme carditis treatment is a 14-28 day antibiotic regimen. Asymptomatic patients with positive serology should not be treated.

According to the recommendations, the following medications are effective [7]:

- ceftriaxone 2g/day i.v.
- doxycycline 2 x 100 mg/day p.o.
- amoxicillin 1.5-2 g/day p.o.
- macrolides - in case of allergy or intolerance

No justification exists for months of antibiotic treatment. Fever, chills, and hypotension may occur in 10-15% of patients in the first days of antibiotic therapy. It is a Jarisch-Herxheimer reaction associated with a massive release of spirochete antigens and an increase in the amount of cytokines [1].

Appropriate treatment results in complete resolution of conduction disorders in more than 90% of individuals - even advanced block may resolve within a week, and 1st block within 6 weeks [17,18].

However, conduction disturbances can also rapidly progress to a complete block (average in 35% of patients), **temporary transvenous or transcutaneous pacing** may be required in some situations (up to 30%). Only a small percentage of the reported cases permanent complete block that required pacemaker implantation occurred [5,7].



According to current guidelines, temporary stimulation should be avoided whenever possible, and if it is used, the duration of treatment should be kept as short as possible. This position is associated with a high pacing complication rate for the procedure and an increased risk of infection and thromboembolic events. Side effects outweigh the beneficial effects of temporary stimulation. **Permanent pacemaker implantation** is recommended only in case of treatment failure or symptomatic complete block with haemodynamic disturbances. Cases of unnecessary implantation of pacemakers in patients with LC have been described. Repeatedly, the pacemakers were subsequently removed or a negligible or no pacing rate was found at follow-up visits [17].

Patients suffering episodes of syncope, second- or third-degree atrioventricular block, or a PQ >300 ms should be hospitalized for continuous rhythm monitoring, and the hospital should have the ability to temporarily implant pacemaker [1,7].

### **Prognosis**

The prognosis for patients with cardiac involvement is favorable. In more than 90% of patients, complete recovery of heart abnormalities occurs after 3-42 days of standard antibiotic therapy [5]. The literature has 9 reports of deaths in the course of LC. Acute lymphocytic myocarditis resulted in sudden cardiac mortality in 7 instances. Advanced atrioventricular block was unlikely to be the direct cause of death in these cases. Non-cardiac problems led to mortality in 2 instances [18].

### **Conclusion**

It is usually worthwhile to take Lyme disease into consideration when making a differential diagnosis of enigmatic cardiac symptoms, especially in young patients. By raising awareness of the condition, it will be possible to diagnose patients more quickly thus implementing the targeted treatment and simultaneously sparing the patients from unnecessary invasive therapy, such as constant stimulation of the heart.

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### **Author's contribution**

Conceptualization, Z.L.; writing, review and editing: Z.L., J.F., M.M., U.Ž., D.S., E.S. All authors have read and agreed to the published version of the manuscript.

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