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LYME DISEASE AND THE HEART

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1. ABSTRACT

Lyme carditis is typically characterized by varying degrees of intermittent atrioventricular block occurring within weeks of infection with *Borrelia burgdorferi*. Myocarditis and/or pericarditis may occur. Cardiomyopathy has been associated with *B. burgdorferi* in Europe, but not in the United States. Patients with unexplained atrioventricular block or myopericarditis should be questioned for recent travel to tick-endemic areas, and for a history of erythema migrans rash, "viral-like" illness, aseptic meningitis, cranial nerve palsy, radiculitis, or oligoarthritis. However, the absence of a recognized tick bite or rash does not rule out Lyme disease. The diagnosis of Lyme carditis should be supported by the presence of concurrent erythema migrans, or by positive results of 2-step laboratory testing for antibodies to *B. burgdorferi*. False positive results may occur, emphasizing the importance of clinical judgment in attributing specific manifestations to *B. burgdorferi* infection. Carditis generally resolves spontaneously, but antimicrobial therapy can shorten symptom duration and prevent potential cardiac and non-cardiac sequelae. Cardiac manifestations generally resolve spontaneously, but antimicrobial therapy can shorten symptom duration and prevent potential cardiac and non-cardiac sequelae. The prognosis for Lyme carditis is excellent.

2. INTRODUCTION

Lyme disease, the most common vector-borne illness in the United States, is a bacterial infection, caused by the spirochete *Borrelia burgdorferi* sensu lato (1,2). Cutaneous, cardiac, neurologic and rheumatologic manifestations may occur (1, 2). The skin rash, erythema migrans, is a hallmark of disease (Figures 1, 2).

Lyme disease is endemic in the Northeastern and Middle Atlantic regions of the US as well as in parts of the Midwest and the Pacific Coast. It also occurs in much of Europe, Russia, Japan, and China (1,2). Infection is transmitted by ticks of the *Ixodes ricinus* complex,

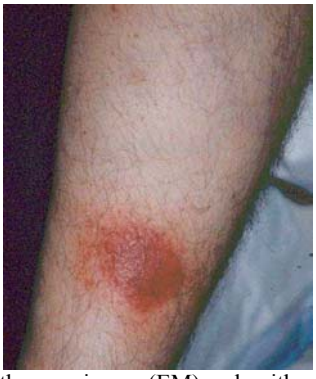

Figure 1. Erythema migrans (EM) rash with a homogenous character. Central clearing occurs in less than half of cases of EM occurring in the US.

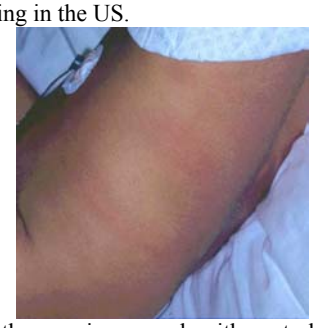

Figure 2. Erythema migrans rash with central clearing in a 21-year old landscaper with Lyme carditis. Borrelia burgdorferi (RFLP type 2) grew in culture from a skin biopsy performed at this site.

primarily in temperate zones of the Northern hemisphere (1,2).

In this review we will focus on the cardiac manifestations of Lyme disease. Our understanding of these manifestations is limited by several factors. First, because of the relatively few cases of cardiac disease compared with the number of patients with erythema migrans, insufficient numbers of patients have been available to enroll in controlled clinical trials. Therefore, much of our knowledge is based either upon case reports or upon observations made 20 years ago before "the antibiotic era" of Lyme disease. In those days, prior to the recognition of appropriate treatment for this infection, Lyme carditis was probably more common than it is now and the typical course was likely to have been much different from that seen today (see below; Epidemiology). Thus, much of the data presently available to us may be somewhat misleading.

In addition, the recognition of Lyme carditis almost always requires laboratory support for the diagnosis, unlike erythema migrans, which usually has a unique and readily distinguishable clinical presentation. *B. burgdorferi* is difficult to isolate from patients with Lyme disease lacking this rash (2), and thus most cases of Lyme carditis are diagnosed on the basis of positive serology. Unfortunately, problems with specificity are common with laboratory testing for this infection (3) (see below; Laboratory diagnosis). Therefore some cardiac manifestations may have been erroneously attributed to Lyme disease in the published literature and should be reevaluated.

3. SETTING

Approximately 7-10 days (range 3-30 days) after the bite of certain *Ixodes* ticks, an expanding rash, erythema migrans, develops at the former site of tick attachment (1,2,4,6). The rash may or may not be associated with systemic symptoms such as fever, arthralgia, myalgia, and headache (but rarely respiratory or gastrointestinal complaints). Although often thought to resemble a "bull's eye" or target, most erythema migrans lesions in the US lack central clearing (Figure 1) (4,5,6). Multiple lesions, associated with hematogenous dissemination of the spirochete, occur in approximately 15% of US patients with erythema migrans rash and in a smaller percentage of European patients (7,8,9). Extracutaneous manifestations such as carditis, cranial nerve palsies and/or meningitis may develop weeks later. Months later, oligoarthritis may occur, usually affecting the knee at some point (10).

In the US, and probably in most European cases, Lyme carditis typically occurs within weeks of initial infection (median of 21 days [range 4-83 days] after onset of erythema migrans), at a time when the erythema migrans rash may still be visible (11). In Europe, dilated cardiomyopathy and heart failure have been attributed to infection with *B. burgdorferi* that presumably occurred years previously (12,13). The likelihood of carditis has been postulated by one European group to correlate with the length of the incubation period, duration of untreated erythema migrans, size of erythema migrans and presence of systemic symptoms (14).

4. EPIDEMIOLOGY

Estimates of the incidence of Lyme carditis in the US have varied (15,16,17). In a 1978 report by Steere *et al*, overt carditis primarily manifesting as conduction disturbances was observed to occur in 8% of untreated patients with Lyme disease, mostly acquired in New England (15). Years later, the Connecticut health department described the incidence of Lyme carditis to be 2% (16). Shapiro reported even a lower incidence (0.5%) in 201 consecutive children diagnosed with Lyme disease in the same state (17). The reasons behind this decline may be related to the recognition and treatment of early Lyme disease (primarily erythema migrans) with resultant prevention of extracutaneous sequelae.

At least two studies support this conclusion. In a prospective study conducted in 1992, Lyme carditis (as demonstrated by atrioventricular block) was identified in only 1.6% of 61 patients with early Lyme disease characterized by erythema migrans (18). All patients had an electrocardiogram (EKG) obtained at enrollment prior to receiving antibiotics. The only patient with heart block at presentation had complete resolution of his symptoms and normalization of his EKG after treatment with antibiotics. No patient in the study developed new conduction

Table 1. Proposed Case Definitions of Lyme Carditis

	USA (CDC [1])	Europe (EUCALB [2])
Clinical case definition	Acute onset of high grade (2nd or 3rd degree) atrioventricular conduction defects that resolve in days to weeks and are sometimes associated with myocarditis. *Palpitations, bradycardias, bundle branch block, or myocarditis alone are not criteria for cardiovascular involvement*	Acute onset of atrioventricular (II-III) conduction disturbances, rhythm disturbances, sometimes myocarditis or pancarditis
Laboratory criteria for diagnosis [3]	Isolation of *Borrelia burgdorferi* in culture from clinical specimen ***or*** Demonstration of diagnostic IgM or IgG antibodies to *B. burgdorferi* in serum or cerebrospinal fluid (CSF) (A two-test approach using a sensitive enzyme immunoassay or immunofluorescence antibody assay followed by western blot is recommended) (75)	Culture of *B. burgdorferi* from endomyocardial biopsy is considered supportive evidence Significant change in levels of specific IgG antibodies is considered essential

[1] CDC = Centers for Disease Control and Prevention (31); [2] EUCALB = European Union Concerted Action on Risk Assessment in Lyme Borreliosis (32); [3] Required for diagnosis of extracutaneous Lyme disease

abnormalities at follow-up 20 days after enrollment, or had abnormal cardiac examination or cardiac symptoms at 3- and 12- month follow-up visits (18).

In addition, a retrospective report, using multivariate analysis, concluded that the prevalence of cardiac events, including electrocardiographic abnormalities, in treated Lyme disease patients was not statistically different from that of the general population (19). This study, together with the prospective trial above (18), thus suggest that the treatment of early Lyme disease can prevent the development of cardiac complications.

In Europe the incidence of carditis has been estimated to be much lower than that in the US, even in untreated patients (20). Possible reasons for this discrepancy are differences in case reporting, selection bias and, perhaps most importantly, differences in tissue specificity of European genospecies (*B. garinii* and *B. afzelii*) compared to that of *B. burgdorferi* sensu stricto (see below; Etiology) (7,20).

A high male to female ratio (3 to 1) has been described for Lyme carditis (21), although there is no difference in the overall incidence of Lyme disease in men versus women (22). Conceivably, sex-related electrophysiologic factors could account for these differences (23). Another potential explanation could be the well-described gender bias in the diagnosis of cardiac disease. Men may be more likely to get an electrocardiogram when they present with chest pain or palpitations in the emergency room (24).

5. ETIOLOGY

Three genospecies of *B. burgdorferi* sensu lato have been widely reported to cause disease in humans, although there have been many others isolated from animals and arthropods (7). So far all of the clinical isolates in the US belong to the genospecies *B. burgdorferi* sensu stricto whereas in Europe *B. afzelii* and *B. garinii* also cause disease (7). Only the latter 2 genospecies have been thus far implicated as the cause of Lyme disease in Asia (25). A fourth genospecies *B. bissettii* has been cultured from Slovenian patients with Lyme disease, but has not been isolated from clinical specimens by other groups (26). This genospecies has, however, been identified in ticks and rodents in the US (27), although it has not yet been implicated as a cause of North American Lyme disease.

Because cardiac involvement appears to be more common in the US than in Europe, one might predict that most cases of Lyme carditis might be related to infection with *B. burgdorferi* sensu stricto, since other Borrelia genospecies have not been isolated from US patients (7). To date, there is limited information regarding specific genospecies in Lyme carditis. However, in a Dutch study of 66 culture-positive patients with various manifestations of Lyme disease, *B. garinii* was isolated from the only patient with carditis (manifested by atrioventricular block). This patient also had arthritis (28).

Recently recognized differences in US strains of *B. burgdorferi* sensu stricto, based upon restriction fragment length polymorphism (RFLP) analysis, have been associated with differences in virulence (29). A mouse model of Lyme disease has been used to study whether some strains are more likely to cause cardiac disease (30). Two distinct RFLP types of *B. burgdorferi* sensu stricto, both originally isolated from human clinical specimens, were inoculated into mice. One specific RFLP type was significantly more frequently recovered from heart tissue than other types, and was associated with more severe carditis (and arthritis) based on histologic scores (30). To our knowledge only two culture positive patients with Lyme carditis have had RFLP typing performed. Both had RFLP type 2 (Ira Schwartz, personal communication).

6. CLINICAL MANIFESTATIONS OF LYME CARDITIS

6.1. Definition

The Centers for Disease Control and Prevention (CDC) have published a guideline to define the various manifestations of Lyme disease for surveillance purposes (31). Although not originally intended for clinical diagnosis, the definition is nevertheless useful (Table 1). Both clinical and laboratory parameters are required for the diagnosis of extracutaneous Lyme disease such as carditis, as distinguished from erythema migrans, for which a clinical diagnosis alone is considered sufficient. Patients with only 1st degree atrioventricular block and positive serology for antibodies to *B. burgdorferi* do not meet the requirements for the diagnosis of Lyme carditis. First degree atrioventricular block has many causes and may be unrelated to Lyme disease; positive serology may reflect prior infection or a false positive result (3).

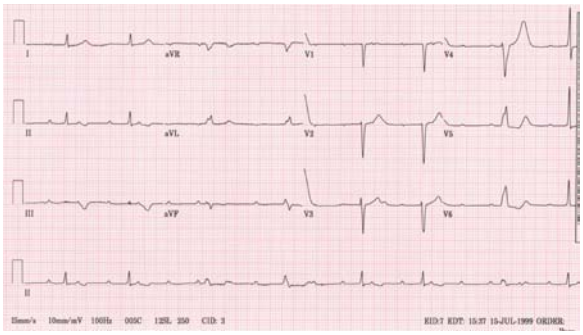

Figure 3. An electrocardiogram showing complete atrioventricular block (same patient whose rash is depicted in Figure 2).

In Europe, the European Union Concerted Action on Risk Assessment in Lyme Borreliosis (EUCALB) has also published a case definition for the diagnosis of Lyme disease (usually referred to as Lyme borreliosis in Europe) (Table 1) (32). This guideline is similar in many respects to the CDC document. Unlike the CDC guidelines, a change in levels of specific IgG antibodies is required for laboratory diagnosis (32). It should be noted that in the EUCALB definition, chronic cardiac conditions such as dilated cardiomyopathy, are not clearly considered to be caused by *B. burgdorferi*, despite the reported isolation of this organism from several endomyocardial biopsies (33,34). Specifically, it was proposed that cardiomyopathy "may predispose to colonization" with *B. burgdorferi* as opposed to this organism being the etiology of cardiomyopathy (32,33).

6.2. General

Lyme carditis may or may not present with symptoms referable to conduction disturbances (Figure 3) (11). Patients with atrioventricular block may present with syncope, chest pain, palpitations, and dyspnea, or less specific symptoms such as dizziness and fatigue (11,35,36,37,38,39,40). Although a history of tick bites has been solicited in approximately half of cases of European Lyme carditis, this incidence is lower in the US (21). The absence of a history of a tick bite does not make the diagnosis less likely. The relatively high rate of recall of tick bite in patients with carditis compared with those with erythema migrans (≈ 25% [6]) may be due to selection bias. Patients with cardiac disease are more likely to be worked up for Lyme disease if a history of tick bite is elicited. Those without a history of tick bite may remain undiagnosed if no serologic tests are obtained.

On physical examination, bradycardia, tachycardia (or bradycardia alternating with tachycardia), flow murmur, murmur of mitral insufficiency, gallop rhythm, rales, and pericardial friction rub may be present (11,35,36). In a cohort of 20 US patients reported in 1980, an erythema migrans rash had been recognized in 19 of 20 patients with carditis, and was still present in 15 of these patients at the time cardiac disease was manifest (11). In most of these patients the rash was characterized by multiple (secondary) lesions (11).

Erythema migrans may, however, go unnoticed since it is usually unassociated with significant local symptoms, may be unaccompanied by systemic symptoms in approximately one third of cases (6), and typically develops on parts of the body that are not easily visualized (e.g., buttocks, back, or popliteal fossa) (6). The reason for this is that ticks feeding on readily visible sites (e.g., the forearm) are more likely to be noticed and removed before infection can be transmitted, whereas ticks attached to other parts of the body can feed long enough for infection to take place. Transmission of Lyme disease is believed to require ≥ 48 hours of tick attachment (41). An examination of the entire patient (i.e., with all clothes removed) should be performed to look for erythema migrans if the diagnosis of Lyme disease is suspected, regardless of whether or not the patient has clinical signs or symptoms of carditis.

Patients with Lyme disease should also be assessed for the presence of other infections that may be present simultaneously as a result of the same Ixodes tick vector that transmits B. burgdorferi infection (42,43). Patients with unexplained leukopenia, thrombocytopenia or anemia, should be evaluated in particular, since these findings do not result from Lyme disease, but are typical of human granulocytic ehrlichiosis (42) and/or babesiosis (43).

Patients with cardiomyopathy and heart failure may be expected to present in a similar fashion to those with other causes of these syndromes (i.e. chronic symptoms of shortness of breath and lower extremity edema) (12,13). An erythema migrans rash would be expected to be absent in a patient with long-term symptoms (i.e., months as opposed to days or weeks). A comparison of some aspects of Lyme carditis in the US versus Europe is depicted in Table 2.

6.3. Rhythm and Conduction Disturbances

Lyme carditis typically presents with conduction disturbances, the most common of which is atrioventricular block (11, 21). Different forms of block tend to occur intermittently in a single patient. In Steere's 1980 description of a cohort of patients with Lyme carditis, 18 of 20 patients had documented 1st degree atrioventricular block, while 8 of these patients also had 2nd degree atrioventricular block, and 8 in addition had complete atrioventricular block (11). The extent and location of atrioventricular block in patients with Lyme carditis has been studied using electrophysiological techniques (11,18,35,39,44,45). These reports and findings are summarized in Table 3 and Figure 4.

In a 1989 review, 8 of 9 patients with Lyme carditis who had electrophysiological studies performed had block above the His bundle (36). The remaining patient, who had block at or below the His bundle, required a permanent pacemaker. Three patients in this series also had sinus node dysfunction. Fluctuating left or right bundle branch block was reported as well.

Van der Linde, in a review of the clinical characteristics of 66 cases of Lyme carditis in Europe and

Table 2. Lyme Carditis in the US vs. Europe [1]

	United States	Europe
Tick vector	*Ixodes scapularis* [2]	*I. ricinus*
	I. pacificus [3]	*I. persulcatus*
Organism [4]	*Borrelia burgdorferi* sensu stricto	*B. burgdorferi* sensu stricto and *B. garinii*; ?*B. afzelii*, ?*B. bissettii*
Atrioventricular block[5]		
First degree	20%	8%
Second degree	13%	18%
Third degree	51%	48%
Erythema migrans[6]	82%	58%
Multiple lesions	More common	Uncommon
Neurological illness [56]	28%	26%
Joint involvement [6]	61%	45%
Clinical heart failure	10%	15%
Pericarditis	5%	23%
Cardiomyopathy	Not reported	Occasionally reported
Temporary pacemaker required	48%	27%
Complete recovery [7]	97%	92%

[1] Modified from van der Linde, *et al*: Lyme carditis: clinical characteristics of 105 cases of Lyme carditis (21); [2] Formerly known as *I. dammini*; [3]Accounts for small percentage of cases in the Western US; [4] Only *B. burgdorferi* sensu stricto and *B. garinii* have thus far been reported to be isolated from clinical specimens from patients with Lyme carditis; [5] Maximal degree of block (patients with carditis typically have intermittent forms of atrioventricular block); 1st degree atrioventricular block is not considered to be a specific manifestation of Lyme carditis according to CDC criteria; [6] Unspecified whether extracardiac illness was simultaneous or occurred previously; [7] Failure reflects death or permanent pacemaker.

Table 3. Location of Atrioventricular Block in Lyme Carditis

Level of block	Site of block in Figure 4	Electrophysiologic finding [1]	Reference
Supra-His	A,B	Prolonged AH	11
			35
			44
AV node	B	Prolonged AH	18
			39
Intra-His	C	Prolonged HH	37
			39
			45
Intra-His and Infra-His	C,D	Prolonged HH and Prolonged HV	40
Diffuse	A,B,C,D	Prolonged AH and Prolonged HV	(9

[1] AH: Atrio-His interval; HH: His-His interval; HV: His-ventricular interval

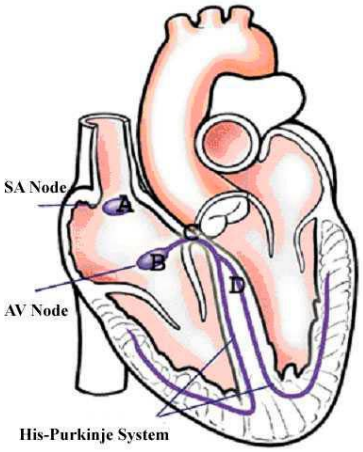

Figure 4. Potential locations of conduction disturbance as indicated by various electrocardiographic studies (see Table 3) (Reprinted with the permission of The Cleveland Clinic Foundation)

39 cases from the US, found that complete heart block was the most common form of atrioventricular block in both groups (21). Electrophysiological studies, performed in 19 patients, showed a supraventricular origin of the block in 68%. One third of patients studied were believed to have had diffuse conduction system disease based upon simultaneously prolonged intra-atrial, atrio-His and His-ventricular conduction.

In a prospective study of 220 Slovenian patients with solitary erythema migrans, atrioventricular block occurred no more frequently than in healthy controls (14). Electrocardiographic abnormalities such as short Q wave duration and deep S wave were observed in patients with Lyme disease. The etiology and significance of these findings remain unknown (14). In one US report, evidence was presented suggesting that subclinical exposure to *B. burgdorferi* may be associated with slowing of the sinus node (46). In this study, "healthy" ambulatory adults from an endemic area (Wisconsin) had serology for antibodies to *B. burgdorferi* and a 12-lead EKG performed. Athletes and persons with a history of "major medical problems" or Lyme disease were excluded. Seropositive persons were more likely to have bradycardia (53% vs. 27%; p=0.02), and also had a slightly lower mean heart rate (59 [range 45-81] vs. 66 [range 39-11]; p=0.04). All subjects were asymptomatic and no significant difference was observed in the occurrence of abnormal atrioventricular conduction, QRS morphology, axis, rhythm, or overall EKG interpretation. The study was limited by the omission of western blot analysis and by the failure to control for differences in physical activity among seropositive and seronegative groups. The ramifications of the study

findings are thus unclear, and the conclusions require confirmation.

Various arrhythmias including atrial tachycardia, non-sustained ventricular tachycardia and asystole have also been reported (38,47,48). However, in at least one case of ventricular tachycardia (48), the relationship to Lyme disease was tenuous because of negative serology, the absence of inflammation on myocardial biopsy, and the potential for other etiologies of ventricular tachycardia (e.g., increased alcohol intake in a 67 year old man). Although arrhythmias attributed to Lyme disease have usually been preceded by other stigmata of infection such as erythema migrans, the occurrence of atrioventricular block in the absence of other findings of *Borrelia* infection has been reported (49,50). It is likely, however, that in a large percentage of such patients erythema migrans occurred but was unrecognized before it resolved (either spontaneously or with treatment).

Rare fatalities have been attributed to Lyme carditis (51,52). In one 66 year-old patient with coexistent babesiosis, the cause of death was unknown but may have resulted from complete heart block, ventricular arrythmias or both (51). However, an EKG was not performed during the patient's hospital course. Neither tissue nor blood cultures were obtained, but an indirect immunofluorescence assay (IFA) was positive for antibodies to *B. burgdorferi*, although an immunoblot was not performed. No antibiotic treatment was administered for Lyme disease prior to death. Autopsy showed findings of severe pancarditis with forms resembling spirochetes on Dieterle silver impregnation stain. The role of babesiosis in this patient's outcome could not be ruled out. In another patient who presumably had sudden death, carditis was evident on autopsy but details were not provided (52). Antibodies to *B. burgdorferi* were detected by ELISA but no other supporting laboratory tests were performed. The diagnosis of Lyme carditis in this patient should thus not be considered to have been firmly established.

6.4. Myocarditis and Pericarditis

Myocarditis may occur with or without pericardial involvement (51,53,54). Myopericarditis was reported to occur in 13 of 20 (65%) patients with Lyme carditis at a single center (11), but in less than 15% of 84 patients reported to the CDC from all over the US (55). Selection bias and different definitions for Lyme carditis might explain the considerable disparity in these results. In a review of European and US patients with Lyme disease involving the heart, clinical evidence of congestive heart failure was reported to occur in more than 10% of patients (21). This estimate may be high as a result of a reporting bias favoring the publication of descriptions of sicker patients. Electrocardiographic changes suggestive of myocarditis may include ST depression or T wave inversions (11,35,36). A variety of imaging studies may support the diagnosis of myocarditis (See below; Laboratory). In general, myocarditis associated with Lyme disease is relatively mild and transient (11,35,36).

Lyme pericarditis has been reported to be less common in the US than in Europe (~5% vs. 23%) (21). Chest pain may be an uncommon presentation, in contrast to other causes of pericarditis, occurring in only 2 of 11 patients with both Lyme disease and electrocardiographic changes suggestive of pericarditis (11). Pancarditis was evident on autopsy of a patient with both Lyme carditis and simultaneous babesiosis (51).

Unusual manifestations of pericardial involvement have been described. Pericardial tamponade, associated with Lyme disease was reported in a seropositive patient in Holland (56). After presenting with chest pain, fever, dyspnea, and non-productive cough, the patient developed pulsus paradoxus and was noted to have a large pericardial effusion. Pericardiocentesis was performed and fluid showed a few macrophages, granulocytes and lymphocytes. Although cultures for *B. burgdorferi* were not reported, spirochete-like structures were demonstrated in pericardial fluid using two different methods, including indirect immunofluorescence and monoclonal antibody directed against the flagellar antigen of *B. burgdorferi*, combined with immuno-gold-silver staining. The patient recovered after a 2-week course of ceftriaxone and remained well during 2 years of follow-up. A separate European report described a 54-year-old woman with recurrent pericardial effusion that was attributed to Lyme disease (57). This assessment was made on the basis of a history of a tick bite and erythema migrans rash (antedating the effusion by 1 year), reactive antibodies to *B. burgdorferi* in serum and pericardial fluid, and resolution after intravenous ceftriaxone. The effusion had previously been refractory despite treatment with corticosteroids and one year of "tuberculostatics".

6.5. Cardiomyopathy

Lyme disease has been implicated as a possible cause of dilated cardiomyopathy in Europe, based upon the isolation of *B. burgdorferi* from heart tissue (32,33), and upon serologic study of patients with cardiomyopathy (12,58). Although spirochete-like forms have been periodically detected in cardiac tissue of some patients with presumed Lyme carditis (33,34,52,58,59,60,61), *B. burgdorferi* has been isolated in culture from the hearts of only rare patients (33,34). All were Europeans with clinical evidence of congestive heart failure including one with long standing dilated cardiomyopathy (33). It has been postulated that the inability to detect *B. burgdorferi* in more patients with chronic heart disease could be due to infection in the remote (rather than the recent) past (62). In this hypothesis, cardiomyopathy results from residual scarring and fibrosis as opposed to continued active infection. This process has yet to be confirmed experimentally in an animal model.

Other possible evidence for Lyme-associated cardiomyopathy comes from sero-surveys (12,13) and case reports (34,62,63). In a small Austrian study, 11 (24%) of 46 patients with dilated cardiomyopathy were seropositive for *B. burgdorferi*, with 9 of 11 having histories of erythema migrans and tick bite (62). These patients had a mean left ventricular ejection fraction of 30% by cardiac

catheterization and echocardiography. Endomyocardial biopsy results were not reported. Nine patients (82%) with cardiomyopathy attributed to Lyme disease, had improved or normalized left ventricular function six months after completion of a two week course of intravenous ceftriaxone (62,63).

Evidence for the existence of Lyme associated cardiomyopathy in the US is less compelling. A seroprevalence study conducted in an endemic area (Minnesota) was unable to link severe congestive heart failure to infection with *B. burgdorferi* (64). In another US study, *B. burgdorferi* outer surface protein (Osp) A antigen sequences were not demonstrated in explanted hearts of 68 patients with dilated cardiomyopathy even though they lived in a Lyme endemic area and had antibodies to *B. burgdorferi* (65). If there are true differences in the occurrence of chronic cardiac Lyme disease between Europe and the US, it is possible that they relate to differences in Borrelia genospecies (7,28). There are presently insufficient data to address this possibility, in part because of the rarity with which *B. burgdorferi* has been isolated from heart tissue.

The association between Lyme disease and cardiomyopathy is not certain for the vast majority of patients in whom the diagnosis of Lyme carditis was based on laboratory tests other than culture. For instance, since cardiac tissue contains collagen fibrils that somewhat resemble the helical form of a spirochete, false positive results might arise from using silver staining to detect *Borrelia* in cardiac specimens. Although patients with presumed Lyme associated cardiomyopathy may have high antibody levels to *Borrelia*, this might reflect false positive results, unrelated past infection and/or higher B-cell activation (64). Therefore, it may be problematic to attribute manifestations of chronic heart disease to *B. burgdorferi* infection.

6.6. Other Cardiac Disorders

Based on elevated IgG antibody levels in several patients, *B. burgdorferi* has been proposed as an etiology of valvular degeneration, myocardial infarction and subacute bacterial endocarditis (66,67,68). However, in none of these cases were spirochetes identified pathologically, and for none was the purported evidence for a *Borrelia* associated cardiac problem compelling. It should be noted, moreover, that patients with nonspirochetal subacute bacterial endocarditis may have false positive antibodies (both ELISA and immunoblot) to *B. burgdorferi* (69,70). Until more evidence is forthcoming, Lyme disease should not be considered a recognized etiology for subacute bacterial endocarditis, myocardial infarction or valvular degeneration.

7. PATHOLOGICAL FINDINGS

7.1. Mouse Models

A mouse model has been used to study the effects of *B. burgdorferi* on the heart. Ten days after needle inoculation with *B. burgdorferi*, two different strains of mice (C3H/HeNCrl [C3H] and C57B1/6J [B6]) developed evidence of carditis (71). Mixed leukocyte infiltration and fibroblastic proliferation were detected. The spirochete infiltration was greatest 15 days after infection. After 30 days, lymphocytes and macrophages replaced neutrophils as the predominant cell type. Although EKG evidence of conduction disturbances was not noted, some infected mice developed transient tachycardia or bradycardia, without an elevation of cardiac enzymes (71). Cardiac inflammation subsided after day 15; however, a residual periaortic lymphoplasmacytic infiltrate persisted until day 90 when the experiment ended (71). Compared with B6 mice, detection of spirochetes occurred earlier in C3H mice, and was associated with more severe cardiac infection, as measured by histologic changes, spirochete numbers, incidence of bradycardia and tachycardia, and time required for spirochete clearance.

In a separate study, immunodeficient mice lacking class II major histocompatibility complex (MHC) (i.e., depleted of CD4+ lymphocytes) and immunocompetent (C3H/HeJ and C57BL/6) mice were infected with *B. burgdorferi* (72). The immunodeficient mice shared >95% homozygosity at unlinked loci with the immunocompetent C57BL/6 strain. Similar histopathology was observed in the three groups. Thus, the development of carditis was not dependent on either antigen presentation to CD4+ T-lymphocytes or on class II MHC molecule expression. Lyme carditis was postulated to result from the direct interaction of spirochetes with macrophages, which predominated in cardiac infiltrates.

The role of T- and B- cells in the development of Lyme carditis was studied by infecting with *B. burgdorferi* immunocompetent (C57BL/6J [B6]) and immunodeficient mice, the latter group either lacking B-cells but bearing T-cells (B6-*Igh6* KO [knockout]) or lacking T- and B-cells (B6-*Rag1* KO) (73). B-cells appeared both necessary and sufficient for the resolution of carditis. In contrast, CD4+ T-cells appeared important in the induction and exacerbation of carditis.

A murine model was recently developed for the conduction abnormalities characteristic of Lyme carditis, using C3H/HeJ (C3H) mice that were infected with *B. burgdorferi* at only 3 weeks of age (74). Two weeks from the onset of infection, the mice developed EKG abnormalities that resolved spontaneously 8 weeks later, mimicking the natural course in humans. Wider QRS complexes were observed in infected mice compared to their age and gender matched controls, however no evidence of AV nodal conduction abnormality was demonstrated. Upon pathologic examination, the hearts showed evidence of epicardial and subepicardial leukocytic infiltration with mononuclear cells and macrophages. The degree of inflammation correlated closely with the presence of conduction abnormality. The pathologic findings resolved after 8 weeks of infection paralleling the resolution of EKG changes (74).

7.2. Humans

The pathologic findings of Lyme carditis in humans are based on relatively few cases (33,34,35,52,59,60). In human endomyocardium, inflammation consists of areas of dense lymphoplasmacytic

infiltrates, mostly in interstitial areas, and usually unassociated with microangiopathy or neutrophilic or eosinophilic infiltrates (33,34). Myocyte necrosis has been described (35,52). Lymphoplasmacytic pericardial inflammation may also be present (51). Forms resembling spirochetes have been visualized in human cardiac biopsies near and in inflammatory infiltrates between muscle fibers and in the endocardium using methods of silver staining (33,51,60,61).

B. burgdorferi has rarely been isolated from hearts of European patients with Lyme carditis (33,34). Extremely large and vesicular myonuclei, atrophic and hypertrophic myocardial fibers, and thickening of the walls of the small endomysial vessels were described in a patient with longstanding cardiomyopathy whose endomyocardial biopsy culture grew *B. burgdorferi* (33). In another European patient who had cardiomegaly, hypokinetic left ventricle and severe heart failure, endomyocardial biopsy grew *B. burgdorferi*, although 5 biopsy samples from the left ventricle showed no histologic evidence of myocarditis (34).

8. LABORATORY DIAGNOSIS

In patients with a clinical syndrome suggestive of Lyme carditis (e.g. unexplained atrioventricular block in a patient who has recently traveled to an endemic area) certain laboratory tests may be helpful in supporting the diagnosis (1,2,3,75,76,77). The "gold standard" for the diagnosis of an infection is the isolation in culture of the etiologic agent. In the case of Lyme disease, the causative organism, *B. burgdorferi* is readily cultured from skin biopsy specimens (6,7), and from blood (78) in patients with erythema migrans. Unfortunately, *B. burgdorferi* is rarely isolated from specimens obtained from patients with only extracutaneous disease. There are several reasons for this. First, specific techniques and culture medium (Barbour-Stoenner-Kelly [BSK]) are required (6,7,78), and are not readily available. Moreover, even when specialized laboratories are utilized, negative cultures may result because of sampling error due to the spirochetes being present in tissue in low concentrations.

In addition, some tissues (e.g., cardiac conduction pathways) are not easily accessible to biopsy, and the organism may no longer be in the blood or skin at the time cardiac symptoms are prominent. Alternatively, cardiac disease may be a result of para-infectious phenomena (e.g., inflammation) rather than the result of direct damage from viable spirochetes (79). Efforts to detect nucleic acids of *B. burgdorferi* (e.g., polymerase chain reaction [PCR]) are limited by some of these same factors. PCR may be subject to false positive results (e.g., contamination) or false negative results (e.g., due to blood inhibition of detection) (80). Other putative direct detection methods are even more problematic. At present, these techniques (e.g. urine antigens assays) have no role in a clinical practice setting in the diagnosis of any manifestation of Lyme disease.

Because of the difficulties in direct detection of *B. burgdorferi*, the laboratory diagnosis of extracutaneous Lyme disease presently relies primarily upon serologic assays. These tests measure antibodies to the organism that develop in most patients within several weeks of infection (77). A first step test, generally an enzyme linked immunosorbent assay (ELISA) or indirect immunofluorescence assay (IFA) is used to detect antibodies to either whole cell sonicates of *B. burgdorferi* or to specific recombinant proteins (76). Because many of these antibodies are non-specific, the use of a second-step test, using an immunoblot technique, has been recommended when the ELISA is positive or equivocal (75,76). Immunoblots are interpreted as positive or negative based upon the number of reactions with *Borrelia* antigens of specific molecular weights that have been separated by electrophoresis. A negative immunoblot following a positive or equivocal ELISA is likely to reflect a false positive ELISA. However, serology is negative in approximately half of patients with erythema migrans, particularly in patients ill for less than 2 weeks (77). A positive IgG blot is required to support the diagnosis of Lyme disease in a patient ill for more than one month (75,76). Since the reagents used in both 1st and 2nd step tests are similar, the immunoblot is not truly an independent assay and thus should not be called a confirmatory test (81). A positive test may reflect active infection, prior (resolved) infection, or a non-specific cross reaction. Results of antibody assays (IgM and/or IgG) may remain positive for years after clinical recovery, and thus serology has no role in measuring response to treatment (82). As with other tests, the positive predictive value is directly proportional to the prevalence of disease in the population tested (3).

The diagnosis of Lyme carditis has rarely been established by culturing *B. burgdorferi* from the myocardium of European patients with congestive heart failure and/or with cardiomyopathy (33,34). This organism has also been isolated from the skin biopsy culture of a 12 year old American boy with multiple erythema migrans lesions and carditis (83). His illness was characterized by non-specific atrioventricular conduction abnormalities, cardiac uptake on gallium scanning, and left ventricular inflammation and edema on magnetic resonance imaging (MRI).

Other tests such as silver staining (11,60), immunostaining (57,71), and PCR (80) have also been used to support the diagnosis of Lyme disease but have various shortcomings (Table 4). Radiographic imaging procedures may be useful in demonstrating the diagnosis of carditis in patients with clinical or laboratory evidence of Lyme disease. Transient cardiomegaly on chest radiography and depressed ejection fraction on 2D echocardiography have been described (11). Gallium scanning, magnetic resonance imaging (MRI) and indium scanning have been used to detect Lyme myocarditis (54,84,85). In one case, gallium-scanning uptake was positive in the heart of a 15-year-old girl who presented with syncope and erythema migrans. Her scan returned to normal 8 weeks later (86). Another patient with Lyme myocarditis showed resolution of the diffuse uptake on an indium cardiac antimyosin scan after antibiotic treatment (54).

Table 4. Laboratory Methods for Supporting the Diagnosis of Lyme Carditis

Method	Advantages	Disadvantages
Culture	Gold standard for diagnosis	Labor intensive; requires invasive procedure and special laboratory; false negative results (sampling error)
Silver staining	Readily available; can be performed on stored tissue	Requires invasive procedure; false positive results (e.g. fibrils); may not reflect viable organisms; false negative results (sampling error)
Direct antigen staining	Can be performed on stored tissue	Requires invasive procedure; may not reflect viable organisms; false negative results (sampling error); false positive results (cross reaction)
Polymerase chain reaction	Very sensitive; can be performed on stored tissue	Requires invasive procedure; false positive results (e.g. contamination); may not reflect viable organisms; false negative results (sampling error)
Serology	Readily available; relatively inexpensive; does not require an invasive procedure	False positive results; may remain positive after resolution of infection

Table 5. Partial Differential Diagnosis of Lyme Carditis [1]

Manifestation	*Infectious Causes*	*Non-infectious Causes*
Conduction disturbances	Rheumatic fever *Trypanosoma cruzi* (Chagas disease) Kawasaki disease *Treponoma pallidum* (syphilis) *Rickettsia rickettsii* (Rocky mountain spotted fever)	Beta-blockers, Digoxin, Coronary artery disease, Structural cardiac abnormalities, Anthracyclines, Ethanol, Cocaine
Myocarditis and/or Pericarditis	Rheumatic fever, Coxsackie virus, Human immunodeficiency virus *Trypanosoma cruzi* (Chagas disease) *Corynebacterium diphtheriae, Toxoplasma gondii*, Kawasaki disease, *Treponoma pallidum* (syphilis), *Yersinia enterocolitica, Rickettsia rickettsii* (Rocky mountain spotted fever)	Sarcoidosis Scleroderma Systemic lupus erythematosus (SLE)

[1] Most common presentation is fluctuating atrioventricular block

9. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Lyme carditis includes the causes of myocarditis and atrioventricular conduction abnormalities. A partial list of these entities, both infectious and non-infectious, is shown in Table 5.

10. MANAGEMENT AND ROLE OF ANTIMICROBIAL THERAPY

The majority of cases of atrioventricular block are reversible and as with most other manifestations of Lyme disease, resolve without interventions. Antibiotics are recommended because they decrease the duration of most manifestations of illness in humans and prevent serious sequelae (87). It has been observed that atrioventricular block resolves gradually after treatment, progressing from complete atrioventricular block to 2nd degree, and then to 1st degree block with decreasing PR intervals (36). Most cases resolve within 1 or 2 weeks (36).

In patients with first and second degree atrioventricular block associated with Lyme carditis, treatment with an oral antimicrobial regimen is generally sufficient (Table 6). Although no studies have been performed to compare various treatment durations, there is no reason to believe that long courses are required. In a recent trial of patients with erythema migrans without carditis there was no difference between outcome in patients treated with 10 days versus 20 days of doxycycline (88). There is no evidence that intravenous treatment is better than oral treatment for early-disseminated Lyme disease (89). It has been recommended that patients with third degree atrioventricular block should be treated in the hospital with an intravenous antibiotic such as ceftriaxone (87). The placement of a temporary pacemaker may be required (87,90,91). Patients with carditis and concurrent central nervous system manifestations or peripheral neuropathy related to Lyme disease should be treated with intravenous antibiotics, regardless of the degree of atrioventricular block (87). Patients with cranial nerve palsy and 1st or 2nd degree atrioventricular block may be treated with oral antibiotics (87).

In Steere's 1980 series 7 of 8 patients with atrioventricular block received aspirin and prednisone with subsequent resolution of atrioventricular block within 24 to 48 hrs (11). However, in view of the intermittent nature of atrioventricular block and its typically spontaneous resolution, it is unclear whether treatment ameliorated disease. The benefit of steroids and non steroidal anti-inflammatory drugs in conduction disturbances associated with Lyme carditis has not been substantiated and is not routinely recommended.

The role of antibiotics in the treatment of cardiomyopathy attributed to Lyme disease remains debatable. An uncontrolled trial of 46 European patients reported improvement after intravenous antimicrobial treatment (62). These patients also received specific treatment for congestive heart failure including digoxin, diuretics, and angiotensin converting enzyme inhibitors. Improvement was significantly more common in patients seropositive to *B. burgdorferi* compared with seronegative patients (82% versus 26%; $P<0.01$). Since some patients with myocarditis due to other causes (e.g., viral) may have spontaneous resolution of disease, these findings need to be confirmed by other groups. Evidence that *B. burgdorferi*

Table 6. Antimicrobial Treatment for Manifestations of Lyme Carditis [1]

Manifestation	Treatment
Atrioventricular block	
1st degree	Oral doxcycline 100 mg twice daily or Amoxicillin 500 mg three times daily for 2-3 weeks
2nd degree	Oral doxcycline 100 mg twice daily or Amoxicillin 500 mg three times daily for 2-3 weeks
3rd degree [2]	Intravenous ceftriaxone 2 grams once/daily for the duration of hospital stay; switch to oral regimen upon discharge (as above) to complete 2 weeks
Any of above blocks *plus* meningitis, Peripheral neuropathy,or encephalopathy	Intravenous ceftriaxone 2 grams once/daily for 2 weeks
1st degree *or* 2nd degree block, *plus* cranial nerve palsy	Oral doxcycline 100 mg twice daily or Amoxicillin 500 mg three times daily for 2-3 weeks
Cardiomyopathy [3]	Intravenous ceftriaxone 2 grams once daily for 2 weeks [4]

[1] Adapted from the Infectious Diseases Society of America (IDSA) guidelines (87); tetracyclines are not recommended in children below 8 years of age and are contraindicated in pregnant or lactating women; doses provided are for adults; consult reference (87) for pediatric dosages; [2] Hospitalization with monitored bed and temporary pacemaker may be required; [3] No good evidence that cardiomyopathy may occur in the US although cases have been reported in Europe; [4] No controlled trials; intravenous ceftriaxone effective anecdotally (62,63).

causes cardiomyopathy in the US has thus far been unconvincing (64,65). Antibiotic treatment of seropositive US patients with cardiomyopathy did not result in clinical improvement. To date, there are insufficient data to make recommendations regarding antimicrobial treatment in patients with cardiomyopathy who have antibodies to *B. burgdorferi*.

11. CONCLUSIONS

The most common cardiac manifestation of Lyme disease is a varying degree of intermittent atrioventricular block that typically occurs within weeks of infection. Other manifestations, such as myopericarditis may occur. Cases of cardiomyopathy have been attributed to *B. burgdorferi* infection in Europe, but there is insufficient evidence for similar disease in the United States. Clinicians should especially consider the diagnosis of Lyme carditis in a patient with unexplained heart block who has recently been in an area endemic for the *Ixodes* ticks that transmit this spirochetal infection. Patients should be closely questioned for a recent preceding history of tick bite, erythema migrans rash, or "viral-like" illness. In some cases, patients may have experienced neurologic signs and symptoms (e.g., aseptic meningitis, cranial nerve palsy, or radiculitis) or oligoarthritis. Patients with unexplained heart block should have a complete examination of the skin to look for an erythema migrans rash that may not have been noticed. However, the absence of a history of recognized tick bite or rash does not rule out the possibility of Lyme disease. A presumed diagnosis of Lyme carditis should be supported by either the presence of a concurrent erythema migrans rash or by positive results of 2-step laboratory testing for antibodies to *B. burgdorferi*. However, since false positive results may occur (e.g., in persistently seropositive patients who previously had successful treatment of Lyme disease), it is important to use clinical judgment in attributing specific manifestations to *B. burgdorferi* infection.

Although carditis generally resolves spontaneously, the use of antimicrobial therapy is strongly recommended to shorten the duration of symptoms and prevent potential cardiac and non-cardiac sequelae. Oral agents such as doxycycline and amoxicillin are suggested for 1st or 2nd degree atrioventricular block. For patients with complete heart block, hospitalization in a monitored setting and intravenous ceftriaxone are recommended. A permanent pacemaker is almost never required. The prognosis for Lyme carditis is excellent.

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