Cardiovascular manifestations of Lyme disease

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Lyme disease is caused by the treponema-like spirochete Borrelia burgdorferi. Since Steere et al. described the geographic clustering of cases in Lyme, Connecticut, over a decade ago, the disease has been recognized to be worldwide in distribution and has become the leading tick-associated illness in North America and Europe. Although Lyme disease is known to affect primarily the skin, heart, nervous system, and joints, the cardiac manifestations that occur in 4% to 10% of cases remain the least well documented. The purpose of this report is to summarize the manifestations and management of cardiac involvement in Lyme disease.

HISTORICAL BACKGROUND

The characteristic cutaneous lesion of Lyme disease is erythema migrans. While this lesion provided important clues about the cause of the illness, it also linked Lyme disease in the United States with syndromes previously described in Europe. It was the Swedish physician Arvid Afzelius who introduced the term erythema migrans, to designate a hitherto undescribed clinical entity, in a report to the Dermatological Society in Stockholm in 1909. His observations were published later, in 1921. Garin and Bujadoux described a case of erythema migrans with meningopolyneuritis in 1922, and Hellerström reported on an association between erythema migrans and meningoencephalitis in the following decade. In 1944, Bannwarth defined a syndrome consisting of erythema migrans, radicular pain, and subsequently chronic lymphocytic meningitis, that still bears his name. Lennhoff, in 1948, described spirochete-like structures in skin biopsies of erythematous lesions including erythema migrans. This led to the successful use of penicillin to treat both the erythema migrans as well as the associated central nervous system (CNS) involvement.

Lyme disease was first recognized in epidemic form in Lyme, Connecticut, where a cluster of 59 cases appeared between 1974 and 1975. This “outbreak” was investigated, characterized, and described in 1977 by Steere et al. at Yale University. The earliest cases of Lyme disease in the United States were traced retrospectively to Cape Cod in 1962, and to Lyme, Connecticut, in 1965, and the first published case was reported from Wisconsin by Scrimenti in 1970. The precise etiology of Lyme disease was not resolved until spirochetes were cultured from ticks by Burgdorfer et al. in 1982, and later from the skin, blood, and spinal fluid of infected patients.

MICROBIOLOGY

Along with the leptospira and treponema, borrelia species belong to the eubacterial phylum of spirochetes. The biology of the borrelia species and of B. burgdorferi in particular has been reviewed elsewhere. The geographic distribution of Lyme disease has been strongly correlated with the presence of hard-bodied ticks (Ixodidae), belonging to the Ixodes ricinus complex, which includes I. ricinus, I. persulcatus, I. dammini, I. pacificus, and I. scapularis. The latter three species occur in North American woodlands where mammalian and avian hosts are abundant.

Ticks are among the most efficient vectors of disease because they are persistent bloodsuckers, survive for 2 to 3 years, have few natural enemies, and have a high reproductive ability. The pathophysiology of B. burgdorferi in Ixodid ticks has been well described. In the Northeastern U.S., larvae and nymphs of I. dammini acquire B. burgdorferi when feeding from a variety of hosts, especially the white-footed mouse. Adults of I. dammini are prevalent during fall, winter, and spring and prefer the white-tailed deer as hosts. Between hosts, ticks commonly inhabit tall grasslands and wooded areas where con-
Table I. Stages of Lyme disease

<table>
<thead>
<tr>
<th>Stage 1 (3 days—few weeks)</th>
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<tr>
<td>Begins with tick bite</td>
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<tr>
<td>Initially presents with erythema migrans</td>
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<tr>
<td>Generalized flu-like symptoms</td>
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<td>Some are asymptomatic</td>
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<th>Stage 2 (3 weeks—5 months)</th>
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<tr>
<td>Cardiac abnormalities in approximately 10% of documented cases</td>
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<tr>
<td>Neurologic abnormalities in approximately 11% of documented cases</td>
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<th>Stage 3 (5 months—years)</th>
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<tr>
<td>Musculoskeletal involvement in approximately 50% of documented cases</td>
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<tr>
<td>Late neurologic manifestations</td>
</tr>
<tr>
<td>Limb numbness, memory lapses, and overpowering fatigue</td>
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CLINICAL PRESENTATION

Lyme disease is recognized as causing a wide spectrum of clinical illness. It has been traditionally divided into three stages (Table I). Stage 1 begins with the tick bite, which is only noted by a third of patients. This stage lasts between 3 days and a few weeks, averaging 7 days. The characteristic skin lesion of erythema migrans is seen in 30% to 90% of patients and usually fades after 3 to 4 weeks. There may be accompanying flu-like symptoms, such as fatigue, malaise, and lethargy in 80% of cases. Approximately 10% of patients are asymptomatic.9, 12, 47, 48

Stage 2 develops between 3 weeks and 5 months after disease onset, usually within the first 3 to 11 weeks. Approximately 10% of all patients in this stage develop cardiac abnormalities, and about 11% develop neurologic signs. Neurologic complications include headache, Bell’s palsy, radiculoneuritis, transverse myelitis, meningitis, and encephalitis. Examination of the cerebrospinal fluid (CSF) is consistent with an aseptic meningitis.9, 12, 47

Stage 3 develops between 5 months to years after disease onset, but typically within 6 to 24 months. The most common feature is musculoskeletal involvement in up to 50% of patients. Large joints are commonly affected, usually as an asymmetric and monoarticular arthritis. Late neurologic manifestations involving demyelination with multiple sclerosis-like symptoms have been reported. Limb numbness, memory lapses, and overpowering fatigue may occur.9, 12, 49 Also described are chronic encephalopathy, polyneuropathy, and rarely, leukoencephalitis.50

LABORATORY DIAGNOSIS

Definitive diagnosis of Lyme disease requires culture. Culture of blood and/or tissue is positive in 2-7% of patients with well-defined clinical illness.25, 26, 51, 52 Because culture may require 4 to 12 weeks of incubation and the yield is low, it is impractical for routine diagnostic use.

Laboratory diagnosis rests on serologic testing. Enzyme-linked immunosorbent assays (ELISA) and indirect immunofluorescent Ab (IFA)48 identify 40% to 60% of patients in the first few weeks of infection when erythema migrans and constitutional symptoms predominate, and most patients with late complications.54-57 In general, IgM Ab levels peak between the 3 to 6 weeks after clinical illness compared with IgG levels, which are detectable months to years later.25 Theoretical improvements in early B. burgdorferi antibody detection have included the use of IgM capture ELISA and Western blots. The detection of five bands on an IgG or IgM immunoblot are
very significant, but there is no consensus on the specific combination of bands. The clinical value of urinary antigen and polymerase chain reaction technology needs further assessment.*

Dattwyler et al.61 studied 17 patients with acute Lyme disease who received prompt treatment with oral antibiotics. These patients developed chronic Lyme disease without diagnostic antibodies, as measured by ELISA, IFA, or Western blot. Diagnosis of *B. burgdorferi* exposure was based solely on the presence of T-cell lymphoproliferative responses. Although this technique of disease diagnosis is intriguing, Zoschke et al.62 have questioned the specificity of lymphocyte proliferative responses because of the presence of reactivity in normal controls. Schutzer et al.63 have also demonstrated the presence of *B. burgdorferi* antibody containing immune complexes in 10 seronegative patients with Lyme disease based on Western blot detection after immune complex dissociation. Thus seronegativity using current serologic techniques does not exclude the possibility of Lyme disease.

Pitfalls in the specific diagnosis relate to antigenic cross-reactivity among Borrelia species and between *B. burgdorferi* and *Treponema pallidum*. Patients with *B. burgdorferi* may develop positive treponemal tests for syphilis (e.g.: fluorescent treponemal antibody absorption [FTA-ABS], microhemagglutination assay for *T. pallidum* [MHA-TP]), but they generally do not develop positive non-treponemal tests (e.g.: venereal disease research laboratory [VDRL], rapid plasma reagin [RPR]). The clinical picture and the presence of a positive non-treponemal test may help differentiate syphilis from Lyme disease.55,56

Epidemiologic seroprevalence surveys have shown that many people with positive serology give no history of clinical illness.43 Until the standardization and specificity of *B. burgdorferi* detection systems improve, definitive diagnosis in the absence of clear clinical syndromes will be problematic.65

**CARDIAC MANIFESTATIONS**

Cardiac involvement is the least well documented complication of Lyme disease, affecting 4% to 10% of all North American patients infected with *B. burgdorferi*.6,8,10 and 0.3% to 4.0% of all European patients with the disease.66 Although *erythema migrans* appears to be more common in North America compared with Europe,48,67 it has also been suggested that there may be differences between the virulence of European and North American *B. burgdorferi* isolates.50,58,69

Cardiac involvement usually occurs 4 to 6 weeks (range of 4 days to 7 months) after the initial illness.5-7 Manifestations include rhythm disturbances, atrioventricular block, cardiomyopathy, heart failure, myocarditis, and pancreatitis50,71 (Table II). Of 84 patients with cardiac complications of Lyme disease reviewed by the Centers for Disease Control in Atlanta,5 palpitations occurred in 69%, conduction defects occurred in 19%, myocarditis occurred in 10%, and left ventricular failure occurred in 5%. Overall, 21% of the patients required hospitalization.5

### Table II. Cardiac manifestations of Lyme disease

<table>
<thead>
<tr>
<th>1 Conduction system disease</th>
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<tr>
<td>1°, 2°, 3° AV block</td>
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<tr>
<td>Wenckebach periodicity</td>
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<tr>
<td>Left bundle branch block</td>
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<tr>
<td>Right bundle branch block</td>
</tr>
<tr>
<td>Fluctuating bundle branch block</td>
</tr>
<tr>
<td>2 Other cardiac disease</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Myocarditis</td>
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<tr>
<td>Pericarditis</td>
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<tr>
<td>Atrial and ventricular tachycardias</td>
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</table>

Cardiac involvement as well as the most troublesome.70 In 52 cases reviewed by McAlister et al.,71 87% had documented atrioventricular block that was usually asymptomatic. Up to 98% of patients with atrioventricular conduction disturbances demonstrated first-degree atrioventricular block at some time during their course. Wenckebach periodicity occurred in 40% and complete atrioventricular block occurred in 50% of patients. A temporary pacemaker was required in about 38% of affected individuals.72 Individual patients may develop several types of atrioventricular block.70

Steere et al.5 reported 20 patients with Lyme carditis, the largest single series in the literature. Ninety percent of these patients experienced fluctuating degrees of atrioventricular block, and 50% had high-grade atrioventricular block. Eight patients developed complete atrioventricular block and six required a temporary transvenous pacemaker for variable periods of time.6 The most common clue to cardiac involvement was alternating tachycardia/bradycardia.5

Kimball et al.73 described a patient presenting solely with complete heart block who came to medical attention because of the recent onset of easy fatigability and weakness. At the time of presentation,
than 0.3 second. Progression from first-degree to third-degree atrioventricular block can occur within minutes. Usually, block is at or above the atrioventricular node, predicting a benign prognosis. Electrophysiologic studies have shown that atrioventricular block can occur at different levels within the atrioventricular conduction system. Sinoatrial and intranodal conduction disturbances have also been described.

More sinister conduction disturbances include: (1) escape rhythms in some patients with severe atrioventricular block that are slow and of wide QRS pattern; (2) transient lack of any escape rhythm, with brief asystoles; and (3) fluctuating bundle branch block suggesting either transient His-Purkinje involvement or intranodal atrioventricular block. Electrophysiologic investigation of one patient with Lyme carditis demonstrated supra-Hisian block with complete absence of an escape mechanism. Rapid progression from 2:1 atrioventricular block to complete heart block was seen with subsidiary pacemaker failure, requiring insertion of a temporary transvenous pacemaker.

Atrioventricular block frequently resolves gradually, usually within 6 weeks. Presumably this is related to resolution of the underlying inflammation. There may be a distinct progression from complete heart block through intervening degrees of heart block to first-degree atrioventricular block with a gradually decreasing PR interval, and ultimately back to normal sinus rhythm. The risk of developing complete atrioventricular block has been said to be higher in those patients who develop first-degree atrioventricular block with a PR interval greater than 0.3 second.

Other forms of cardiac involvement. In addition to conduction disturbances, B. burgdorferi can cause inflammation of all heart layers. Lorcerie et al. described three patients whose only manifestation of Lyme disease was pericarditis with typical clinical features. B. burgdorferi was isolated from the myocardium of a patient with an unexplained dilated cardiomyopathy of 4 years' duration. Diffuse T wave flattening or inversion, S1 segment depression, transient and reversible depression of left ventricular function, cardiomegaly, and pericarditis have been noted in up to 65% of patients. Other reports include evidence of congestive heart failure on chest x-ray examination, flow murmurs, mitral regurgitation murmurs, and various tachycardias including asymptomatic nonsustained ventricular tachycardia. These are nonspecific findings and it would be impossible to discriminate between chance associations and true signs of Lyme carditis.

Clinical investigation. Clinical investigative aids are insensitive and nonspecific in identifying Lyme carditis. The electrocardiogram may be normal or may identify any of the patterns previously described. The chest x-ray film is usually normal unless a car-diomyopathy or congestive heart failure is present. Gallium-67 myocardial scanning has been documented by a number of authors to show intense, diffuse uptake in the myocardium of at least some patients with Lyme carditis. This nonspecific test for inflammation may be used to assess for suspected cardiac involvement. Normalization of gallium uptake parallels resolution of Lyme carditis.

Pathology. The histology of Lyme carditis most commonly shows a transmural inflammatory infiltrate. The endocardial zone is affected by a characteristic band-like infiltrate of lymphoid cells. Small inflammatory nodules of neutrophils and macrophages are seen with hyperacutec disease. Isolated evidence of myocyte necrosis is sometimes seen. Endocardial and interstitial fibrosis may be prominent. Spirochetes characteristic of B. burgdorferi can be found near and in the infiltrates, between muscle fibers, and in the endocardium (Table III).

Inflammatory changes suggestive of a form of vasculitis may involve scattered small and large intramyocardial vessels. Swelling of endothelial cells is sometimes seen in small vessels, and this is associated with a tight perivascular response. Large vessels, by contrast, show adventitial infiltrates with loose reticulin and increased deposition of collagen.

The findings in Lyme carditis differ from the histologic changes seen in other carditis entities. Rheumatic myocarditis is more focal and granulomatous. Bacterial myocarditis is often characterized by granulomatous infiltrates and neutrophils, or by lymphocytic infiltrates with small vessel vasculitis, as in infections by T. pallidum.

Other pathologic entities include myocarditis with early traces of myocardial fiber degeneration, and fibrinous pericarditis occurring in a patient with symptoms and signs of pericardial constriction. Fibrinous pericarditis is also described, with more dif-

### Table III. Pathology of Lyme carditis

<table>
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<tr>
<th>Condition</th>
<th>Features</th>
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<tr>
<td>Transmural lymphoplasmacytic infiltrate</td>
<td>Inflammatory nodules of neutrophils and macrophages</td>
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<tr>
<td>Necrosis of myocardial fibers</td>
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<tr>
<td>Prominent interstitial fibrosis</td>
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<tr>
<td>Vasculitis of intramyocardial vessels</td>
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<tr>
<td>Fibrinous pericarditis</td>
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<tr>
<td>Presence of spirochetes in the myocardium</td>
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</table>
fuse evidence of cardiac inflammation. In one
autopsy case, an additional finding of endodermal
heterotopia ("mesothelioma") of the atrioventricular
node was reported. Although this was likely a
incidental finding, the possibility of this lesion being
secondary to Lyme disease and accounting for the
commonly seen conduction disturbances was raised.

It appears that the presence of spirochetes in the
myocardium is intrinsic to the pathophysiology of
Lyme carditis. Whether continued disease activity
requires the persistence of live spirochetes, or whether
it results primarily from immune-mediated mecha-
nisms is unclear. The discrepancy seen at histopa-
thology between the small number of spirochetes re-
covered and the extent of the lymphoplasmacytic in-
filtrate suggests a combined effect of local spirochetal
infection with an immunologic reaction to the infec-
tion. Transvenous endomyocardial biopsy effectively
aids in clinical diagnosis by revealing the band-like
cardiogain infiltrate. This is seen so often that the
diagnosis of Lyme carditis is strongly suggested in an
appropriate clinical setting, even if the quality of the
endomyocardial biopsies is limited. If the biopsy
includes underlying myocardial fibers, then the
interstitial lymphoplasmacytic infiltrate will be
seen.

**Prognosis.** Although cardiac involvement in Lyme
disease is generally benign, with most patients re-
covering without permanent sequelae, fatalities may
occur. Marcus et al. reported a 66-year-old man
with babesiosis who died unexpectedly in the hospi-
tal. Autopsy showed pancarditis with a diffuse lym-
phoplasmacytic infiltrate and spirochetes in the my-
cardium. Antemortem sera were positive for *B.
burgdorferi*. The authors concluded that the pa-
tient’s sudden demise was likely due to atrioventric-
ular block or to an arrhythmia. Their report has since
been much quoted to suggest that cardiac involve-
ment in Lyme disease could both be asymptomatic and
yet not invariably benign. Since neither block nor
arrhythmia was ever objectively demonstrated, this
hypothesis cannot be considered conclusive and
inferences regarding a cause and effect relationship
should not be deduced from that report.

More recently, a fatal case of Lyme carditis occur-
ring in an English farm worker has been reported.

**THERAPY**

Oral antibiotic therapy generally shortens the du-
ration of *erythema migrans* and associated symp-
toms, while preventing or attenuating late illness in
most patients. Although antibiotic therapy in the early stages of Lyme disease has been reported
to prevent or ameliorate later complications, its role
in treating or preventing Lyme carditis has not been
adequately assessed. It does not appear that early
antibiotic therapy has decreased the duration of car-
diac involvement, but formal testing of the effective-
ness of antibiotic regimens in the treatment of Lyme
carditis has not been possible, owing to the small
number of cases.

Patients with minor cardiac involvement (i.e.,
first-degree atrioventricular block with PR interval
less than 0.30 second) and no other symptoms should
receive treatment with doxycycline, tetracycline, or
amoxicillin as for early disease. Those with more
severe conduction system disease (including first-
degree atrioventricular block with a PR interval
greater than 0.30 second) should be hospitalized and
given either intravenous ceftriaxone or high-dose in-
travenous penicillin G. Advanced atrioven-
tricular block is customarily treated with salicylates
and steroids. One disadvantage to the use of steroids
is that recurrent CNS and/or joint symptoms may be
precipitated on steroid withdrawal. Therapy for 2 to
4 months before weaning is possible.

Asystole may be the major fatal complication of
Lyme disease. Therefore telemetry in a coronary care
unit (CCU) setting is advocated for patients present-
ning with second- or third-degree atrioventricular
block, or for first-degree block with a PR interval
greater than 0.3 second. Prompt insertion of a tem-
porary transvenous pacemaker is suggested when
aggravating features develop or when hemodynamic
support is required. Direct heart involvement is
generally brief, and the pacemaker can usually be re-
moved within a week. Temporary cardiac pac-
ing was used in 16 of 26 patients with high-grade or
complete atrioventricular block reported in the liter-
ature. Nine patients with similar degrees of block
were treated conservatively, some with atropine
and/or isoproterenol. Outcome did not differ
between the groups. Chronic or irreversible atrio-
ventricular conduction defects are being reported
despite early and adequate antimicrobial therapy.
Serious atrioventricular conduction disturbances
generally resolve within 2 to 6 weeks but they
may last 2 years or even longer. Permanent
cardiac pacing has been reported in the setting of
complete heart block secondary to Lyme carditis. In
most instances, pacemakers were inserted prior to
obtaining a firm diagnosis. However, permanent
pacemaking was required in one patient whose complete
atrioventricular block was refractory to aggressive
pharmacologic therapy with antibiotics and ste-
roids.
SUMMARY

Although the cardiac manifestations of Lyme disease may be diverse, in general they are treatable with currently available therapies. A high index of suspicion is required to make a diagnosis, especially for patients who may lack a suggestive history of tick exposure or residence in an endemic region. Lyme disease-related heart block may require pacemaker insertion and supportive care. The efficacy of antibiotics in the therapy of acute and chronic cardiac Lyme disease will require further study. Serologic testing and cardiac histopathology are the most precise methods of diagnosis. There is a need to develop more sensitive and specific diagnostic tests for Lyme disease and for Lyme carditis in particular.

REFERENCES

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