The clinical challenge of Lyme disease

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■ Lyme disease is a systemic infection with protean clinical manifestations. In the past decade the disease has evolved from a medical curiosity to the most common vector-borne disease in the United States. The diverse clinical manifestations together with the lack of standardized serologic tests pose a significant diagnostic challenge for the practicing physician. The epidemiology, clinical presentation, diagnosis, and recommended therapy of Lyme borreliosis are reviewed.

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LYME DISEASE IS THE MOST commonly reported vector-borne disease in the United States.[1] Sporadic cases were first recognized in the northeastern United States in 1975,[2] but in recent years the disease has become endemic in many areas. Since 1982, approximately 13,825 cases of Lyme disease have been reported to the Centers for Disease Control.[2] The annual incidence has increased nearly tenfold from 492 cases in 1982 to 4,572 cases in 1988.[2]

Lyme disease is a multisystem disorder caused by the spirochete *Borrelia burgdorferi*. The infection most commonly affects the skin, heart, nervous system, and joints, but numerous reports have described less common manifestations.

The protean and enlarging clinical spectrum of Lyme disease, together with the lack of standardized serologic tests, can make the diagnosis difficult for the practicing physician. This review focuses on the epidemiology, clinical manifestations, diagnosis, and current therapeutic recommendations for Lyme borreliosis.

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HISTORY

Lyme disease is not a new disease. Erythema chronicum migrans (ECM), an annular expanding skin lesion and the hallmark of early Lyme disease, was first recognized by Afzelius in Sweden in 1909.[3] Subsequent reports in the European literature in the 1920s through the 1940s by Garin-Bujadoux,[4] Hellerstrom,[5] and Bannwarth[6] described an illness now recognized as characteristic of neuroborreliosis, which consisted of painful radiculitis, aseptic meningitis, and cranial neuritis. In some instances, this followed a tick bite. A number of terms were employed to describe this clinical syndrome, including lymphocytic meningoradiculitis, Bannwarth's syndrome, tick-borne meningopolyneuritis, and meningopolyneuritis.

The first report of tick-induced ECM in the United States appeared from Wisconsin in 1970,[7] although retrospective serologic studies have documented cases as early as 1962 on Great Island, Massachusetts.[8] In 1975 a high incidence of "juvenile rheumatoid arthritis" was recognized in Lyme, Old Lyme, and East Haddam, Connecticut. Subsequent epidemiologic and clinical investigations led to the recognition of the major clinical syndromes of Lyme disease[1] and incriminated the tick vector *Ixodes dammini* in disease transmission.[9–11]

Over the past 10 years Lyme disease has become the most commonly reported vector-borne disease in the

United States.[2] Cases have also been reported from Canada, Europe, the Soviet Union, Australia, Japan, and China.[12–17]

ETIOLOGY

The discovery of the Lyme spirochete was serendipitous. Dr. Willy Burgdorfer was attempting to identify a tick reservoir for *Rickettsia rickettsii*, the etiologic agent of Rocky Mountain spotted fever. During his dissections in search of *Rickettsia*, he identified and recovered spirochetes associated with the microvillus brush border of mid-gut epithelium in adult *Ixodes dammini* ticks.[18] Burgdorfer realized that *I dammini* had been incriminated as the likely vector of Lyme disease and correctly hypothesized that the observed spirochetes were the infectious agent.

Serum specimens from patients with Lyme disease were demonstrated by indirect immunofluorescence to contain antibodies to this spirochete and further studies corroborated its etiologic role in human disease. Steere and Benach isolated the spirochete from blood, skin, and cerebrospinal fluid in several patients with Lyme disease who also demonstrated a concomitant rise in specific antispirochetal antibodies.[19,20] Investigators from Europe subsequently recovered the spirochete from clinical specimens from patients with Bannwarth's syndrome, ECM, and acrodermatitis chronica atrophicans.[21–23] The Lyme disease spirochete was designated *Borrelia burgdorferi* in honor of Burgdorfer's discovery.

The organism is 20 μ to 30 μ in length, 0.2 μ to 0.3 μ in diameter, and possesses 7 to 11 flagella.[24] Although *B burgdorferi* is fastidious and microaerophilic, cultivation is possible at 32°C to 37°C on Barbour-Stoenner-Kelly medium.[25] Isolation of the spirochete from clinical specimens is difficult, but the organisms can be readily recovered from infected ticks.

Strain differences in DNA and plasmid composition, outer surface proteins, and ultrastructure have been identified in American and European isolates of *B burgdorferi*.[24,26–28] These biologic differences may account for the diversity of clinical manifestations of Lyme disease in different geographic locales.

EPIDEMIOLOGY AND TRANSMISSION

Ixodid ticks are the principal vectors of Lyme disease worldwide. Different species are responsible for transmission in different parts of the world, including *I dammini* in the northeastern and midwestern United States, *Ixodes pacificus* in the northwestern United States, *Ixodes scapularis* in the southeastern United States, and *Ixodes ricinus* and *Ixodes persulcatus* in Europe and Asia.[29] Mosquitos, deerflies, and other species of ticks, such as *Amblyomma americanum* and *Dermacentor variabilis*, are known to harbor the spirochete.[30–32] Of these, only the lone star tick *A americanum* has been implicated in the transmission of *B burgdorferi* to humans.[32] Because of its ubiquity, however, the possibility exists that this tick vector may contribute to the spread of Lyme disease in the future.

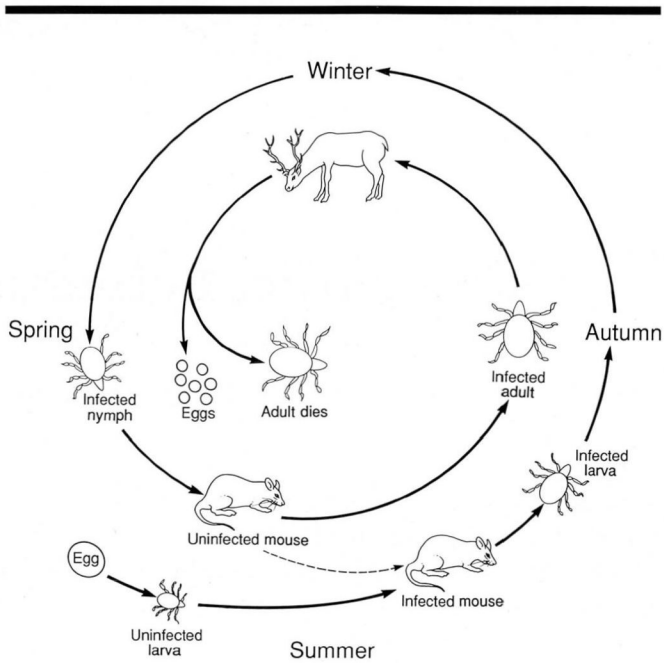

FIGURE 1. Life cycle of *Ixodes dammini*. Eggs hatch in the spring and produce uninfected larvae which preferentially feed on the white-footed mouse in late summer or early fall. An infected mouse may transmit the spirochete to the larva, which detaches and molts to produce the nymphal stage of the tick. Nymphs also feed on white-footed mice. This occurs in the late spring or early summer and may result in transmission of the spirochete to uninfected white-footed mice. Nymphs then detach and mature to adult ticks, which preferentially feed on the white-tailed deer in the autumn, winter, or early spring. Eggs are deposited in the spring and the adults die.

B burgdorferi is ubiquitous in the animal kingdom and many wild and domestic vertebrates can serve as intermediate hosts for the spirochete.[29] The white-footed mouse *(Peromyscus leucopus)* is the preferred host for nymphal and larval stages of *I dammini*, while adult stages of this tick preferentially feed on white-tailed deer *(Odocoileus virginianus)*.

Ixodid ticks have a complex life cycle that spans 2 years *(Figure 1)*.[33] Larval ticks hatch in the spring and in-

TABLE 1
COMMON CLINICAL MANIFESTATIONS OF LYME BORRELIOSIS

Stage of disease	Skin	Heart	Nervous system	Joints
I	Erythema chronicum migrans (ECM)		Headache	Arthralgias
II	Recurrent ECM	Carditis	Aseptic meningitis Cranial neuritis Peripheral radiculoneuritis Mild encephalitis	Migratory arthralgias Brief bouts of arthritis
III	Acrodermatitis chronica atrophicans		Chronic encephalomyelitis Chronic polyneuritis	Chronic or prolonged attacks of arthritis

gest a blood meal from the murine host, usually in late summer, at which time transmission of the spirochete from infected white-footed mice to the ticks may occur. Larvae then detach from their hosts, molt, and develop into nymphs the following spring. Nymphal ticks preferentially feed in the late spring and early summer and may transmit *B burgdorferi* to uninfected white-footed mice (or to other animals, including man).

The transmission from infected nymphs to uninfected mice in the early summer is important for subsequent transmission of the spirochetes to uninfected larvae later in the summer. Nymphal ticks mature into adult male and female ticks, which feed on white-tailed deer throughout the fall, winter, and subsequent spring. Fertile females deposit eggs in the spring, which ultimately hatch to larvae, thereby completing the life cycle.

Autochthonous cases of Lyme disease have been reported from 43 states, but nine states accounted for 94% of the reported cases in 1987 and 1988.[2,12] These included Massachusetts, New York, New Jersey, Rhode Island, Connecticut, Pennsylvania, Minnesota, Wisconsin, and California. In New England and the upper Midwest, most infections are acquired between May and August, while in California and the Pacific Northwest onset of disease is more common between January and May.[2] Lyme disease tends to be a disease of children and middle-aged adults, with age-specific incidence rates highest for individuals younger than 15 years of age and between 25 and 44 years of age.[2]

CLINICAL MANIFESTATIONS

The clinical manifestations of Lyme disease have been divided traditionally into three separate stages, which appear chronologically after the original tick bite *(Table 1)*.[8,34] A more recent classification scheme has been proposed, in which stages I and II are combined and classified as "early infection," while stage III is classified as "late infection."[12,35] Lyme disease is a multisystem disorder, but clinically predominant organ involvement may differ at each stage of disease. In addition, even in the absence of specific therapy, many patients do not develop stage II or stage III disease after initial infection.

Stage I

Erythema chronicum migrans is the hallmark of stage I Lyme disease and usually appears at the site of the tick bite. Only about one third of individuals will recall a tick bite, and ECM may never develop in up to 20% to 40% of patients with stage I Lyme disease.[36] Erythema chronicum migrans begins 3 to 32 days after the tick bite as an erythematous macule or papule and gradually enlarges to form an annular plaque with a diameter ranging from 3 cm to 68 cm *(Figure 2)*. Although central clearing is characteristic, some lesions may exhibit diffuse erythematous induration and, rarely, vesiculation, hemorrhage, or ulceration.[35] If unrecognized or untreated, lesions resolve in about 3 weeks on the average, although they may persist or recur for up to 1 year.

The lower extremity is the most common site of involvement, but ECM may occur anywhere on the body. Satellite lesions in proximity to the original lesion occur in 17% to 48% of individuals with ECM.[36,37] These are typically smaller and may lack central clearing. Atypical cutaneous manifestations, including malar rash, diffuse maculopapular rash, and papular urticaria may occur on occasion. Some patients have displayed concomitant granuloma annulare, erythema nodosum, morphea, or Henoch-Schonlein-like purpura, but whether these lesions are attributable to direct infection by the spirochete has not been determined.[35]

Erythema chronicum migrans is felt to arise due to local cutaneous infection with *B burgdorferi*. Warthin-Starry–stained biopsy specimens of ECM may demon-

strate spirochetes in up to 40% of cases.[37] Cultivation of the spirochete from skin biopsy specimens is possible, but of low yield.

In addition to ECM, systemic manifestations are common in most patients with stage I Lyme disease.[36] Symptoms include headache, malaise, fatigue, lethargy, fever, chills, stiff neck, arthralgias, myalgias, and adenopathy. Adenopathy is frequently regional in the distribution of ECM, although rarely may be generalized. Fever tends to be low-grade, but occasionally may be prominent. About 10% of patients complain of anorexia, nausea, and vomiting, and may exhibit right upper quadrant tenderness suggestive of hepatitis.[36] When untreated, symptoms of stage I disease usually persist for several weeks and then subside.

Stage II

The clinical manifestations of stage II Lyme disease arise as a consequence of disseminated infection. The most common syndromes involve the heart, nervous system, and skin. Numerous reports have described less common clinical manifestations of stage II disease, including myositis, hepatitis, orchitis, and ocular involvement consisting of iritis, choroiditis, panophthalmitis, or retinal hemorrhage or detachment.[12,38,39] Lymphocytoma, a bluish-red nodular swelling most commonly involving the ear lobe or breast, has been reported in the European literature but has not been recognized in the United States.[35]

Recurrent erythema chronicum migrans has been described in about 10% of untreated patients and may relapse and remit for up to a year. Those who receive appropriate antibiotics usually do not exhibit recurrent skin involvement unless they become reinfected.

Cardiac manifestations develop in 4% to 10% of individuals and appear, on average, 5 weeks (range 4 days to 7 months) after the tick bite.[40–42] The pathogenesis of disease may relate to active spirochetal infection of the myocardium.[43] Clinically evident cardiac involvement is usually brief and self-limited, lasting from 3 days to 6 weeks.[41] The most common manifestation is varying degrees of atrioventricular (AV) block. First-degree AV block, Wenckebach, and complete heart block may be seen. Patients may progress rapidly from first-degree to complete heart block. In the largest published review of cardiac Lyme disease, 45 of 52 patients had documented atrioventricular block, of which 28 had complete or high-grade block.[40] Electrophysiologic studies suggest that the site of atrioventricular block is at or above the level of the AV node.

Other manifestations of myocardial involvement may include mild and reversible left ventricular dysfunction, diffuse ST-T wave abnormalities on electrocardiography consistent with myocarditis, clinical and electrocardiographic evidence of pericarditis, and intermittent supraventricular tachyarrhythmias. Fatal myocarditis has been reported rarely.[43] In the largest review, 85% of patients with Lyme carditis demonstrated ECM at presentation, which provided a useful clinical clue to the diagnosis.[40]

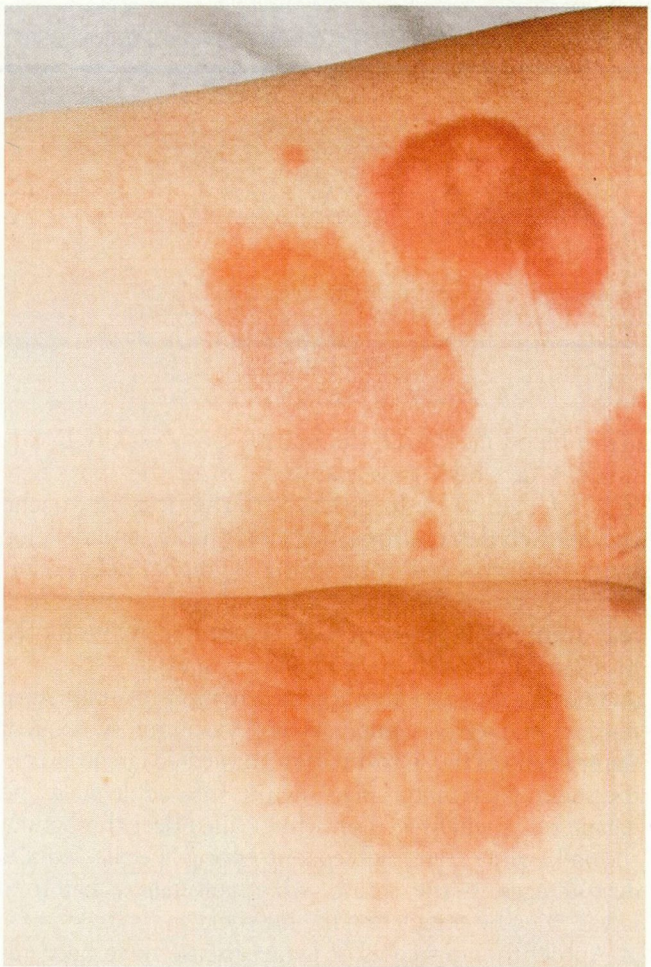

FIGURE 2. Erythema chronicum migrans involving the legs. Note the annular borders, central clearing, and satellite lesions (courtesy of Kenneth Tomecki, MD).

Clinically apparent neurologic disease develops in 10% to 20% of individuals within several weeks to months following the original tick bite.[12,44] The clinical manifestations can be highly variable, but the classic triad of neurologic involvement in Lyme disease consists of aseptic meningitis, cranial nerve palsies, and peripheral radiculoneuropathy. Aseptic meningitis is the most common manifestation.

Cerebrospinal fluid analysis typically demonstrates a lymphocytic pleocytosis with about 100 white blood cells, together with a normal glucose and normal to mildly elevated protein. Intrathecal production of IgG antibodies specific to *B burgdorferi* has been demonstrated.[45] In addition, T lymphocytes specific for *B burgdorferi* have been identified in cerebrospinal fluid of patients with Lyme meningitis.[46]

Cranial neuropathies occur in up to 50% of individuals with neurologic involvement. Bell's palsy is the most common and may be unilateral or bilateral. Waxing and waning cranial neuropathies are an important clinical clue to the diagnosis of Lyme disease. Radiculoneuritis is common; it may be sensory, motor, or mixed; and it often occurs in the dermatomal distribution of the original tick bite.[44,47] Electromyographic and nerve conduction studies usually disclose axonal neuropathy with demyelination. Histopathologic examination of involved nerves, however, has not revealed evidence of direct spirochetal infection. Rather, an immunopathologic mechanism for the neuropathy has been proposed, based on the demonstration of IgM antibodies to *Borrelia burgdorferi* which cross react with neuronal antigens.[48]

Symptoms suggesting mild encephalitis have been described in up to two thirds of patients with neurologic involvement.[44] These have included lethargy, depression, emotional lability, difficulty with concentration and memory, or altered behavior. Electroencephalographic abnormalities are common but typically nonspecific. Computerized tomography is usually normal. Uncommon manifestations of stage II neurologic Lyme disease include transverse myelitis,[49] mononeuritis multiplex, Guillain-Barré syndrome,[50] cerebellar ataxia,[44] pseudotumor cerebri,[51] and chorea.[44]

Stage III

Relapsing and remitting arthritis is the hallmark of stage III Lyme disease. Steere evaluated the clinical evolution of Lyme arthritis by prospectively following 55 patients with untreated erythema chronicum migrans over an average of 6 years.[52] In 20%, no subsequent manifestations of Lyme disease developed. Eighteen percent had episodic joint or musculoskeletal pain that began 1 day to 8 weeks after the onset of ECM and persisted for up to 6 years, but none had objective signs of joint inflammation. Intermittent bouts of arthritis, involving mainly large joints, occurred in 51% of the patients. A few had polyarticular involvement. Attacks began 4 days to 2 years after the onset of ECM and relapses occurred in many patients for as long as 7 or 8 years. Episodes of arthritis were occasionally separated by months or even years. In 11% of the patients, chronic synovitis developed in one or more large joints beginning 4 months to 4 years after the onset of ECM. Several had radiographic evidence of erosive joint disease that mimicked rheumatoid arthritis.

The knee is the most commonly affected joint in Lyme arthritis, followed in descending order of frequency by the shoulder, elbow, temporomandibular joint, ankle, wrist, hip, and small joints of the fingers and toes.[52,53] Joint fluid analysis in patients with arthritis is typically mildly inflammatory. Leukocyte counts are highly variable, ranging from 500 cells/mm^3 to 98,000 cells/mm^3.[1,32] Polymorphonuclear leukocytes account for 60% to 80% of leukocytes. Total protein is usually elevated between 3 g/dL to 8 g/dL. Joint fluid complement levels, rheumatoid factor, and antinuclear antibody are usually normal, although cryoglobulins are frequently present.

In those experiencing recurrent attacks, multiple joints may be involved. The usual duration of an attack is highly variable, ranging from several days to many months. Patients who experience recurrent attacks may note that each subsequent recurrence is milder than the preceding one. The number of patients with recurrent attacks diminishes by 10% to 20% per year, and the disease often slowly subsides over time, even in the absence of specific therapy.

A propensity to develop chronic Lyme arthritis has been detected in individuals expressing major histocompatibility antigens HLA-DR4, HLA-DR3, or HLA-DR2.[53,54] Although *B burgdorferi* has been isolated from joint fluid in patients with chronic Lyme arthritis,[55] the increased frequency of chronic joint disease in patients expressing these D-locus antigens suggests that the pathogenesis of Lyme arthritis may have an immunogenetic component.

Acrodermatitis chronica atrophicans is an unusual and slowly progressive cutaneous disorder that begins with erythema and pigmentation, usually of an extremity, and is followed over years by hypopigmentation, atrophy, and thinning of the skin.[35,56] The Lyme spirochete has been isolated from several individuals with this disorder, often many years after initial acquisition of infection, and some patients have responded to penicillin.[56] Acrodermatitis chronica atrophicans is more common in Europe and has rarely been reported in the United States.[57]

A number of reports have incriminated *B burgdorferi* as the cause of neuropsychiatric symptoms, fatigue, and focal central nervous system disorders occurring years after initial infection.[58-64] This is an area of some con-

troversy and it is likely that the entire clinical spectrum of late neuroborreliosis remains to be elucidated.

Ackermann and associates recently reported 48 patients with late neuroborreliosis of 7 months' to 12 years' duration.[64] All patients had evidence of intrathecal production of *Borrelia*-specific antibodies. Several clinical syndromes were noted, including chronic meningitis in 34, myelitis in 29, cranial neuropathies in 22, encephalitis in 18, and neuropathy in 2. Most patients had objective abnormalities on physical or cerebrospinal fluid examination. Halperin and co-workers performed neurophysiologic and neuropsychologic testing on a large cohort of patients felt to have late Lyme neuroborreliosis.[62,63] These patients had immunologic evidence of infection or a history of ECM, multiorgan involvement, and disease of at least 1 month's duration. *Borrelia*-specific intrathecal antibody production was not required for inclusion in this series. Nerve conduction studies disclosed motor or sensory abnormalities of peripheral nerves in 64 of 137 individuals tested.[63] Sixty patients were studied several months after a course of parenteral ceftriaxone or penicillin and demonstrated improvement. Seventeen patients with clinically evident cognitive dysfunction underwent formal neuropsychologic testing, which disclosed abnormalities on the California Verbal Learning Test and Booklet Categories Test. Wechsler Memory Scale was below normal. After antibiotic therapy, repeat testing disclosed statistically significant improvement in these individuals.[62,63] Magnetic resonance imaging of the brain in some patients with late Lyme disease and encephalopathy has demonstrated focal white matter abnormalities.[62–64]

Computerized tomography is usually normal, but has rarely disclosed hypodense foci as well.[64] These data suggest that *B burgdorferi* may rarely produce late neurologic sequelae. The spectrum of clinical manifestations is probably only partially defined at this time. In addition, the appropriate criteria for diagnosis, indications for treatment, and optimal therapy of late neuroborreliosis remain controversial.

DIAGNOSIS

The diagnosis of Lyme disease has been the subject of several excellent recent reviews.[65–69] For many infectious diseases, definitive diagnosis is confirmed by isolation of the responsible pathogen from appropriate specimens. In the case of *B burgdorferi*, this is time-consuming, technically difficult, expensive, and not routinely available in most diagnostic microbiology laboratories. Histopathologic examination for the spirochete in specimens of joint fluid, synovium, or cerebrospinal fluid is extremely insensitive and seldom helpful in establishing the diagnosis of Lyme disease. As mentioned previously, Warthin-Starry–stained skin biopsy specimens of ECM may be positive in up to 40% of individuals and may therefore help support the diagnosis of early Lyme borreliosis.

The application of monoclonal antibodies against *B burgdorferi* for histopathologic visualization of the spirochete has also been reported.[70] Unfortunately, these reagents are not widely available at present. The detection of *B burgdorferi* antigens in urine has recently been suggested as a possible diagnostic test for Lyme disease.[71] The utility of this approach remains to be defined.

Serologic diagnosis remains the most widely available method for confirming a diagnosis of Lyme borreliosis. Indirect fluorescent antibody assays (IFAs) and, more recently, enzyme-linked immunosorbent assays (ELISAs) have been developed.[72–75] ELISAs for IgM and IgG are preferred at present because of their superior sensitivity and specificity.[12,73] There is great variability in the antigens employed in these tests and the diagnostic criteria for seropositivity among the available kits. In addition, the number of commercially available assays has increased dramatically over the past year. Unfortunately, standardization among the various assays has not been achieved and rigorous proficiency testing programs have not been implemented for laboratories performing Lyme serologic testing.

Most ELISAs employ intact spirochetes or sonicates of *B burgdorferi* as test antigens. Some investigators have reported enhanced sensitivity and specificity with ELISAs utilizing flagellum or flagellum-enriched preparations of the spirochete.[76,77] An antibody capture enzyme immunoassay for IgM has demonstrated promise in the diagnosis of early Lyme disease.[78] Immunoblotting may also improve specificity without sacrificing sensitivity,[79] but is unfortunately expensive and not widely available. A sensitive and specific assay for *B burgdorferi* DNA utilizing polymerase chain reaction technology has recently been described.[80] The application of this technique to clinical specimens from patients with various stages of Lyme borreliosis has not been evaluated and its role in diagnostic testing is experimental.

These various diagnostic tests have some drawbacks. The lack of standardization from one laboratory to another may lead to discrepant results on the same sera.[81,82] In addition, these tests are often insensitive in patients with erythema chronicum migrans or other manifestations of stage I Lyme disease. In one study, only 10% of such individuals were positive by ELISA at pre-

TABLE 2
TREATMENT RECOMMENDATIONS FOR LYME BORRELIOSIS*

Syndrome	Regimen
Erythema chronicum migrans	
Adults	Tetracycline 250 mg po qid × 10–30 d
	Alternatives:
	Doxycycline 100 mg po bid × 10–30 d
	Amoxicillin 500 mg po qid × 10–30 d
Children	Amoxicillin 250 mg po tid or 20 mg/kg/d in three divided doses × 10–30 d
	Alternatives:
	Penicillin V 250–500 mg po qid or 50 mg/kg/d in four divided doses × 10–30 d
	Erythromycin 250 mg po qid or 30 mg/kg/d in three divided doses × 10–30 d
Carditis	
Primary atrioventricular block with PR <0.3	Oral regimens above
Other	Penicillin G 20 million U/d IV in four to six divided doses × 10–14 d
	Ceftriaxone 2 g/d IV × 10–14 d
Neurologic	
Isolated Bell's palsy	Oral regimens above
Other	Ceftriaxone 2 g/d IV × 14 d
	or
	Penicillin G 10–20 million U/d IV in four to six divided doses × 14 d
Arthritis	Ceftriaxone 2 g/d IV × 14 d
	or
	Penicillin G 20 million U/d IV in four to six divided doses × 14 d
	Alternatives:
	Doxycycline 100 mg po bid × 30 d
	Amoxicillin 500 mg plus probenecid 500 mg po qid × 30 d

*From references 12, 87.

sentation.[83] The diagnosis of stage I Lyme disease is therefore primarily a clinical diagnosis and is established on epidemiologic grounds and based upon the appearance of the characteristic rash. Antibiotic therapy in patients with ECM may also abort the serologic response to the spirochete and patients may never seroconvert.

Patients who present with carditis, neurologic manifestations, or arthritis are usually seropositive and thus a negative serology militates against the diagnosis of stage II or stage III Lyme disease. A recent report, however, described 17 patients who presented with ECM, received at least 10 days of conventional oral antibiotic therapy, and subsequently nevertheless developed later manifestations of Lyme disease.[84] These patients remained seronegative, but demonstrated *Borrelia* antigen-specific T-cell blastogenic responses in vitro. It is important to emphasize that such findings have not been described in patients without antecedent antibiotic therapy who present with stage II or stage III Lyme disease.

There is variability in the sensitivity and specificity of the available serologic tests for Lyme disease. False-negative results are common in stage I disease. False-positive results have been reported in patients with rheumatoid arthritis, systemic lupus erythematosus, Rocky Mountain spotted fever, infectious mononucleosis, and other spirochetal diseases such as syphilis and leptospirosis.[65,66,72–74] A positive Lyme serology must therefore be interpreted with caution in patients who do not have classic clinical findings of Lyme disease and in whom connective tissue disease or spirochetal infections are differential diagnostic possibilities. In addition, a single positive IgG titer does not distinguish remote from recent infection and may simply indicate past exposure to the spirochete. In geographic areas with a low prevalence of Lyme disease, the positive predictive value of a positive serologic test may be as low as 50%.[75] Indiscriminate serologic testing in patients with atypical clinical syndromes or nonspecific symptoms such as fatigue may lead to the inappropriate administration of antimicrobials.

THERAPY

Even before the identification of *B burgdorferi*, antibiotic therapy was known to shorten the course of erythema chronicum migrans.[85] The optimal therapy for some forms of Lyme disease remains controversial. Current treatment recommendations are summarized in *Table 2*.

The treatment of choice for adults with stage I Lyme disease appears to be tetracycline, 250 mg po qid for 10 to 30 days.[12,86,87] In the original comparative study examining the efficacy of oral antibiotics in the treatment of early Lyme disease, late complications developed in none of 88 patients treated with tetracycline, compared with 8% of penicillin-treated patients and 14% of erythromycin-treated patients.[86] Tetracycline failures have, however, been reported.[88] Doxycycline, 100 mg po bid has been suggested as an acceptable alternative,[89] but studies have not yet been published confirming the efficacy of this regimen. In children younger than 8 years in whom tetracycline or doxycycline is contraindicated, penicillin V, 50 mg/kg/day in four divided doses, or amoxicillin, 250 mg tid or 20 mg/kg/day in three divided doses, can be given for 10 to 30 days. Erythromycin, 250 mg po qid (or 30 mg/kg/day for children), may be employed for penicillin- and tetracycline-allergic patients, but appears to be less effective.[87]

The duration of therapy is dictated by the clinical course. In the original studies of oral therapy for early Lyme disease,[86] many patients experienced persistent or recurrent symptoms after 10 days of therapy. In such individuals, therapy should be extended for an additional 10 to 20 days. Jarisch-Herxheimer reactions occasionally complicate the therapy of early Lyme disease and may be attributable to inflammatory mediators released by dying spirochetes.

The therapy for stage II cardiac and neurologic Lyme disease is more empiric, since well-designed prospective studies have not been published defining optimal therapy for most patients with these syndromes. Oral antibiotic therapy with tetracycline, doxycycline, or amoxicillin has been recommended for patients with isolated Bell's palsy or first-degree atrioventricular block with PR intervals <0.3 seconds.[86,87] In those with other neurologic or cardiac manifestations, parenteral penicillin G (20 million units per day for 10 to 14 days) or ceftriaxone (2 g per day for 10 to 14 days) has been recommended.[86,87] One study compared high-dose penicillin with corticosteroids in patients with neurologic Lyme disease and demonstrated a significantly shorter duration of meningitic symptoms in penicillin recipients.[90] Corticosteroids probably have no role in the treatment of early neurologic Lyme disease. A recent small prospective randomized trial from West Germany suggested that 10 days of high-dose parenteral penicillin G or cefotaxime are comparably effective in patients with Lyme meningitis or radiculitis.[91]

Cardiac Lyme disease is usually a self-limited illness. In addition to antimicrobial therapy, supportive measures are indicated. Heart block is usually reversible and placement of a permanent transvenous pacemaker is seldom necessary. Corticosteroids may have a role in the treatment of serious cardiac Lyme disease which does not promptly respond to antibiotic therapy.[12,41]

Until recently, intravenous penicillin G (20 million units per day for 10 days) was the recommended therapy for established Lyme arthritis. A double-blind placebo-controlled trial compared 2.4 million units of intramuscular benzathine penicillin weekly for 3 weeks with placebo in patients with Lyme arthritis.[92] Thirty-five percent of penicillin-treated patients responded compared with none of the patients who received placebo. In a follow-up study that used 20 million units of intravenous penicillin G per day for 10 days, 55% of treated individuals had complete resolution of Lyme arthritis and remained well thereafter.[92]

Because of *B burgdorferi*'s in vitro susceptibility to ceftriaxone, a long-acting third-generation cephalosporin, there has been considerable interest in the potential utility of this drug for the treatment of established Lyme arthritis and late Lyme neuroborreliosis. A preliminary study demonstrated ceftriaxone's efficacy in patients who failed high-dose intravenous penicillin.[93] A recent study compared parenteral ceftriaxone at doses of 4 g per day and 2 g per day for 14 days with high-dose parenteral penicillin (24 million units per day for 10 days) in patients with late Lyme disease, predominantly arthritis.[94] Fifty percent of patients responded to penicillin, while 89% responded to ceftriaxone. Response was comparable in groups given 2 g and 4 g of ceftriaxone per day. Diarrhea was more common, however, in patients receiving high-dose therapy. Although these data require validation by other investigators, ceftriaxone may be the agent of choice at present for the therapy of stage III Lyme disease. The relative utility of other third-generation cephalosporins remains to be defined.

Treatment of Lyme disease during pregnancy is controversial. An apparent failure of oral therapy resulting in infant mortality from Lyme borreliosis was recently described.[95] In this single case report, the patient presented with ECM during the first trimester of pregnancy and received a 1-week course of low-dose oral penicillin. She subsequently delivered a full-term infant who died within 24 hours and had *B burgdorferi* in the brain at postmortem examination. Despite the fact that this patient only received a short course of low-dose oral therapy, some authorities recommend parenteral therapy for all women with Lyme disease in pregnancy. Others believe that conventional oral chemotherapy is satisfactory for early Lyme disease as long as the drug is administered at an appropriate dose for a period of time in line with the recommendations outlined in *Table 2*.

A 30-day regimen of oral tetracycline or doxycycline has been recommended for the treatment of acrodermatitis chronica atrophicans.[12] The utility of empiric oral antibiotic therapy following tick bites in areas of highly endemic Lyme disease has not yet been established.[96]

PREVENTION

A vaccine for Lyme disease is unlikely to be developed in the foreseeable future. In addition, control of the responsible tick vectors would be costly and impractical. Prevention of Lyme disease therefore depends upon avoidance and prompt recognition of potentially infectious ticks.[97]. Travelers or residents in highly endemic areas should wear light-colored long pants, high socks, long-sleeved shirts, and adequate shoes to minimize skin exposure when hiking in high-risk wooded or grassy areas where ticks are most likely to be found. The use of insect repellents such as DEET or permethrins should also be considered.

Since prolonged tick attachment (24 to 48 hours) is probably required to transmit infection,[96] careful examination for ticks should be performed daily or after every potential exposure when in endemic areas. If ticks are identified, they should be carefully removed with forceps or gloved fingers by pulling straight out from the skin.[98] Twisting or shearing may result in retention of infected mouth parts in the skin and should be discouraged. Care should be taken to avoid squeezing the body of the tick to prevent the theoretic danger of injecting *B burgdorferi* from an infected tick into the wound. The involved skin should be thoroughly cleansed following tick removal.

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