Lyme Disease—Part II: Clinical Features and Treatment

Norma J. Montiel, DO; Jana M. Baumgarten, MD; Animesh A. Sinha, MD, PhD

GOAL

To discuss the clinical features and treatment of Lyme disease (LD)

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the clinical features of LD at its different stages.
2. Delineate options available to diagnose LD.
3. Outline treatment choices for LD.

CME Test on page 454.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: May 2002.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom, Inc. The Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Albert Einstein College of Medicine designates this educational activity for a maximum of 1.0 hour in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

This activity has been planned and produced in accordance with ACCME Essentials.

Lyme disease (LD) is the most common vector-borne disease in the United States. Generally presenting with a characteristic rash, myalgia, and fatigue, LD can progress to chronic arthritis, central nervous system manifestations, and cardiac abnormalities, if left untreated. The number of cases continues to rise each year. Early diagnosis and proper therapy are required to halt disease progression to late chronic stages. By adhering to simple guidelines, many potential cases of LD can be prevented. In this article, the second in a 2-part series on LD, we discuss clinical features and treatment.

From the Department of Dermatology, Weill Medical College of Cornell University, New York, New York. Drs. Montiel and Baumgarten are fellows. Dr. Sinha is an Assistant Professor. Reprints: Animesh A. Sinha, MD, PhD, Department of Dermatology, Weill Medical College of Cornell University, 510 E 70th St, Room LC-702, New York, NY 10021 (e-mail: ans2003@med.cornell.edu).

The number of reported cases of Lyme disease (LD)—defined as the presence of an erythema migrans (EM) rash greater than 5 cm in diameter or evidence of at least one musculoskeletal, neurologic, or cardiac manifestation, as well as laboratory confirmation—has been rising over the past 20 years. Prevention and early diagnosis of LD are key to preventing long-term multisystem complications.

Clinical Features

The Centers for Disease Control (CDC) describes LD in 3 stages: 1) early, 2) early disseminated, and 3) late. If left untreated, LD will advance to more chronic stages. Early localized disease occurs within 3 to 30 days of an infected tick bite and manifests with EM, as well as constitutional symptoms such as myalgia, fatigue, headache, fever, lymphadenopathy, photophobia, sore throat, nausea, vomiting, anorexia, and monoarticular arthralgia.[1]

Although early studies found that EM was noted in 50% to 70% of patients, more recent studies have demonstrated that up to 90% of people with LD have identified lesions of EM.[2,3] On average, the rash appears 9 days after the arthropod bite. The lesion typically enlarges at a rate of 1 to 2 cm in diameter per day to approximately 30 cm in diameter[4] and is rarely pruritic. It may be mildly tender, and a burning sensation is not uncommon. The rash fades spontaneously within 4 weeks.

In untreated patients, early disseminated disease manifests from 30 to 120 days after inoculation of *Borrelia burgdorferi*. Symptoms include multiple lesions of EM, lymphadenopathy, and conjunctivitis.[5] Central and peripheral nervous manifestations include meningitis, meningoencephalitis, cranial neuritis, motor neuropathies, Guillain Barré–like syndromes, radiculoneuritis (the most common presentation of neuroborreliosis in Europe), and facial palsy (the most common neurologic manifestation of LD in North America).[1,5] Patients presenting with bilateral facial palsy in endemic areas should be suspected to have LD.[6] Three percent of children with LD develop seventh-nerve palsy, which lasts from 2 to 8 weeks, with or without treatment.[6] In Europe, there is a greater frequency of neuritis and Bannwarth syndrome (meningopolyneuritis) among people with LD.[2] Less than 10% of patients manifest cardiac abnormalities, including rhythm disturbances (specifically varying degrees of arteriovenous block) and myocarditis.[1] Patients with arteriovenous block present with dizziness, palpitations, syncope, and dyspnea.[5] Lyme arthritis initially presents with a sudden onset of large joint pain (especially in the knee) and swelling.[7] With or without treatment, symptoms last a few days to a few weeks.[7]

Late LD occurs from 4 months to 1 year after inoculation in the untreated patient. Chronic arthritis, chronic synovitis, encephalopathy, and fatigue are common symptoms. Other organ systems rarely become involved and may manifest as conjunctivitis, keratitis, hepatitis, myositis, and osteomyelitis.[1,2,8] Lyme lymphocytoma, characterized by red-blue nodules in the dermis or subcutaneous tissue of the nipples of adults and earlobes of children, is a rare presentation.[5] This manifestation resolves without treatment. Acrodermatitis chronica atrophicans (ACA), a chronic, atrophic sclerotic lesion of the skin rarely seen in the United States, affects 10% of LD patients in Europe.[1] Other dermatologic atrophic lesions, such as morphea, lichen sclerosus et atrophicus, anetoderma, and atrophoderma of Pasini and Pierini, also have been noted in late LD.[1]

Plaquelike morphea seen in late LD presents as a well-demarcated, indurated, round, or oval lesion. Initially, it manifests as an erythematous lesion with a violaceous hue.[1] As the lesion progresses, it becomes a smooth, shiny, sclerotic plaque with a yellow center.[1] Typically painless, morphea can be accompanied by dysesthesia, hypoesthesia, and hyperesthesia.[1] Histologically, early lesions have superficial and deep perivascular lymphohistiocytic infiltrate with plasma cells and, on occasion, eosinophils.[1,9] The dermis demonstrates sclerosis and hyalinization of collagen bundles.[1] As the lesion ages, the dermis becomes more sclerotic, and the infiltrate dissipates. Morphea may last months to years, resolving spontaneously and leaving pigmented and/or atrophic changes.[1] The etiology of morphea in LD is still unknown. In 1985, Aberer et al[10] reported an inability to histologically distinguish morphea from ACA and suggested *B burgdorferi* as a causative agent. Reports of *B burgdorferi* detection by polymerase chain reaction (PCR) in both morphea and ACA lesions seemed to provide evidence for this theory.[11-13] However, in a more recent and comprehensive study using patient questionnaires, serologic evaluation, and PCR, Weide et al[14] were unable to find significant evidence to prove an association.[8]

Diagnosis

The CDC recommends that the diagnosis of LD be based on the possibility of tick exposure, clinical manifestations, and laboratory confirmation.[15] Patients with classic early symptoms of EM do not necessarily require diagnostic testing, and treatment can be initiated based on clinical findings alone.[5] Laboratory diagnosis is most relevant for patients presenting with borderline or no symptoms. Culture, PCR, visualization of spirochetes in tissue section, and serology all have been used in the diagnosis of LD.

The gold standard for the diagnosis of LD is the detection of causative organisms in culture.[5] Tissue from punch biopsies of EM lesions, and, in rare cases, cerebrospinal fluid can be cultured for *B burgdorferi*.[5] Anecdotally, *B burgdorferi* also has been cultured from blood, the heart, and synovial fluid.[16] Unfortunately, the protracted incubation times and requirements for special media make culturing impractical in most office settings.[4,5,16] Although positive cultures are diagnostic, growth is not always demonstrated in infected individuals. In one study, cultures on modified Barbour-Stoennar-Kelly medium at 33°C to 37°C for 1 to 4 weeks were shown to be only 72% positive in patients confirmed to have LD by other criteria.[4,16]

Moreover, positive results decrease as the duration of EM lesions increases and in patients who have initiated antibiotic treatment.[4]

Serology is the most practical laboratory technique to confirm LD where there is clinical suspicion. The CDC recommends indirect immunofluorescence assays or enzyme–linked immunosorbent assay (ELISA) confirmed with Western blot.[17] However, these tests have not been standardized; there are variations of sensitivities and specificities among laboratories.[16,18] False-positive results are possible, and clinical correlation is important. Patients with borderline symptoms and positive serology may not have LD, and further investigation is recommended to determine the appropriate diagnosis.[4]

Nevertheless, testing for humoral immunity is diagnostically useful. Using whole cell lysates or partially purified *B burgdorferi* as antigens, ELISA captures anti-*B burgdorferi* antibody from human serum.[5] ELISA is preferred over indirect fluorescent antibody assay because of its suitability for processing a large number of samples.[5] ELISA may be used to detect IgG or IgM responses. However, false-positive IgM testing may occur in patients with autoimmune disease, Epstein-Barr virus infection, bacterial endocarditis, and other tick-born diseases such as ehrlichiosis and babesiosis.[3,5] False-positive IgG serologic testing has been demonstrated in patients with syphilis, *Helicobacter pylori* infection, and systemic lupus erythematosus.[3,5] Because of the unreliability of ELISA testing, a positive test should be corroborated with a Western blot. Western blots separate borrelial antigens by gel electrophoresis that are then transferred to membranes and exposed to patient serum.[5] This technique is more specific for LD than ELISA.[5] As with ELISA, immunoblots can be used to detect both IgM and IgG anti-Lyme titers; the IgG response is more specific.[5] It should be noted that IgM remains negative for the first 30 days of infection; thus, serologic testing cannot be used to confirm early disease.[5] Determination of IgG titers is the preferred testing for long-standing disease.[5] Typically, IgG titers are elevated at 6 to 8 weeks after infection.[3] IgM and IgG levels remain elevated even subsequent to therapy; therefore, titers may not be used to assess treatment efficacy.[5]

On histologic examination, lesions of EM are characterized by a superficial and deep perivascular and interstitial infiltrate composed of lymphocytes with plasma cells and eosinophils.[9] Plasma cells usually are demonstrated in the periphery of the lesion, and eosinophils are seen in the area of inoculation. Definitive diagnosis of LD is not confirmed unless spirochetes, typically found in the upper dermis, epidermis, and follicular epithelium, are demonstrated. However, the demonstration of spirochetes in tissue using silver stains or polyclonal or monoclonal antibodies to *Borrelia* antigens is not straightforward, and there is the risk for overdiagnosis and underdiagnosis.[16]

Recently, molecular techniques became available for diagnostic purposes. PCR technology can be used to detect *B burgdorferi* in skin, cerebrospinal fluid, synovial fluid, urine, and blood.[5] Despite exquisite sensitivity, host variation and nonstandardized procedures (primers and protocols) can produce a wide variability in results. More important, PCR is not approved for diagnostics purposes, because it cannot distinguish viable from nonviable spirochetes.[5,18]

Treatment

Systemic therapy is required to ensure the prevention of disease progression from early and early disseminated to late disease.[5] Although children have an excellent prognosis even if intervention occurs in late disease, it is imperative that adults be diagnosed and receive proper treatment during the early stages.[3] First-line treatment of early disease is doxycycline or amoxicillin (Table). Doxycycline has the added advantages of good central nervous system absorption, good oral absorption, and high activity against human granulocytic ehrlichiosis (coinfection rates are 10% in endemic areas).[7] Azithromycin also is effective in early disease; 250 mg of azithromycin twice a day for 2 days, followed by 250 mg once a day for 8 days, has been shown to be as effective as doxycycline.[19] Minocycline is an acceptable alternative to doxycycline and is prescribed at the same dose as doxycycline.

Intravenous (IV) therapy is reserved for patients with neurologic symptoms, carditis, and/or arthritis. First-choice IV therapy is ceftriaxone 2 g/day, which has the advantage of once-a-day dosing.[20] Poor response of Lyme arthritis to IV antibiotic treatment has been associated with histocompatibility antigen HLA DR4 in 10% of cases.[18] Arthritis that continues after antibiotic treatment may be treated with nonsteroidal anti-inflammatory drugs, intra-articular steroid injections, or arthroscopic synovectomy.[7] Cardiac abnormalities generally resolve with oral antibiotic treatment. However, patients with P-R interval greater than 0.3 seconds should be treated with IV antibiotics and considered for telemetry admission and temporary pacemaker insertion.[21] Oral antibiotics can be restarted when there are no further indications for pacemaker usage.[21] IV therapy also is recommended for the subset of patients that continue to have symptoms consistent with

Treatment Options for Lyme Disease*

Stage	Drug	Dose	Treatment Duration
Early localized			
Adult	Doxycycline	100 mg po bid	14–21 days
	Amoxicillin	250–500 mg po tid	14–21 days
	Cefuroxime axetil	500 mg po bid	14–21 days
Children	Doxycycline (>9 y)	100 mg po bid	14–21 days
	Amoxicillin	30–50 mg/kg/d	14–21 days
	Erythromycin	30 mg/kg/d	14–21 days
	Phenoxymethylpenicillin	25–50 mg/kg/d	14–21 days
Early disseminated and late disease			
Adults			
Neurologic	Ceftriaxone sodium	2 g/d IV	14–28 days
	Cefotaxime sodium	2 g q8hr IV	14–28 days
	Penicillin G	3.5–4 million U IV	14–28 days
Cardiac	Doxycycline	100 mg po bid	21 days
	Minocycline	100 mg po bid	21 days
	Amoxicillin	500 mg po q8h	21 days
Arthritis	Ceftriaxone	2 g/d IV	21 days
	Amoxicillin	500 mg po tid	30–60 days
	Doxycycline	100 mg po bid	30–60 days
	Ceftriaxone	2 g/d IV*	14 days
Children			
Neurologic	Ceftriaxone sodium	50–100 mg/kg/d IV	14–28 days
Neurologic/cardiac	Cefotaxime sodium	90–180 mg/kg/d IV	14–28 days
Arthritis	Penicillin G	20 million U in divided doses IV	14–28 days
	Amoxicillin	50 mg/kg/d po tid	30–60 days

*po indicates periorally; bid, twice a day; tid, 3 times a day; IV, intravenous.

neuroborreliosis, despite oral treatment of early disease.[7] The subset of patients who do not respond to treatment also should be tested for coinfection with *Ehrlichia* or *Babesia*.[3] A recent study demonstrated that long-term (90 days) IV antibiotic use following previous antibiotic treatment of acute LD was ineffective in alleviating long-term LD symptoms, including musculoskeletal pain, neurocognitive symptoms, and fatigue.[22]

Prevention and Vaccination

By adhering to simple guidelines, a significant number of potential LD cases can be prevented. When outdoors in rural areas with a known tick population or in

endemic areas, one should wear protective clothing, including long-sleeved shirts and pants tucked into socks.[1] Application of N,N-diethyl-m-toluamide (DEET) to skin surfaces and permethrin to clothing also reduces the risk for transmission.[1,5] A full inspection for ticks is recommended after excursions in high-risk geographic areas. If an attached tick is found, it should be grasped with tweezers as close to the skin as possible and gently pulled off.[16] Previously, there were no recommendations for antibiotic prophylaxis in any scenario. Studies suggested that prophylaxis was not cost-effective unless the risk for infection was greater than 3.6% in a given area.[23] A recent study by Nadelman et al[24] reexamined the usefulness of antibiotic prophylaxis, using a more cost-effective single-dose of doxycycline (200 mg). In this study, only 1 of 235 (0.4%) individuals in the treatment group developed EM compared with 8 of 247 (3.2%) individuals in the placebo group.[24] None of the subjects developed other manifestations of LD nor asymptomatically seroconverted.[24] Although this study concluded that single-dose doxycycline within 72 hours of a tick bite was effective in preventing the development of LD, few individuals in the placebo group actually developed LD. These findings are cause to rethink whether or when prophylaxis is needed, to reassess if single-dose treatment is a possibility, and to reassure patients with "Lyme disease anxiety" about the risks for disease and response to treatment.

Recombinant OspA has been approved by the US Food and Drug Administration as a vaccine for LD since 1998. In trials of more than 10,000 people, the efficacy rate of the 3-dose vaccine was 76%.[25] Indeed, Recombinant OspA appears to decrease or eliminate *B burgdorferi* populations in the gut of the *Ixodes* tick even before inoculation into the host. Currently, the CDC and Committee on Infectious Diseases recommend that only people between the ages of 15 to 70 years who live, work, recreate, or travel to high-risk areas should be considered for vaccination.[26] The vaccine is not recommended for pregnant women or immunocompromised people.[26] To date, a 3-dose schedule at 0, 1, and 12 months has been approved. However, recent studies have shown similar efficacy rates for both a 0-, 1-, and 2-month schedule and a 0-, 1-, and 6-month schedule.[27] Systemic side effects noted in the clinical trials were rare and included fatigue, headache, rash, and arthralgia. The most commonly noted reaction was local tenderness at the injection site.[28]

REFERENCES

1. Malane MS, Grant-Kels JM, Feder HM Jr, et al. Diagnosis of Lyme disease based on dermatologic manifestations. *Ann Intern Med*. 1991;115:490-498.
2. Rahn DW, Felz MW. Lyme disease update. Current approach to early, disseminated, and late disease. *Postgrad Med*. 1998;103:51-64.
3. Sigal L. Pitfalls in the diagnosis and management of Lyme disease. *Arthritis Rheum*. 1998;41:195-204.
4. Habif TP. *A Color Guide to Diagnosis and Therapy: Clinical Dermatology*. 3rd ed. St. Louis, Mo: Mosby; 1996.
5. Hu LT, Klempner MS. Update on the prevention, diagnosis, and treatment of Lyme disease. *Adv Intern Med*. 2001;46:247-275.
6. Shapiro ED, Gerber MA. Lyme disease. *Clin Infect Dis*. 2000;31:533-542.
7. Steere AC. Diagnosis and treatment of Lyme arthritis. *Med Clin North Am*. 1997;81:179-194.
8. Hercogova J, Brzonova I. Lyme disease in central Europe. *Curr Opin Infect Dis*. 2000;14:133-137.
9. Lever WF, Schaumburg-Lever G. *Histopathology of the Skin*. 7th ed. Philadelphia, Pa: Lippincott; 1990.
10. Aberer E, Neumann R, Stanck G. Is localised scleroderma a *Borrelia* infection. *Lancet*. 1985;2:278.
11. Ozkan S, Atavey N, Fetil E, et al. Evidence of *Borrelia burgdorferi* in morphea and lichen sclerosus. *Int J Dermatol*. 2000;39:278-283.
12. Schempp C, Bocklage H, Lange R, et al. Further evidence for *Borrelia burgdorferi* infection in morphea and lichen sclerosus et atrophicus confirmed by DNA amplification. *J Invest Dermatol*. 1993;100:717-720.
13. Fujiwara H, Fujiwara K, Hashimoto K, et al. Detection of *Borrelia burgdorferi* DNA (*B garinii* or *B afzelii*) in morphea and lichen sclerosus et atrophicus tissues of German and Japanese but not of US patients. *Arch Dermatol*. 1997;133:41-44.
14. Weide B, Schittec B, Klyscz T, et al. Morphoea is neither associated with features of *Borrelia burgdorferi* infection, nor is this agent detectable in lesional skin by polymerase chain reaction. *Br J Dermatol*. 2000;143:780-785.
15. Recommendations for the use of Lyme disease vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1999;48(RR07):1-17,21-25.
16. Fitzpatrick T, Eisen A, Wolff K, et al. *Dermatology in General Medicine*. 4th ed. New York, NY: McGraw-Hill; 1993.
17. Centers for Disease Control and Prevention. Lyme disease—United States, 1996. *MMWR Morb Mortal Wkly Rep*. 1997;46:531-535.
18. Terkeltaub RA. Lyme disease 2000. Emerging zoonoses complicate patient work-up and treatment. *Geriatrics*. 2000;55:34-44.
19. Loewen PS, Marra CA, Marra F. Systemic review of the treatment of early Lyme disease. *Drugs*. 1999;57:157-173.
20. Committee on Infectious Diseases. Prevention of Lyme disease. *Pediatrics*. 2000;105:142-147.
21. Edlow JA. Lyme disease and related tick-borne illnesses. *Ann Emerg Med*. 1999;33:680-693.

22. Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med*. 2001;345:85-92. Available at: http://www.nejm.org. Accessed June 12, 2001.
23. Centers for Disease Control and Prevention. Lyme disease—United States, 1999. *MMWR Morb Mortal Wkly Rep*. 2001;50:181-185.
24. Nadelman RB, Nowakowski J, Fish D, et al. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite. *N Engl J Med*. 2001;345:79-84. Available at: http://www.nejm.org. Accessed June 12, 2001.
25. Evans J. Lyme disease. *Curr Opin Rheumatol*. 2000;12:311-317.
26. Thanassi WT, Schoen RT. The Lyme disease vaccine: conception, development, and implementation. *Ann Intern Med*. 2000;132:661-668.
27. Rahn DW, Evans J. *Lyme Disease*. Philadelphia, Pa: The American College of Physicians; 1998.
28. Steere AC, Sikand VK, Parenti DL, et al. Vaccination against Lyme disease with recombinant *Borrelia burgdorferi* outer-surface lipoprotein A with adjuvant. Lyme Disease Vaccine Study Group. *N Engl J Med*. 1998;339:216-222.