

## Lyme Disease: Recognition, Management, and Prevention in the Primary Care Setting

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This activity is designed for practitioners who see patients with tick bites, Lyme disease, or suspected Lyme disease in their practice, whether or not the practitioner is in an endemic area for Lyme disease.

### GOAL

To help primary care practitioners recognize and treat Lyme disease and provide preventive counseling.

### OBJECTIVES

1. Be familiar with the terminology used for the causative agent of Lyme disease, its tick vector and reservoirs in nature, and where the disease is endemic.
2. Know the features of the common, characteristic clinical forms of Lyme disease.
3. Appreciate the uses and limitations of laboratory testing for this infection.
4. Understand early antibiotic treatment of Lyme disease, the management of a tick bite, and preventive measures.

A common misconception about Lyme disease is that the infection, once acquired, is difficult to cure. This may lead to the impression that prolonged and sophisticated treatment is typically necessary. On the contrary, the vast majority of pa-

tients can be treated inexpensively in a primary care setting, provided the nature of the infection is explained carefully to the patient.

Lyme disease, or Lyme borreliosis, is a localized or disseminated infection caused by *Borrelia burgdorferi*, a spirochete transmitted to humans and other mammals through the bite of hard-bodied ticks of the genus *Ixodes* (*I scapularis* in the Northeast and upper Midwest, *I pacificus* in the West). Although *I scapularis* is found in the south-central and southeastern United States as well, only the northern variety, the deer tick (previously *I dammini*) is associated with transmission of the infection. Higher ambient temperatures and lack of a suitable population of a mammalian reservoir for the spirochete have been proposed to explain why Lyme borreliosis is not endemic in the South.

The range of both infected and noninfected *I scapularis* is gradually increasing in the North. Increased human inhabitation in wooded areas has resulted in more peri-domestic tick exposure to humans. Tick-borne illness is associated with proximity to both the white-tailed deer, the main host for the adult tick, and the white-footed mouse, the main host for the nymphal stage tick and the main reservoir for the spirochete.

### Clinical Features and Diagnosis

Following the modern description of the clinical manifestations of Lyme disease in the mid-1980s, manifestations were originally classified into three stages: (1) erythema migrans (EM); (2) neurologic involvement; and (3) arthritis. These classifications are no longer valid because it is now known that dissemination can occur soon after the initial infection, and that any of the major systems can be affected either early or late in the course of infection. For example, arthritis can be an early manifestation, occurring days after an infected tick bite, whereas persistent neurologic involvement or acrodermatitis chronica atrophicans can manifest months to years later. Therefore, acute infection in an individual patient can manifest as either localized cutaneous infection or disseminated infection. Patients with disseminated infection may have an increased risk for

### CONTINUING MEDICAL EDUCATION ACCREDITATION

The Long Island Jewish Medical Center, the Long Island campus for the Albert Einstein College of Medicine, designates this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association.

The Long Island Jewish Medical Center is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. This activity is cosponsored by the Johns Hopkins University School of Medicine.

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presenting with late Lyme disease and developing extracutaneous manifestations.

A diagnosis of Lyme borreliosis should not be daunting if it is recognized that in the vast majority of cases the symptoms and signs are characteristic of the disease (Table). In a recent large community-based study of children,<sup>1</sup> the presenting manifestations were single EM (66%), multiple EM (23%), arthritis (6%), facial palsy (3%), aseptic meningitis (2%), or carditis (0.5%). Early diagnosis is important to prevent the increased effort and expense of managing the manifestations that occur later in the course of disease and to prevent long-term morbidity.

**Erythema Migrans.** EM is best diagnosed clinically as an expanding annular red rash, although some variations occur, eg, a plaque without central clearing, vesicular rash, and noncircular shapes. In a recent study of culture-proved EM in New York, the incubation period was 1 to 27 days (mean 10 days) following the tick bite; the diameter at presentation was between 6 cm and 73 cm.<sup>2</sup> The reader is referred to this paper for an excellent pictorial review.

**Lyme Arthritis.** Lyme arthritis presents as inflammation that usually involves four or fewer joints. The typical patient reports a mildly symptomatic large joint (eg, knee) effusion, occurring episodically with periods of complete remission. Earlier in the course of disease, polyarthralgia, perhaps associated with constitutional symptoms, may be the main symptom. Lyme disease would not be readily suspected. The interval between acquisition of infection and appear-

ance of frank arthritis varies from a few days to 2 years, but typically exceeds 6 weeks. Thus Lyme arthritis is a late manifestation of infection. Arthritis may be erosive, and in fewer than 5% of patients, chronic. The differential diagnosis includes septic arthritis, viral or postinfection reactive arthritis, and, in children, juvenile rheumatoid arthritis. Synovial fluid findings are typical for an inflammatory arthritis with marked leucocytosis and polymorphonuclear cell predominance.

**Neurologic Disease (Neuroborreliosis).** The most common neurologic manifestations of acute disease, occurring within approximately 8 weeks from the onset of infection, are VII nerve palsy and lymphocytic (aseptic) meningitis. Facial palsy can be the sole and an early manifestation, and may be bilateral. An acute lymphocytic meningitis may occur alone or accompany the palsy. Thus, patients may present with signs of meningeal irritation. Other manifestations such as pseudotumor cerebri are occasionally seen. Unlike in encephalitis or pyogenic meningitis, patients are not severely ill. The differential diagnosis includes enteroviral aseptic meningitis.

It is important to distinguish Lyme facial palsy from idiopathic Bell's palsy. The latter condition is sometimes treated with steroids, which can be deleterious in an infection. A positive screening serologic test confirming the presence of specific IgM antibodies by immunoblot is helpful.

**Radiculoneuritis (Garin-Bujadoux-Bannwarth Syndrome).** This is a well-recognized manifestation of European Lyme disease in adults. Features include lancinating pain in a dermatomal distribution. As in VII nerve palsy, cerebrospinal fluid (CSF) pleocytosis is often present.

**Chronic Encephalopathy, Encephalomyelitis (Leucoencephalomyelitis).** The pathogenesis and clinical spectrum of chronic central nervous system (CNS) involvement in Lyme disease are controversial. Since patients with persistent neuropsychiatric symptoms are seen months to years after the acute infection, antibody levels may have waned and serologic results may be equivocal. Chronic symptoms resulting from infection may persist in a very small proportion of patients. Current CSF assays are not adequately sensitive or specific. Although antigen and immune complexes have been detected in some patients, *B burgdorferi* is typically not recovered from CSF. Detection of *B burgdorferi* DNA by probable causal relationship also has a poor yield. In a recent study, detection of *B burgdorferi* in the tick by probable causal relationship was found to be an unreliable predictor of infection in the patient.<sup>3</sup> There is experimental evidence of cross-reactivity of human axonal proteins

**Table.** Clinical Presentations of Lyme Disease

<b>Localized</b>	
■	Acute: erythema migrans*
■	Persistent: acrodermatitis chronica atrophicans, borreliolymphocytoma
<b>Disseminated</b>	
■	Multiple EM*
■	Lyme arthritis*
■	Facial palsy*
■	Aseptic meningitis*
■	Flu-like illness
■	Radiculoneuritis
■	Encephalomyelitis
<b>Other</b>	
■	Asymptomatic seroconversion
■	Possible transplacental

\*Commonly encountered in the United States.

with monoclonal antibodies to *B burgdorferi*, suggesting an autoimmune process as partial explanation of the pathogenesis of cerebral disease.

Given the uncertain etiology of many neurologic disorders, and the temptation to draw parallels between neuroborreliosis and neurosyphilis, a variety of conditions have been ascribed to *B burgdorferi* infection in adults, albeit with poor evidence. It is worth noting, however, that both multiple sclerosis and amyotrophic lateral sclerosis have been well investigated in this regard. In fact, some evidence exists for a greater rate of seropositivity to *B burgdorferi* among patients with amyotrophic lateral sclerosis in an endemic area. Even in a patient with objective neurologic findings and who is seropositive for *B burgdorferi* infection, it is essential that other neurologic diseases be ruled out, since positive serology may reflect previous infection that is unrelated to current complaints.

Another poorly understood manifestation is the post-Lyme disease syndrome. In some patients, symptoms persist despite appropriate antibiotic treatment. Many return with constitutional symptoms compatible with fibromyalgia. Whether persistent *B burgdorferi* infection is present in all these patients is unknown, especially because some patients are seronegative.

*Carditis.* Cardiac involvement is an uncommon complication, occurring early in the course of infection and affecting the conduction system. A resulting heart block may be asymptomatic; however, it is usually not persistent.<sup>4</sup> Retrospective studies of patients with Lyme disease have not revealed evidence of chronic cardiac abnormalities.<sup>5</sup>

*Other Manifestations.* Data on the incidence of clinical forms that are *not* accompanied by characteristic physical findings are limited. Asymptomatic seroconversion<sup>3</sup> and a viral-like illness without EM have been described.<sup>6</sup> Transplacental infection is extremely rare. Large prospective studies have failed to demonstrate an association between maternal infection and congenital malformations.<sup>7,8</sup>

### Laboratory Diagnosis

Culture for the spirochete has a poor yield from all bodily fluids and tissues. Fortunately, the cumulative experience with serologic assays now enables us to confirm a clinical diagnosis. In 1994, a consensus panel convened by CDC/Association of State and Territorial Public Health Laboratory Directors recommended a two-step approach for laboratory confirmation: (1) that physicians screen with any of several commercially available enzyme-immunoassays or indirect immunofluorescence assays; and (2) that any positive or equivocal result be confirmed by a Western immuno-

blot.<sup>9</sup> Uniform criteria were adopted for interpretation of a positive IgG immunoblot (5 or more of the following bands: 18, 23, 28, 30, 39, 41, 45, 60, 66, 93 kilodalton) and a positive IgM immunoblot (2 or more of the following bands: 23, 39, 41 kilodalton). Individual bands represent antibodies to different polypeptides of *B burgdorferi*. An IgM immunoblot is a valid assay only in the first 4 weeks of the infection. After that period, only the IgG immunoblot is valid.

The diagnosis of Lyme disease should rest on an evaluation of three factors: opportunity for exposure, characteristic clinical features, and serologic confirmation. EM is an exception because, although the patient can be seronegative early in the course of the infection, a clinical diagnosis can be made. Serologic testing ordered without evaluation of the other two factors may result in unnecessary costs. In a California health maintenance organization, 1 in 5 serologic tests for Lyme disease was performed because the physician suspected the disease; however, only 1 of 117 patients was diagnosed seropositive.<sup>10</sup> A large proportion of the tests were ordered at the patient's request or as part of a battery of tests for nonspecific symptoms.

### Treatment

For most forms of Lyme disease, oral antibiotic therapy, administered for 3 to 4 weeks, is effective.<sup>11</sup> Because of the risk of teeth-staining with tetracyclines, amoxicillin is the drug of choice for patients under 9 years of age. Doxycycline or amoxicillin are indicated after age 9. Following effective treatment, patients will remain seropositive indefinitely. In invasive CNS disease—such as meningitis and in cases of recurrent arthritis—parenteral therapy with a third-generation cephalosporin, administered for 2 to 4 weeks, is recommended.

### Management of a Tick Bite

Because Lyme disease can be associated with severe and occasionally persistent disease, some physicians administer an antibiotic following a tick bite. However, this practice is controversial, and the efficacy of such treatment is uncertain. The incidence of infection following an individual tick bite is low, even in an endemic area, and must be balanced against the incidence of adverse effects from an antibiotic and the growing problem of antibiotic resistance. Shapiro et al conducted a controlled trial of prophylaxis with amoxicillin versus placebo following a deer-tick bite in a highly endemic area in Connecticut.<sup>12</sup> They found no evidence for efficacy, given the low likelihood of infection. Conversely, Majid et al conducted a cost-effectiveness analysis to evaluate the wisdom of em-

piric treatment of all persons bitten by a deer tick.<sup>13</sup> They concluded that such a strategy was only indicated in areas where the probability of infection was 3.6% or higher. A number of variables influence the risk of infection, including geographic area, stage of tick, time of year, and duration of attachment.

**Geographic Location.** The prevalence of *I scapularis* infected with *B burgdorferi* varies significantly even within an endemic area. Surveys of tick infection have shown rates of 47% to 100% on Shelter Island and Long Island, New York, and 10% to 35% in Connecticut. In contrast, only 1.5% of *I pacificus* ticks in California were found to be infected. Unfortunately, such information is lacking for most other areas.

**Stage of Tick and Time of Year.** Most cases of infection result from the nymphal stage. The nymph feeds in the spring and early summer when people are outdoors. It is much smaller than an adult tick, which is about the size of a sesame seed, and often goes unnoticed, resulting in prolonged attachment that may facilitate spirochete transmission. Variations in weather conditions, such as mild winters, has not been proved to influence the annual incidence of Lyme disease.

**Duration of Attachment.** A recent prospective study in humans has extended our previous knowledge about duration of tick attachment and the risk of Lyme disease.<sup>3</sup> Animal studies suggest that the ability of *I scapularis* to transmit *B burgdorferi* increases exponentially between 48 and 60 hours. The study demonstrated a 20-fold higher risk of *B burgdorferi* infection for tick attachment of 72 hours or greater.

Management of a tick bite should include identification of the tick. Only deer ticks transmit the spirochete. However, not all deer ticks carry the spirochete. Fewer than 4% of deer-tick bites will result in transmission of infection, even in endemic areas, since the risk is partly dependent upon the duration of attachment. Prophylactic treatment is not considered necessary by most experts, but may be considered, if the tick is known to have been attached for 72 or more hours in an endemic area. Close observation of the skin for the characteristic rash is an acceptable strategy, since treatment is usually effective when the rash has appeared. EM may not be detected in all cases. However, even when acute neurologic disease or Lyme arthritis are the first presenting manifestation, antibiotic therapy is almost universally curative.

### Prevention

The best methods of prevention are avoidance behavior and early tick removal. Persons who spend the day outdoors should inspect their skin carefully each evening. A tick is easily removed with a pair of tweez-

ers. The most commonly used repellent, *N,N*-diethyl-*m*-toluamide (DEET) is effective but has serious limitations. It is short lasting, is absorbed through the skin, and is known to cause seizures and other neurologic disturbances. Therefore, high concentration preparations, which are commonly available over the counter, should be applied sparingly. DEET should be applied only to exposed areas and to clothing, and should be avoided in infants and young children.

The primary care practitioner who treats a person with Lyme disease should emphasize the eminent susceptibility of the causative bacterium to a short course of antibiotics, and that, consequently, the disease usually has a good prognosis. Physicians should seize the opportunity to educate patients about prevention through avoidance and early removal of ticks.

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**CME QUESTIONS: TEST #039707**

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**Instructions**

After reading the article, "Lyme Disease: Recognition, Management, and Prevention in the Primary Care Setting," select the best answer to each of the following questions. In order to receive 1 CME credit, at least 7 of the 10 answers must be correct. Estimated time for this activity is 1 hour. CME credits are distributed on a yearly basis.

1. In 1997, serologic diagnosis remains poorly standardized and unreliable in most commercial laboratories.
  - a) true
  - b) false
  
2. A diagnosis of early Lyme disease should not be made without serologic confirmation.
  - a) true
  - b) false
  
3. Constitutional symptoms, eg, symptoms resembling acute viral illness, joint pains without objective arthritis, or neck pain, should not by themselves raise clinical suspicion of Lyme disease, even in endemic areas.
  - a) true
  - b) false

4. Chronic CNS disease is the most common neurologic manifestation of Lyme disease
  - a) true
  - b) false
  
5. Transplacental transmission is common in another spirochetal disease, syphilis. By analogy, treatment of the baby should be routinely instituted if the mother had Lyme disease during pregnancy.
  - a) true
  - b) false
  
6. Lyme disease in the vast majority of patients is amenable to therapy with an oral antibiotic course of 4 weeks.
  - a) true
  - b) false
  
7. Observation, with treatment at the occurrence of symptoms, is a superior strategy to treatment of a deer-tick bite based on duration of attachment.
  - a) true
  - b) false
  
8. The carriage of *B burgdorferi* in a deer tick that has bitten a person is a useful criterion for deciding if prophylactic treatment should be instituted.
  - a) true
  - b) false
  
9. Although hyperendemic in some areas, Lyme disease can be acquired in almost any state of the United States, as ticks are ubiquitous throughout the country and deer populations are now very widespread.
  - a) true
  - b) false
  
10. Liberal ordering of screening Lyme serology in the absence of a high risk of exposure is costly, and may lead to unnecessary treatment.
  - a) true
  - b) false

<p><b>AMA/CME TEST FORM</b> AJMC Test #039707</p> <p>Lyme Disease: Recognition, Management, and Prevention in the Primary Care Setting</p> <p><i>Application for 1 Credit Hour of AMA Category I</i></p> <p>(Test valid through July 15, 1998. No credit will be given after this date.)</p>	<p>Please circle your answers:</p> <p>1. a b</p> <p>2. a b</p> <p>3. a b</p> <p>4. a b</p> <p>5. a b</p> <p>6. a b</p> <p>7. a b</p> <p>8. a b</p> <p>9. a b</p> <p>10. a b</p>	<p>(PLEASE PRINT CLEARLY)</p> <p>Name _____</p> <p>Address _____</p> <p>City _____</p> <p>State/Zip _____</p> <p>Phone # _____</p> <p>Please enclose a check for \$10, payable to American Medical Publishing, and mail with this form to:</p> <p style="text-align: center;"><b>The AJMC CME Test</b> American Medical Publishing 1816 Englishtown Road, Suite 101 Old Bridge, NJ 08857</p>
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