REVIEW

Diagnosis and Treatment of Lyme Disease

ROBERT L. BRATTON, MD; JOHN W. WHITESIDE, MD; MICHAEL J. HOVAN, MD; RICHARD L. ENGLE, MD; AND FREDERICK D. EDWARDS, MD

Lyme disease is the most common tick-borne disease in the United States. This review details the risk factors, clinical presentation, treatment, and prophylaxis for the disease. Information was obtained from a search of the PubMed and MEDLINE databases (keyword: *Lyme disease*) for articles published from August 31, 1997, through September 1, 2007. Approximately 20,000 cases of Lyme disease are reported annually. Residents of the coastal Northeast, northwest California, and the Great Lakes region are at highest risk. Children and those spending extended time outdoors in wooded areas are also at increased risk. The disease is transmitted to humans through the bite of the *Ixodes* tick (*Ixodes scapularis* and *Ixodes pacificus*). Typically, the tick must feed for at least 36 hours for transmission of the causative bacterium, *Borrelia burgdorferi*, to occur. Each of the 3 stages of the disease is associated with specific clinical features: early localized infection, with erythema migrans, fever, malaise, fatigue, headache, myalgias, and arthralgias; early disseminated infection (occurring days to weeks later), with neurologic, musculoskeletal, or cardiovascular symptoms and multiple erythema migrans lesions; and late disseminated infection, with intermittent swelling and pain of 1 or more joints (especially knees). Neurologic manifestations (neuropathy or encephalopathy) may occur. Diagnosis is usually made clinically. Treatment is accomplished with doxycycline or amoxicillin; cefuroxime axetil or erythromycin can be used as an alternative. Late or severe disease requires intravenous ceftriaxone or penicillin G. Single-dose doxycycline (200 mg orally) can be used as prophylaxis in selected patients. Preventive measures should be emphasized to patients to help reduce risk.

***Mayo Clin Proc.* 2008;83(5):566-571**

CDC = Centers for Disease Control and Prevention; ELISA = enzyme-linked immunosorbent assay; IFA = indirect fluorescent antibody

In the early 1900s, physicians in Europe discovered a disease pattern characterized by an erythematous, migrating rash called *erythema migrans* that was associated with the bite of ticks. In the 1940s, the erythema migrans rash was found to be associated with a systemic illness. After this discovery, the isolation of spirochetelike bacteria (similar to those found in syphilis) from skin specimens of erythema migrans lesions led to the successful use of penicillin for treatment of this tick-borne illness.

In the mid-1970s, physicians in New England identified groups of children in an area around Lyme, CT, who had an unusual rash and associated arthritis. The clinical symptoms and demographic data, including geographic proximity, suggested that the children all had a similar illness, probably transmitted by a tick. The condition was given the name *Lyme disease* in 1977. In 1982, *Borrelia burgdorferi* spirochetes related to the illness were identified in the intestinal tract of the suspected vector, the adult deer tick *Ixodes dammini* (also known as the black-legged tick and currently referred to as *Ixodes scapularis*). The Centers for Disease Control and Prevention (CDC) began surveillance for Lyme disease in 1982, and in 1991 Lyme disease was classified as a nationally reportable disease.[1]

EPIDEMIOLOGY AND RISK FACTORS

Lyme disease is the most common tick-borne disease in the United States.[2-5] It has been reported in all 50 states[1] and is also found in Europe and Asia.[6] Lyme disease is most commonly reported in New England and the mid-Atlantic states, upper north-central regions, and several counties in northwestern California. Variation in zoonotic factors, including the presence of the white-footed mouse and white-tailed deer, which are important hosts in the life cycle of the *Ixodes* tick, account for endemic areas in these geographic locations. In 2005, more than 23,000 cases of Lyme disease were reported to the CDC, with most occurring in New England and the Great Lakes region (Figures 1 and 2).[1,7]

In the first 5 years after the condition was described and officially named (1982-1986), the number of reported cases increased 32-fold,[8] making Lyme disease a national health concern. Since the 1980s, the public increasingly has become aware of the harmful effects of untreated Lyme disease. Because the condition is commonly discussed on Internet sites and in the media, the concerns about its complications and prevalence have, in some cases, been regarded as out of proportion to the actual threat of disease. In 2001, Leonard H. Sigal, MD, was quoted by the *New York Times* as explaining that "Lyme disease, although a problem, is not nearly as big a problem as most people think. The bigger epidemic is Lyme anxiety."[9] Although Lyme disease may not be a problem in many parts of the United States, the disease is a considerable threat to residents of endemic areas. Even President George W. Bush recently received treatment for Lyme disease.

The age distribution of Lyme disease is bimodal, with the highest number of cases occurring in children aged 5 to

From the Department of Family Medicine, Mayo Clinic, Scottsdale, AZ.

Individual reprints of this article are not available. Address correspondence to Robert L. Bratton, MD, Department of Family Medicine, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ 85259.

14 years and adults aged 55 to 70 years.[1] Those who reside or are employed in areas where ticks are commonly found are at increased risk. Outdoor activities such as hiking, camping, hunting, fishing, and gardening place people at risk, as does working around heavy brush or wooded areas. However, most infections occur in residential areas during routine activities.

Lyme disease remains a major focus in public health. The Healthy People 2010 public health goals developed by the US Department of Health and Human Services aimed for a 44% decrease in the incidence of Lyme disease by 2010.[10] Currently, the CDC awards more than $3.5 million per year for new research on Lyme disease.[11] This review details the clinical presentation of the disease as well as risk factors, treatment, and prophylaxis. To obtain information, we used the keyword *Lyme disease* to search the PubMed and MEDLINE databases for articles published from August 31, 1997, through September 1, 2007.

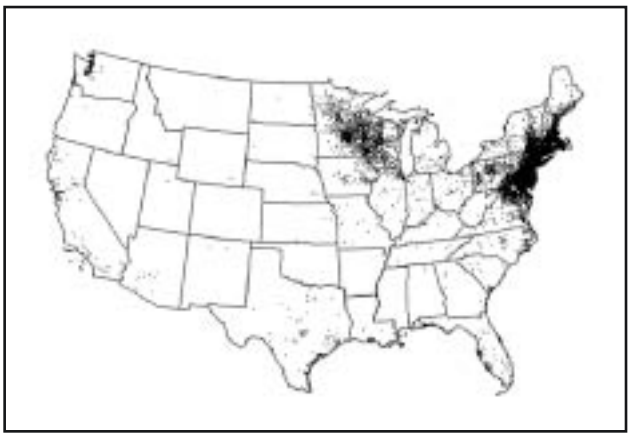

FIGURE 1. Reported cases of Lyme disease in the United States in 2005. Most cases were reported in New England (Connecticut, Rhode Island, New York, Pennsylvania, Delaware, New Jersey, Maryland, and Massachusetts) and in the Great Lakes region (Wisconsin and Minnesota). One dot is placed randomly within the county of residence for each reported case. From the Centers for Disease Control and Prevention.[1]

ETIOLOGY AND VECTOR LIFE CYCLE

The white-footed mouse is the primary animal reservoir for Lyme disease in the United States. Black-legged ticks (*I scapularis*, deer ticks) are responsible for transmitting Lyme disease bacteria (*B burgdorferi)* to humans in the New England and Great Lakes areas. In the West, *B burgdorferi* is transmitted to humans by the western black-legged tick (*Ixodes pacificus*), although the incidence of the bacteria in these ticks is much lower.

The nymphal and larval forms of the *Ixodes* tick feed primarily on the white-footed mouse, whereas the adult ticks are found on deer (Figure 3). *Ixodes* ticks are much smaller than common dog ticks, only a few millimeters in diameter in the larval and nymphal stages. The nymph form of the deer tick, often implicated in bites, is smaller than the adult form. *Ixodes* ticks are most likely to transmit infection after feeding for at least 36 to 48 hours; however, the minimum time may be as little as 24 hours. The infection is usually noted from April to November.[1] Other mammals, including dogs, can be hosts and can develop Lyme disease, but transmission from dogs to humans does not occur. Fleas, flies, and mosquitoes are not vectors for Lyme disease.

CLINICAL FEATURES

Early Localized Infection

Lyme disease presents in most cases with a characteristic lesion resembling a bull's-eye or target, known as erythema migrans. The rash appears as a homogeneous, erythematous, annular lesion that may exhibit partial central clearing late in the clinical course of the disease (Figure 4). In Europe, cases tend to have more prominent central clearing. According to CDC guidelines, the diameter of the lesion must be at least 5 cm (average size, 15 cm) to qualify as erythema migrans, but smaller lesions may be considered erythema migrans in the appropriate clinical situation. A slow progressive growth of lesions is the characteristic pattern.[12] The central zone may become ecchymotic, and necrosis of the area may eventually occur. Areas commonly affected include the thigh, groin, buttock, and axilla.

The characteristic rash is usually associated with virus-like symptoms, including fever, chills, myalgias, fatigue, headache, and malaise, which may precede onset of the rash by a few days. The incubation period from infection to onset of the erythema migrans rash is typically 7 to 14 days; however, it may occur within as few as 3 days or as long as 1 month after contact with the tick. Some people who are

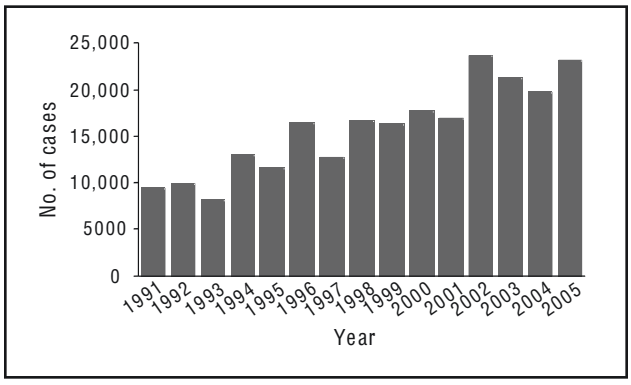

FIGURE 2. Reported cases of Lyme disease in the United States by year, 1991-2005. From the Centers for Disease Control and Prevention.[1]

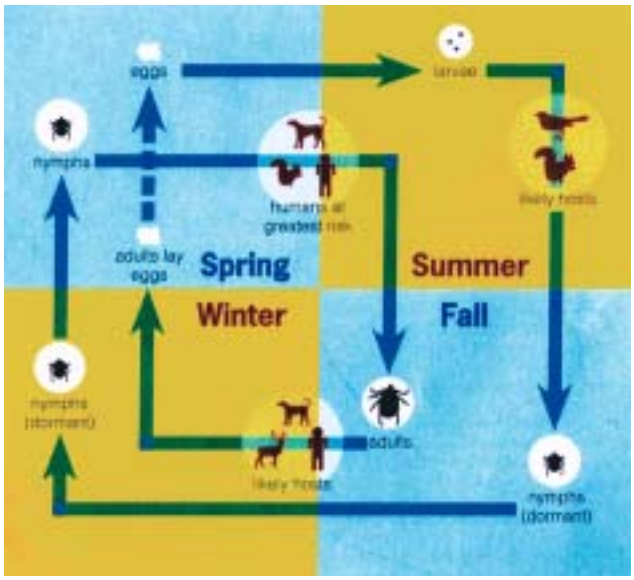

FIGURE 3. Two-year life cycle of the deer tick (*Ixodes scapularis*). Humans are at greatest risk of infection from bites of the nymphal forms of the *Ixodes* tick in the spring and summer. From *Backpacker,*[11] with permission.

infected have no symptoms, and up to 20% may not show the characteristic skin manifestions.[13,14] Many patients also have a low-grade fever and no (or mild) systemic symptoms at presentation. A high fever suggests a coinfection with babesiosis. Lyme disease spreads from the site of the tick bite by cutaneous, lymphatic, and blood-borne routes.

Early Disseminated Infection

Early disseminated infection typically occurs within a few days to weeks after contact with the infected tick. Signs include multiple (secondary) erythema migrans lesions. Additionally, musculoskeletal, neurologic, or cardiovascular symptoms can occur. Musculoskeletal symptoms (present in 60% of those infected) include migratory joint or muscle pain, with or without joint swelling. Neurologic manifestations (present in 15% of cases) may include meningitis, paralysis of the facial cranial nerve, and radicular neuropathies. Cardiovascular symptoms are less common (present in 8% of those infected) but may include temporary atrioventricular blocks of varying degree. Although temporary pacing may be necessary in more than 30% of patients with cardiac involvement, complete heart block rarely develops.[15] Untreated or inadequately treated Lyme disease may progress to late disseminated disease within weeks to months after initial infection.

Late Disseminated Infection

Late disseminated infection (present in 60% of untreated cases)[16] has many manifestations, including intermittent pain and swelling of 1 or more joints. The joints primarily affected are the knees and hips. Patients with the alloantigen *HLA-DR4* have a high risk of developing chronic arthritis, but those with *HLA-B27*, which is usually associated with spondyloarthropathies such as ankylosing spondylitis, do not.

Occasionally, neurologic manifestations develop, including chronic polyneuropathy or encephalopathy. The encephalopathy is usually associated with insomnia, malaise, impaired mentation, and, in some cases, changes in personality. If left untreated, Lyme disease may be responsible for substantial disability, but it is rarely fatal.

DIAGNOSIS

The diagnosis of Lyme disease is based on clinical features in a person who has traveled to or lives in an endemic area. In most cases, it is appropriate to treat patients who have early disease and a high pretest probability, on the basis of signs and symptoms, after a tick bite by the *Ixodes* species. As with other tick-borne diseases, only 50% to 70% of patients recall a tick bite,[16] often because the deer tick nymphs are small and go unnoticed.

Common laboratory tests usually are not revealing in the diagnosis of Lyme disease. The white blood cell count may be elevated or normal. Hemoglobin, hematocrit, creatinine, and urinalysis results are usually normal. If neurologic involvement is present, cerebrospinal fluid samples show moderate lymphocytic pleocytosis of roughly 100 cells/μL (to convert to $\times 10^9$/L, multiply by 0.001),[13]

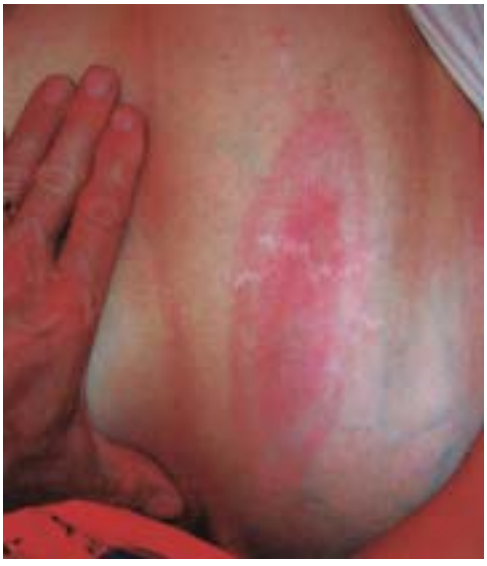

FIGURE 4. Characteristic bull's-eye or target shape of erythema migrans lesion in Lyme disease.

elevated protein concentrations, and normal to slightly low glucose concentrations. Neurologic manifestations usually include headache, seventh nerve palsy (possibly bilateral), neck pain and stiffness, forgetfulness, irritability, emotional lability, and sleep disturbances. Cerebrospinal fluid pleocytosis resolves promptly with appropriate antimicrobial therapy.

Serologic tests for Lyme disease support but are not always essential to the diagnosis. Furthermore, the tests are prone to false-negative and false-positive results and can be misleading, especially early in the course of the disease. When confirmation is necessary, the CDC recommends an enzyme-linked immunosorbent assay (ELISA), which is sensitive but not necessarily specific, followed by the more specific Western immunoblot test. Western blot tests should also be ordered if an indeterminate result is obtained by ELISA or indirect fluorescent antibody (IFA) testing.

The sensitivity of the numerous ELISA and IFA tests is affected by the timing of the test. Antibodies to *B burgdorferi* may not be present early in disease, potentially leading to a false-negative result. False positives can occur with mononucleosis, autoimmune states, and *Treponema pallidum* infection; therefore, serologic testing is not advised when the pretest probability of Lyme disease is low (<20%).[17,18] Likewise, testing is unnecessary when the pretest probability of Lyme disease exceeds 80%. In this setting, empiric treatment should be initiated. In large part, the ELISA and IFA techniques share the same limitations.

The Western blot technique provides serum IgM or IgG results. Its sensitivity, like that of ELISA and IFA, depends on the timing of the test, but it is more specific. When performed at least 4 weeks after exposure, Western blot will identify most patients with Lyme disease, with fewer false-positive results than ELISA returns. Because serologic testing is not 100% sensitive or specific, some people with Lyme disease will not have confirmatory laboratory results, especially patients in endemic areas who have characteristic physical findings at presentation.

After an infection, antibodies often persist for months or years. As a result, serologic tests do not accurately distinguish active from past infection. The overall false-positive rate of Lyme disease testing is approximately 5%.[19] Positive findings on ELISA or the IFA test followed by negative findings on Western blot usually suggest the absence of Lyme disease. This is especially true if the Western blot is performed more than 2 to 4 weeks after exposure. Positive serologic tests and a history of Lyme disease do not ensure protective immunity.

Recurrent Lyme disease has been observed in a few isolated cases. Further diagnostic options include skin biopsy of early erythema migrans lesions; *B burgdorferi* can be detected in 80% of cases. The culture should be taken from the perimeter of the lesion. This test is essentially 100% specific and can distinguish live from dead organisms. However, biopsies are not routinely used because of the need for both a special bacteriologic agar (modified Barbour-Stoenner-Kelly medium) and prolonged observation of cultures, both of which limit the commercial availability of culture testing.[18]

Polymerase chain reaction can detect DNA of *B burgdorferi* in many different types of samples, including those from skin, blood, cerebrospinal fluid, and synovial fluid. However, it is not commonly recommended for the routine diagnosis of Lyme disease.[1] The limited enthusiasm stems from the brief time that *B burgdorferi* circulates in the bloodstream and the possibility of positive test results if dead spirochetes are present.

Other rapid screening tests used in the diagnosis of Lyme disease require further research before their use is recommended. The Lyme Urine Antigen Test has not been approved by the US Food and Drug Administration and is not recommended by the CDC or the American Lyme Disease Foundation. Clinicians should be aware that 15% of patients may be coinfected with a second tick-borne pathogen, including those causing human granulocytic anaplasmosis (formerly known as human granulocytic ehrlichiosis) or babesiosis. Such coinfection can alter both the clinical presentation of Lyme disease and the response to treatment.[18]

TREATMENT

According to guidelines from the Infectious Diseases Society of America,[2] recommended antibiotic treatment for Lyme disease includes doxycycline for nonpregnant patients aged 9 years and older (100 mg orally, twice daily) or amoxicillin for patients younger than 9 years (50 mg/kg per day orally), which are generally effective in early disease. Second-choice treatment for adults is amoxicillin (500 mg orally, 3 times daily). Cefuroxime axetil (500 mg orally, twice daily; or 30 mg/kg per day divided, twice daily [maximum, 2 g/d]) or erythromycin (250 mg orally, 4 times daily; or 30-50 mg/kg per day divided, 3 or 4 times daily [maximum, 2 g/d]) can be used for those allergic to penicillin or unable to take tetracyclines. Oral treatment should be maintained for 14 to 21 days. Treatment for pregnant patients is identical to that for nonpregnant patients, except that tetracycline should be avoided.[2]

Treatment duration varies depending on the stage and severity of infection. Treatment of localized skin infections should continue for 14 days; treatment of early disseminated infection, for 21 days; treatment of acrodermatitis (which occurs predominantly in Europe), for 30 days; and treatment of Lyme disease–associated arthritis, for 30 to 60

days.[13] Late or severe disease, particularly with neurologic (neuroborreliosis) or cardiovascular manifestations, requires treatment with intravenous antibiotics (ceftriaxone [2 g/d], cefotaxime [2 g every 8 hours], or penicillin G [5 million U every 6 hours], each for at least 4 weeks).

For patients with interventricular delay, oral therapy can be started after the patient no longer has high-degree atrioventricular block and should be continued for at least 30 days. Late disease may be associated with treatment failures, and retreatment may be necessary.[20,21] In approximately 15% of patients, a Jarisch-Herxheimer–type reaction develops within 24 hours of the initiation of therapy.[13] This reaction manifests as a transient worsening of symptoms, including fever, sweating, rigors, headache, and general malaise. The reaction is usually less severe than that with other spirochete infections.

A recombinant vaccine, LYMErix (SmithKline Beecham Biologicals, Philadelphia, PA), directed toward a *B burgdorferi* surface protein (lipoprotein outer-surface protein A) was developed in 1998 and was recommended for selected people who were at increased risk of Lyme disease. In February 2002, the manufacturer announced that LYMErix would no longer be commercially available; low demand for the vaccine, as well as its limited efficacy, high price, and possible association with the development of autoimmune-induced arthritis or Lyme disease itself (although sufficient evidence to support such claims was lacking), were factors in this decision.[22] New vaccines are forthcoming.

ANTIBIOTIC PROPHYLAXIS

In many areas of the United States, tick bites are extremely common. *B burgdorferi* is endemic in New England, the mid-Atlantic states, Minnesota, and Wisconsin. In these areas, the risk of infection after a prolonged bite can be high (10%-25%).[23,24] Risk of infection is much lower in the southern and western United States. Furthermore, there is no risk of transmission of *B burgdorferi* from an unengorged tick because the spirochetes require up to 36 hours after a bite to migrate from the tick gut to the salivary glands.[25-27] Because of these factors, routine antibiotic prophylaxis is not recommended. However, if an engorged *Ixodes* tick has been removed from a patient in an endemic area (local rate of infection of ticks with *B burgdorferi* ≥20%), or if the tick has been attached for at least 36 hours, a single 200-mg oral dose of doxycycline can be administered within 72 hours after removal of the tick for prophylaxis against Lyme disease.[2,24] Prophylaxis is generally unnecessary after an *I pacificus* bite unless the local rate of infection with *B burgdorferi* is 20% or greater.[2]

No prophylactic treatments can be recommended for tick bites in children and pregnant women. Doxycycline is contraindicated in pregnant and nursing women and in children younger than 8 years. Amoxicillin has been shown to be effective against *B burgdorferi* in clinical trials of patients with Lyme disease[28,29]; however, no trials have shown that a single dose or shortened course of amoxicillin is effective as a prophylactic treatment. Therefore, a full 10- to 14-day treatment would be necessary but is not recommended for prophylaxis because of the high frequency of associated rash and other reactions. In most cases, those with confirmed bites who are unable to take doxycycline should be observed for the development of erythema migrans or other clinical manifestations of Lyme disease.

The recombinant outer-surface protein A Lyme disease vaccine does not convey long-lasting protection against infection. Furthermore, prior infection does not provide protection against subsequent infection. Therefore, recommendations for prophylactic antibiotics should be applied equally to patients regardless of immunization status or history of infection. Patients who have removed ticks (regardless of whether they have received prophylaxis) should be monitored for signs and symptoms of tick-borne disease for 30 days.[2]

LATE LYME DISEASE

Some manifestations of Lyme disease arise or persist even after a 2-week course of oral antibiotic therapy. For example, a few patients treated with oral agents have subsequently manifested neuroborreliosis, which may require intravenous therapy.[29] Furthermore, up to 10% of patients have persistent or recurrent joint swelling after treatment.[2] Although this swelling eventually resolves, it can last for several months after treatment. Patients whose joint swelling persists after a second 4-week course of antibiotics should undergo synovial biopsy.[29] A skin condition called *acrodermatitis chronica atrophicans*, characterized by reddish-violet skin lesions found predominantly on the arms and legs, may also present late and is treated with a second course of antibiotics. This condition does not occur in North America; the causative organism (*Borrelia afzelii*) is found only in Europe and Asia.

POST–LYME DISEASE SYNDROME

No accepted definition or diagnostic criteria exist for *post–Lyme disease syndrome*, also called *chronic Lyme disease* and *posttreatment chronic Lyme disease*. The term is applied to people with otherwise-unexplained subjective symptoms lasting more than 6 months after completion of antibiotic treatment. Symptoms include fatigue, myalgias, arthralgias (without arthritis), and mood and memory dis-

turbances (which can be shown through neuropsychological testing). Steere et al[30] suggest that these symptoms are the result of slowly resolving inflammation in treated patients. However, no study has shown consistently elevated levels of inflammatory markers in these patients. Further, continued infection with *B burgdorferi* has not been demonstrated in these patients, and patients with ongoing subjective symptoms do not consistently have positive serology against *B burgdorferi*.[30] Trials have shown that extending the initial course of antibiotics does not decrease the incidence of posttherapy subjective symptoms.[28] At least 2 prospective trials have shown that repeated, intensive antibiotic treatment does little to address the pain and altered cognition associated with this syndrome.[31]

PREVENTION

Avoidance of tick bites is the most obvious means to prevent *B burgdorferi* infection. If people must be outside in areas where *Ixodes* ticks are found, they are advised to wear protective clothing and tick repellent containing *N*,*N*-diethyl-*m*-toluamide (DEET). Frequent skin inspection and prompt removal of ticks should also decrease the risk of infection. However, data regarding the efficacy of these measures are limited. Other measures, including burning or removal of vegetation in tick-harboring areas, use of acaricides, and control of the deer population, result in up to a 94% decrease in the population of *I scapularis* ticks.

Studies show that, despite warnings, only 40% to 50% of adults take precautions against tick bites even when they are aware of Lyme disease.[10] Immediate removal of attached ticks can help prevent Lyme disease infection. Therefore, complete inspection of the skin and scalp, particularly for children, is recommended after spending time outside in endemic areas.

CONCLUSION

Lyme disease is not uncommon and may affect people who spend time outdoors, especially in areas where Lyme disease is endemic. Affected people typically present with nonspecific symptoms and the characteristic erythema migrans rash; unfortunately, only 50% to 70% of patients recall a tick bite and thereby alert the physician to the diagnosis. Physicians should have a high index of suspicion for Lyme disease in areas known to harbor the disease. Prompt treatment with antibiotic therapy helps decrease the frequency and severity of complications. Discussion of preventive measures and proper tick removal may be helpful for outdoor enthusiasts.

REFERENCES

1. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/ncidod/dvbid/lyme. Accessed June 25, 2007.

2. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006 Nov 1;43(9):1089-1134. Epub 2006 Oct 2.

3. Montiel NJ, Baumgarten JM, Sinha AA. Lyme disease, II: clinical features and treatment. *Cutis*. 2002;69(6):443-448.

4. Piacentino JD, Schwartz BS. Occupational risk of Lyme disease: an epidemiological review. *Occup Environ Med*. 2002;59(2):75-84.

5. Van Solingen RM, Evans J. Lyme disease. *Curr Opin Rheumatol*. 2001; 13(4):293-299.

6. Marques AR. Lyme disease: an update. *Curr Allergy Asthma Rep*. 2001; 1(6):541-549.

7. Huppertz HI. Lyme disease in children. *Curr Opin Rheumatol*. 2001; 13(5):434-440.

8. Centers for Disease Control and Prevention (CDC). Lyme disease: United States, 1996. *MMWR Morb Mortal Wkly Rep*. 1997;46(23):531-535.

9. Kolata G. Lyme disease is hard to catch and easy to halt, study finds. *The New York Times*. Wednesday, June 13, 2001:A1.

10. Poland GA. Prevention of Lyme disease: a review of the evidence. *Mayo Clin Proc*. 2001;76(7):713-724.

11. Aschwanden C. Bitten: what every hiker needs to know about Lyme disease. *Backpacker*. 2006;34:74-80.

12. Loockingbill DP, Marks JG Jr. *Principles of Dermatology*. 3rd ed. Philadelphia, PA: WB Saunders; 2000:270.

13. Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Janeson JL, eds. *Harrison's Principles of Internal Medicine*. 16th ed. New York, NY: McGraw-Hill Medical Publishing Division; 2005:996.

14. Smith RP. Current diagnosis and treatment of Lyme disease. *Compr Ther*. 2005;31(4):284-290.

15. Pinto DS. Cardiac manifestations of Lyme disease. *Med Clin North Am*. 2002;86(2):285-296.

16. Steere AC. Lyme disease. *N Engl J Med*. 1989;321(9):586-598.

17. Walker DH. Tick-transmitted infectious diseases in the United States. *Annu Rev Public Health*. 1998;19:237-269.

18. Bunikis J, Barbour AG. Laboratory testing for suspected Lyme disease. *Med Clin North Am*. 2002;86(2):311-340.

19. Magnarelli LA, Miller JN, Anderson JF, Riviere GR. Cross-reactivity of nonspecific treponemal antibody in serologic tests for Lyme disease. *J Clin Microbiol*. 1990;28(6):1276-1279.

20. Edlow JA. Erythema migrans. *Med Clin North Am*. 2002;86(2):239-260.

21. Treatment of Lyme disease. *Med Lett Drugs Ther*. 2000;42(1077):37-39.

22. Hanson MS, Edelman R. Progress and controversy surrounding vaccines against Lyme disease. *Expert Rev Vaccines*. 2003;2(5):683-703.

23. Elliott DJ, Eppes SC, Klein JD. Teratogen update: Lyme disease. *Teratology*. 2001;64(5):276-281.

24. Nadelman RB, Nowakowski J, Fish D, et al, Tick Bite Study Group. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite. *N Engl J Med*. 2001;345(2):79-84.

25. Sood SK, Salzman MB, Johnson BJ, et al. Duration of tick attachment as a predictor of the risk of Lyme disease in an area in which Lyme disease is endemic. *J Infect Dis*. 1997;175(4):996-999.

26. Piesman J, Mather TN, Sinsky RJ, Spielman A. Duration of tick attachment and *Borrelia burgdorferi* transmission. *J Clin Microbiol*. 1987;25(3):557-558.

27. Piesman J, Maupin GO, Campos EG, Happ CM. Duration of adult female *Ixodes dammini* attachment and transmission of *Borrelia burgdorferi*, with description of a needle aspiration isolation method. *J Infect Dis*. 1991; 163(4):895-897.

28. Steere AC, Levin RE, Molloy PJ, et al. Treatment of Lyme arthritis. *Arthritis Rheum*. 1994;37(6):878-888.

29. Wormser GP, Ramanathan R, Nowakowski J, et al. Duration of antibiotic therapy for early Lyme disease: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2003;138(9):697-704.

30. Steere AC, Coburn J, Glickstein L. The emergence of Lyme disease. *J Clin Invest*. 2004;113(8):1093-1101.

31. Klempner MS. Controlled trials of antibiotic treatment in patients with post-treatment chronic Lyme disease. *Vector Borne Zoonotic Dis*. 2002;2(4): 255-263.