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Lyme Disease

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ARTICLE

Lyme Disease

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IMPORTANT POINTS

1. **The clinical manifestations of Lyme disease have three stages: early localized disease (erythema migrans), early disseminated disease (multiple erythema migrans, seventh nerve palsy), and late disease (arthritis).**
2. **Nearly 90% of children who have Lyme disease develop the characteristic rash—erythema migrans.**
3. **Misdiagnosis is common, primarily because the specificity of serologic tests for Lyme disease is relatively poor and because tests frequently are performed on patients who have a low probability of the diagnosis (eg, those who have only nonspecific symptoms). As a result, false-positive test results for antibodies are extremely common.**
4. **Antimicrobial prophylaxis is not indicated routinely for persons bitten by a deer tick because the risk of Lyme disease from a recognized bite is low (1% to 2%), and if Lyme disease develops, it usually is treated easily.**
5. **The prognosis for children who are treated for Lyme disease (whatever the stage at the time of presentation) is excellent.**

Introduction

Lyme disease is the most common vector-borne disease in the United States. A cluster of children in Lyme, Connecticut, who had unexplained arthritis was reported by one of their parents in the mid-1970s. Investigation of this "epidemic" of arthritis led to the description of "Lyme" arthritis in 1976 and ultimately to the discovery of its bacterial etiology. Both the reported incidence of the disease and its geographic range have increased dramatically in recent years. Perhaps even more striking has been the increase in publicity about the illness in the consumer media, which has been accompanied at times by near-hysteria about both its risks and its complications. This publicity, combined with a very high frequency of misdiagnoses in people whose symptoms are due to other causes, has resulted in a degree of anxiety about Lyme disease (among both patients and physicians) out of proportion to the morbidity it causes.

Epidemiology and Ecology

Lyme disease is caused by the spirochete *Borrelia burgdorferi*, a fastidious, microaerophilic bacterium that replicates very slowly and requires special media to grow in the laboratory. *B burgdorferi* is transmitted by ticks of the *Ixodid* species—in the United States, primarily *Ixodes scapularis* (previously called *Ixodes dammini*), the deer tick. Lyme disease occurs most commonly in areas where deer ticks are abundant and where the prevalence of *B burgdorferi* in these ticks is high (20% to 50%)—southern New England, southeastern New York, New Jersey, eastern Pennsylvania, eastern Maryland, Delaware, and parts of Minnesota and Wisconsin. Lyme disease is rare in the Pacific states because although *Ixodes pacificus* (the Western black-legged tick) can transmit *B burgdorferi*, very few (<2%) of these ticks are infected with the organism. People who have increased occupational, recreational, or residential exposure to tick-infested woodlands and fields (the preferred habitat of ticks) in endemic areas are at increased risk of developing Lyme disease.

The life cycle of *Ixodid* ticks consists of three stages—larva, nymph, and adult—that occur during a 2-year period (Fig. 1). Each stage feeds only once. The adult female lays eggs in the spring, and the larvae emerge in the early summer. They overwinter and emerge the following spring as nymphs. In the fall, the nymphs molt and become adults. The adults spend the winter on an animal host, a favorite being the white-tailed deer (hence the name, the deer tick). In the spring, the females lay their eggs and die, completing the 2-year life cycle.

Most larvae (98%) are not infected with *B burgdorferi* because transovarial transmission rarely occurs. The larvae feed on a wide variety of small mammals (such as *Peromyscus leucopus*, the white-footed mouse) that are important natural reservoirs for *B burgdorferi* and thereby may become infected. A tick can acquire infection with *B burgdorferi* at each stage in its life cycle, so the proportion of adult ticks that is infected is higher than that of either nymphs or larvae. However, most cases of Lyme disease occur after the bites of nymphal-stage ticks because they are more abundant than adult ticks, they are more difficult to detect due to their small size, and humans frequently enter tick-infested habitats at times of the year when they are prevalent.

A number of factors are associated with the risk of transmission of *B burgdorferi* from ticks to humans. First, a tick has to be infected to transmit the organism. The proportion of infected ticks varies greatly both by geographic area and stage of tick in its life cycle. *I pacificus* often feeds on lizards, which are not a competent reservoir for *B burgdorferi*. Consequently, only 1% to 3% of these ticks, even in the nymphal and adult stages, are infected with *B burgdorferi*. By contrast, *I scapularis* feeds on small mammals that are competent reservoirs for *B burgdorferi*. As a result, in endemic areas, rates of infection of *I scapularis* are approximately 2% for larvae, 15% to 30% for nymphs, and 30% to 50% for adults. Infection rates as high as 60% to 90% have been reported in selected areas.

Lyme disease occurs throughout the world. In Europe, most cases are seen in the Scandinavian countries

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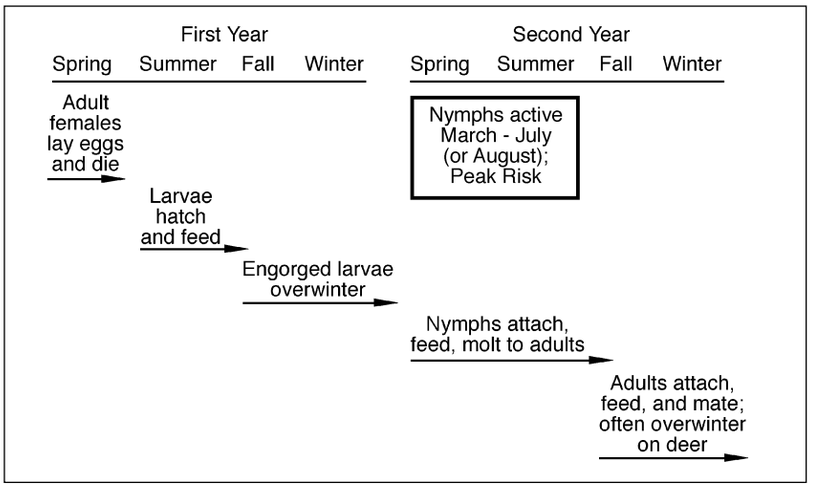

FIGURE 1. The life cycle of Ixodes scapularis *(the deer tick).*

and in central Europe (especially Germany, Austria, and Switzerland), although cases have been reported throughout the continent. The incidence of Lyme disease varies tremendously from region to region and even within local areas. Information about the true incidence of the disease is complicated by reliance, in most instances, on passive reporting of cases as well as by the high frequency of misdiagnosis. Further, studies have indicated that as many as 50% of patients who develop serologic evidence of recent infection with *B burgdorferi* may be asymptomatic.

In 1995, 11,603 cases of Lyme disease were reported to the United States Centers for Disease Control and Prevention (CDC) by 43 states and the District of Columbia, which was the second highest number reported since surveillance began in 1982 (although it was an 11% decrease from the 13,043 cases reported in 1994) (Fig. 2). More than 75% of the reported cases occurred in just 63 counties (Fig. 3). In Connecticut, which has the highest incidence of Lyme disease in the United States, the reported annual incidence of Lyme disease in 1995 was 47.1/100,000 persons and varied from 7.5/100,000 persons in Hartford County to 129.7/100,000 persons in Wyndham County. In certain towns in which the disease is hyperendemic (eg, Lyme), the annual incidence may be as high as 1,000/100,000 persons or more. The incidence of Lyme disease is highest among children. The reported incidence among children 5 to 10 years of age in Connecticut in 1995 was 79/100,000 per year. Because not all cases of Lyme disease are reported, these figures undoubtedly are underestimates.

Pathogenesis

B burgdorferi is transmitted when an infected tick inoculates the organism into the blood vessels of the skin of its host. The risk of transmission from infected deer ticks is related to the duration of feeding. It takes hours for the mouth parts of ticks to implant fully in the host and much longer (days) for the tick to become fully engorged. Experiments with animals have shown that nymphal-stage ticks must feed for 36 to 48 hours or longer and adult ticks must feed for 48 to 72 hours or longer before the risk of transmission of *B burgdorferi* from infected ticks becomes substantial. The duration of time that a tick has fed can be estimated from indices of engorgement derived from experiments with animals. Based on these indices, there is evidence that approximately 75% of persons who recognize that they have been bitten by a deer tick remove the tick fewer than 48 hours after it has begun to feed. Indeed, the majority of persons who develop Lyme disease do not recall a tick bite. Unrecognized tick bites probably are associated with greater risk because unrecognized ticks may feed longer. A history of a tick bite is an indication that the person is at risk and should not be assumed to be the only exposure.

Like other spirochetes, *B burgdorferi* is a cylindrically shaped organism, and its cell membrane is covered by flagella and a loosely associated outer membrane. The three major outer-surface proteins, OspA, OspB, and OspC (which are highly charged basic proteins of molecular weights of about 31, 34, and 23 kd, respectively), as well as the 41-kd flagellar protein, are important targets of the immune

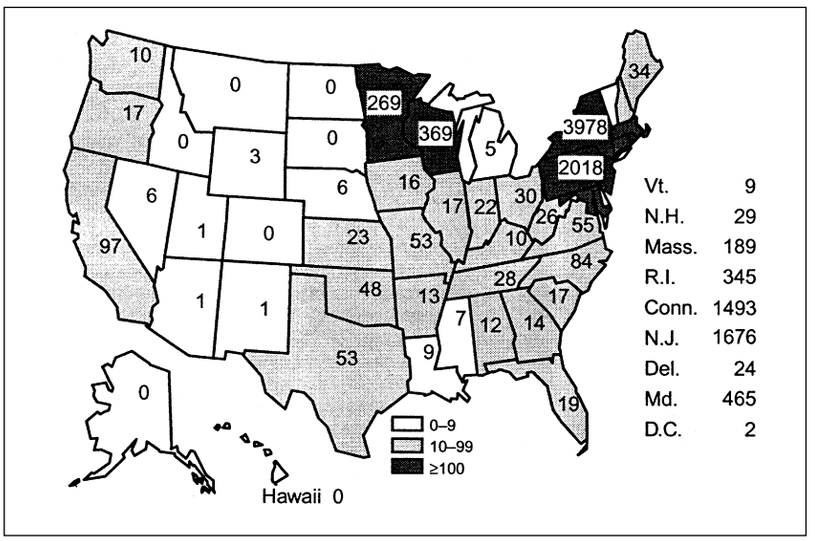

FIGURE 2. Number of reported Lyme disease cases, by state—United States, 1995. From MMWR. *1996;45:483.*

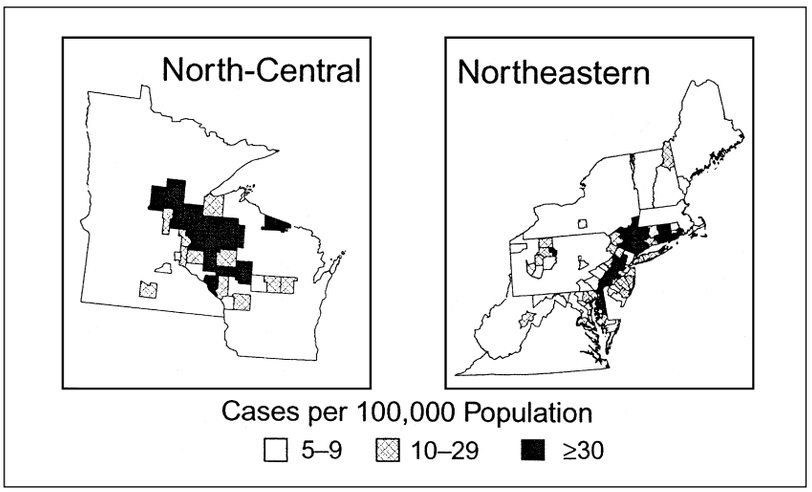

FIGURE 3. Reported rates of Lyme disease, by county—north-central and northeastern United States, 1995. Excludes counties that have fewer than five reported cases. From MMWR. *1996;45:483.*

response of humans. Differences in the frequency of certain clinical manifestations of Lyme disease in Europe and in the United States (eg, the greater frequency of neuritis in European patients) have been attributed to differences in the molecular structure of different strains of *B burgdorferi*.

After *B burgdorferi* is inoculated by the tick into the skin, it begins to spread locally. The inflammation results in a single erythema migrans rash in approximately two thirds of patients who become symptomatic. Days to weeks later, the spirochete may disseminate via either the bloodstream or the lymphatics to many other sites, including the skin (almost 25% of patients develop multiple erythema migrans), eye, muscle, bone, synovial tissue, central nervous system, and heart. Although it may be possible to isolate the organism from cultures of tissue, the small numbers that are present and the fastidious nature of its in vitro growth makes recovery of the spirochete difficult. Nevertheless, *B burgdorferi* has been isolated from the blood or from tissue at all stages of the illness.

The pathogenesis of the symptoms late in the course of Lyme disease appears to be related to long-term persistence of organisms in tissues. It is likely that relatively few organisms actually invade the host, but mediators of inflammation amplify the inflammatory response and lead to much of the tissue damage. The spirochete prefers cell surfaces, but it will adhere to a wide variety of cell types, which may explain why it can cause clinical manifestations in such a broad array of organ systems. Because the organism may persist in tissues for prolonged periods of time, symptoms may appear very late in the course of infection. The symptoms of Lyme disease are due to inflammation, mediated by interleukin-1 and other lymphokines, that is a direct result of the presence of the organism. However, in a small subset of patients who have refractory symptoms despite antimicrobial treatment (such as recurrent Lyme arthritis), the symptoms may have an immunogenetic basis. There is substantial evidence that patients who have a high prevalence of the HLA-DR2, DR3, and DR4 allotypes may be genetically predisposed to develop chronic recurrent Lyme arthritis long after the bacteria have been killed.

Clinical Aspects

The clinical manifestations of Lyme disease generally are divided into two stages: early and late. Early Lyme disease often is subdivided further into early localized and early disseminated disease. The usual clinical manifestations of the different stages of Lyme disease are shown in Table 1.

TABLE 1. Clinical Manifestations of Lyme Disease in Children

STAGE OF THE DISEASE	CLINICAL FINDINGS
Early localized disease*	Erythema migrans Myalgia Fatigue Headache Fever Lymphadenopathy Arthralgia
Early disseminated disease*	Erythema migrans (single or multiple) Lymphadenopathy (regional or generalized) Conjunctivitis Neck pain Cranial neuritis (especially facial palsy) Meningitis Carditis (usually manifests as heart block) Radiculoneuritis Fever Headache Arthralgia Myalgia Fatigue
Late disease	Arthritis

The nonspecific symptoms (eg, headache, myalgia, arthralgia, fatigue) virtually always accompany more specific manifestations of Lyme disease (eg, erythema migrans).

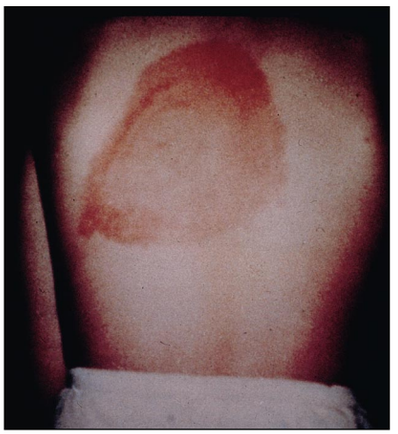

FIGURE 4. Uniform erythema migrans typical of Lyme disease.

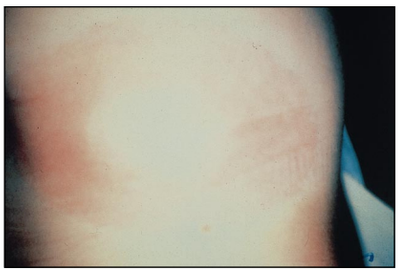

FIGURE 5. Target erythema migrans lesion with central clearing.

EARLY LOCALIZED DISEASE

The skin is the initial target organ for infection by *B burgdorferi*. The first clinical manifestation is the typical annular rash, erythema migrans. It usually occurs 7 to 14 days after the tick bite, although its onset has been reported as few as 3 days and as many as 4 weeks later. The rash may be uniformly erythematous (Fig. 4) or it may appear as a target lesion with variable degrees of central clearing (Fig. 5). Occasionally there may be vesicular or necrotic areas in the center of the rash. The rash may be itchy, painful, or asymptomatic and may be accompanied by systemic symptoms, such as fever, myalgia, headache, or malaise. If the patient is not treated, the rash gradually expands (hence, the name "migrans"), sometimes to more than 1 ft in diameter. It will persist for at least 1 to 2 weeks and usually for longer. Approximately two thirds of children who have Lyme disease will have single erythema migrans.

EARLY DISSEMINATED DISEASE

A substantial proportion of children (nearly 25%) in the United States who are acutely infected with *B burgdorferi* develop multiple erythema migrans lesions, a manifestation of early disseminated disease that occurs approximately 3 to 10 weeks after initial infection. The secondary skin lesions, which may develop several days or even weeks after the first lesion, are smaller than the primary lesion. Fever and myalgia usually accompany the rash. Patients also may complain of headache, neck pain, or malaise, and conjunctivitis and regional lymphadenopathy may develop. Occasionally, when the erythema migrans rash resolves, new evanescent lesions, which usually are small (1 to 3 cm) erythematous annular lesions, appear and disappear over several weeks. These lesions may appear at different sites but generally do not expand.

At this stage of the illness, aseptic meningitis may occur, although it is rare (about 1% of all patients). DNA of *B burgdorferi* has been found in the cerebrospinal fluid of patients at this stage of the illness. Focal neurologic manifestations, specifically cranioneuropathies, also may occur. Seventh-nerve palsy (facial palsy) is relatively common, affecting about 3% of children, and may be the presenting as well as the only manifestation of Lyme disease. The palsy usually lasts from 2 to 8 weeks before complete resolution (with or without treatment). Rarely, the palsy may resolve only partially or not at all. Bannworth syndrome (meningopolyneuritis) has been reported more commonly as a manifestation of Lyme disease in Europe. Encephalitis, with or without focal neurologic signs, occasionally occurs.

LATE DISEASE

Arthritis is the classic manifestation of late Lyme disease, occurring in about 7% of affected children. Patients who have arthralgia, a common, nonspecific symptom that frequently is present among patients who have early Lyme disease as well as those who do not have Lyme disease, should be differentiated from those who have objective evidence of synovitis (eg, an effusion), which is the hallmark of late Lyme disease. The arthritis occurs weeks to months after the initial infection. Primarily the large joints, especially the knee (which is affected in more than 90% of the cases), are involved. Although the affected joint is swollen and tender, the patient usually does not experience the exquisite pain that is typical of acute bacterial arthritis. Joint swelling generally resolves within 1 to 2 weeks (although it may last for several weeks) before recurring, often in other joints. Although the large joints are involved most commonly, any joint, including small ones, may be affected. If untreated, the episodes of arthritis often increase in duration, sometimes lasting for months. However, the disease usually resolves eventually, even in patients who are untreated and who have had many recurrences of arthritis. Most patients will not have a history of erythema migrans because those who have the rash usually are treated with antimicrobials and do not develop late manifestations of disease.

Late central nervous system manifestations of Lyme disease (sometimes termed tertiary neuroborreliosis) rarely have been reported in children. In adults, chronic demyelinating encephalitis, polyneuritis, and impairment of memory have been attributed to Lyme disease, although there is controversy about the frequency with which such late manifestations occur, especially among patients who have been treated. Other very rare manifestations of late Lyme disease include acrodermatitis chronica atrophicans (a chronic, atrophic sclerotic lesion of the skin) and borrelia lymphocytoma, a localized, subcutaneous nodular lesion that usually occurs in either the earlobe or the breast.

In the largest prospective study of children who had Lyme disease (a community-based study of 201 children in Connecticut), the initial manifestations of disease were: single erythema migrans (66%), multiple erythema migrans (23%), arthritis (7%), facial palsy (3%), aseptic meningitis (1%), and carditis (0.5%). Erythema migrans was more likely to occur on either the head or neck in younger children and on the extremities in older children, a finding similar to that recently

reported from Europe. Only about one third of the children who had a single erythema migrans rash had positive serology for *B burgdorferi* at the time of presentation compared with almost 90% of the children who had multiple erythema migrans. More than 25% of the children had early disseminated Lyme disease at the time that they presented to a physician, and 89% had either single or multiple erythema migrans.

CONGENITAL LYME DISEASE

Because clinical syndromes caused by congenital infection have been recognized with other spirochetal infections such as syphilis, the possible transmission of *B burgdorferi* from an infected pregnant woman to her unborn fetus has been of concern. Although case reports have been published in which *B burgdorferi* has been identified from several abortuses and from a few live-born children who had congenital anomalies, the placentas, abortuses, and tissues from affected children did not show histologic evidence of inflammation. In addition, no consistent pattern of congenital malformations (as would be expected in a "syndrome" due to congenital infection) has been identified. In two small longitudinal studies conducted by the CDC of pregnant women who developed Lyme disease, the adverse outcomes could not be attributed to infection with *B burgdorferi*. Furthermore, serosurveys conducted in endemic areas found no difference in the prevalence of congenital malformations among the offspring of women who had serum antibodies against *B burgdorferi* and those who had no such antibodies.

To assess the prevalence of clinically significant neurologic disorders attributable to congenital infection with *B burgdorferi*, two investigators conducted a survey of all pediatric neurologists in areas of the United States in which Lyme disease is endemic (Connecticut, Rhode Island, Massachusetts, New York, New Jersey, Wisconsin, and Minnesota). Of the 162 respondents to the survey (92%), none had seen a child who had a clinically significant neurologic disorder attributable to congenital Lyme disease or whose mother had Lyme disease during her pregnancy.

There is no definitive evidence that *B burgdorferi* causes congenital disease, although the existence of such a syndrome also has not been excluded. If it does exist, congenital Lyme disease must be extremely rare. Finally, it should be noted that transmission of Lyme disease through breastfeeding never has been documented.

Diagnosis

The diagnosis of Lyme disease, especially in the absence of the characteristic rash, may be difficult because the other clinical manifestations of disease are not specific. Seventh-nerve palsy due to Lyme disease is indistinguishable from idiopathic Bell palsy, and Lyme arthritis may mimic either septic arthritis or pauciarticular juvenile rheumatoid arthritis. The clinical manifestations of Lyme meningitis may be difficult to distinguish from those of viral meningitis. Even the diagnosis of erythema migrans can be difficult because the rash initially may be confused with nummular eczema, granuloma annulare, an insect bite, ringworm, or cellulitis. However, the relatively rapid expansion of erythema migrans helps to distinguish it from these other conditions.

Routine laboratory tests rarely are helpful in diagnosing Lyme disease because the associated abnormalities are nonspecific. The peripheral white blood cell count may be either normal or elevated. The erythrocyte sedimentation rate usually is elevated. The white blood cell concentration in joint fluid in patients who have Lyme arthritis may range from 25,000 to 125,000/mL, often with a preponderance of polymorphonuclear cells. When the central nervous system is involved, there usually is a mild pleocytosis with a predominance of lymphocytes.

Because the sensitivity of culture for *B burgdorferi* is poor and patients must undergo an invasive procedure such as a biopsy or a lumbar puncture to obtain appropriate tissue or fluid for culture, such tests are indicated only in rare circumstances. Likewise, diagnostic tests, including the polymerase chain reaction (PCR), that are based on identification of antigens of *B burgdorferi* have not been shown to be sufficiently accurate to be clinically useful under nonexperimental conditions. (However, preliminary studies in research laboratories suggest that PCR is very promising.) Consequently, laboratory confirmation of Lyme disease usually rests on the demonstration of antibodies to *B burgdorferi* in the patient's serum.

It is well documented that the sensitivity and specificity of antibody tests for Lyme disease vary substantially. The accuracy of prepackaged commercial kits is much poorer than that of tests performed by reference laboratories that maintain tight quality control and regularly prepare the materials used in the test. A national study of the prepackaged commercial kits was conducted by the Association of State and Territorial Public Health Laboratory Directors in conjunction with the CDC. In this study, different state laboratories and the CDC used the seven "best" commercial kits (as established by preliminary testing) to determine concentrations of antibodies against *B burgdorferi* in samples of reference sera (with known positives and negatives to which the testers were blinded). The concordance of the results produced in the same laboratory with different test kits as well as the concordance of the results from different laboratories using the same test kit were poor. The estimates of the mean sensitivities of the kits ranged from 26% to 57% and mean specificities ranged from 12% to 60%. The investigators concluded that with

Routine laboratory tests rarely are helpful in diagnosing Lyme disease. Specific immunologic tests should include a two-step procedure: first, an ELISA or IFA and if positive, a Western blot to confirm the diagnosis.

these commercial diagnostic test kits, "serologic testing for Lyme disease will result in a high rate of misdiagnosis." This conclusion is consistent with numerous other reports of the poor reproducibility of most commercially available antibody tests for Lyme disease.

The use of Western immunoblots improves the specificity of serologic testing for Lyme disease. Official recommendations from the Second National Conference on Serologic Diagnosis of Lyme Disease (published in 1995) suggest that clinicians use a two-step procedure when ordering antibody tests for Lyme disease: first, a sensitive screening test, either an enzyme-linked immunosorbent assay (ELISA) or an immunofluorescent assay (IFA), and if that result is positive or equivocal, a Western immunoblot to confirm the result. If the ELISA or the IFA is negative, an immunoblot is not necessary. The ELISA provides a quantitative estimate of the concentration of antibodies against *B burgdorferi*. The immunoblot provides information about the specificity of the antibodies; positive "bands" mean that antibodies against specific protein antigens of the spirochete are present. Most authorities require the presence of antibodies against at least either three (for immunoglobulin M [IgM]) or five (for IgG) specific proteins of *B burgdorferi* (at least one of which is a more specific, low molecular weight outer surface protein) for the immunoblot to be considered positive. Antibody tests are not useful for the diagnosis of early localized Lyme disease because only a minority of patients who have single erythema migrans will have a positive test.

The predictive value of antibody tests (even very accurate tests) depends on the prevalence of the infection among patients who are tested. Unfortunately, because many people, including some physicians, have the erroneous impression that nonspecific symptoms alone (eg, headache, fatigue, or arthralgia) may be manifestations of Lyme disease, parents of children who have only nonspecific symptoms frequently demand testing for Lyme disease (and some physicians routinely order tests for Lyme disease on such patients). Lyme disease will be the cause of the nonspecific symptoms in very few, if any, of these children. However, because the specificity of even excellent antibody tests for Lyme disease rarely exceeds 90% to 95%, some of the tests in children who have no specific signs or symptoms of Lyme disease will be positive; the vast majority of these (>95%) will be false-positive results. Nevertheless, Lyme disease frequently is diagnosed erroneously, based on these results, and such children often are treated unnecessarily with antimicrobials.

Even though a symptomatic patient has a positive serologic test for antibodies to *B burgdorferi*, it is possible that Lyme disease may not be the cause of that patient's symptoms. In addition to the possibility that the test result is falsely positive (a common occurrence), the patient may have been infected with *B burgdorferi* previously, and the current symptoms may be unrelated to the previous infection. Once serum antibodies to *B burgdorferi* develop, they may persist for many years despite adequate treatment and clinical cure. In addition, because a substantial proportion of people who become infected with *B burgdorferi* never develop symptoms, there will be a background rate in endemic areas of seropositivity. When patients who previously had Lyme disease (whether asymptomatic and untreated or clinically apparent and adequately treated) develop any type of symptoms and are tested for antibodies against *B burgdorferi*, their symptoms may be attributed erroneously to active Lyme disease because of the positive serology. Physicians should not order antibody tests for Lyme disease routinely either for patients who have not been in endemic areas or for those who exhibit only nonspecific symptoms. In the future, highly pure, cloned portions of certain proteins of *B burgdorferi* will become available for use in diagnostic tests, which hopefully, will be more accurate than currently available tests.

Treatment of early Lyme disease in children younger than 9 years of age should include either amoxicillin or erythromycin.

Treatment

Recommendations for the treatment of children who have Lyme disease (Table 2) have been extrapolated from studies of adults; no clinical trials of treatment have been conducted among children. Children younger than 9 years of age should not be treated with doxycycline because it may cause permanent discoloration of teeth. Cefuroxime also is effective. Preliminary results with azithromycin have been disappointing. There is little need for new agents because the results of treatment with standard therapy (amoxicillin or doxycycline) have been so good.

Symptoms such as fatigue, arthralgia, and myalgia may persist after a course of treatment for Lyme disease has been completed. These nonspecific symptoms, which may accompany or follow more specific symptoms and signs of Lyme disease but almost never are the sole presenting manifestations, usually resolve over several weeks. There is little evidence that such symptoms are related to persistence of *B burgdorferi*, and there is no evidence that repeated courses of antimicrobials speed their resolution. Because antibodies against *B burgdorferi* persist even after successful treatment of symptoms, there is no reason to obtain routine follow-up tests of antibody concentrations against *B burgdorferi*.

Prognosis

There is a widespread misconception that Lyme disease is difficult to treat successfully and that chronic recurrences are common. In fact, the prognosis for treated children is excellent. The most common reason for treatment failure is misdiagnosis (ie, the patient actually does not have Lyme disease). In a review of

TABLE 2. Antimicrobial Treatment of Lyme Disease

Early Disease
Erythema migrans and disseminated early disease without focal findings
Doxycycline 100 mg bid for 21 days (do not use in children <9 y) or amoxicillin 50 mg/kg per day divided tid (maximum, 500 mg/dose) for 21 days.
For those who cannot take either amoxicillin or doxycycline, erythromycin 30 to 50 mg/kg per day divided qid (maximum, 250 mg/dose) for 21 days.
Facial nerve palsy of other cranial nerves
Treat as for erythema migrans for 21 to 30 days. Do not use corticosteroids.
Carditis
Treat as for late neurologic disease.
Meningitis
Treat as for late neurologic disease.
Late Disease
Neurologic disease*
Ceftriaxone 50 to 80 mg/kg per day in a single dose (maximum, 2 g) for 14 to 21 days administered IV or IM or penicillin G 200,000 to 400,000 U/kg per day (maximum, 20 million U/day) divided q 4 h administered IV for 14 to 21 days
Arthritis
Initial treatment is the same as for erythema migrans, except treat for 30 days. If symptoms fail to resolve after 2 months or there is a recurrence, treat as for late neurologic disease.
For isolated palsy of the facial nerve or of other cranial nerves, see treatment regimen for facial nerve palsy.

65 children who were treated for erythema migrans, all were well and none had developed symptoms of late disease at follow-up a mean of more than 3 years later. In a larger, prospective study of 201 children who had newly diagnosed Lyme disease (most had either early localized or early disseminated disease), all were clinically cured at follow-up a mean of 2.5 years later. The long-term prognosis for patients who are treated for late Lyme disease also is excellent. Although arthritis does recur rarely, especially among patients who have the DR-2, DR-3, or DR-4 HLA-type, most children who are treated for Lyme arthritis are permanently cured. Indeed, long-term follow-up of children diagnosed with Lyme disease before its cause was recognized (most of whom either were not treated with antimicrobials or were treated years after the onset of symptoms) indicated that the arthritis eventually resolved (after multiple recurrences), even in children who never were treated. One group of investigators performed neuropsychologic tests on children up to 4 years after they were treated and found no evidence of any long-term sequelae of the infection. Other investigators who are conducting a community-based study of the long-term outcomes of persons who have Lyme disease have found no evidence of impairment of normal functioning in children 4 to 10 years after diagnosis.

Prevention

In endemic areas it is very common for children to be bitten by deer ticks. Such bites often engender tremendous anxiety. However, the overall risk of acquiring Lyme disease is low (approximately 1% to 2%), even in areas in which Lyme disease is endemic. Furthermore, treatment of the infection, if it develops, is highly effective. Consequently, the routine administration of antimicrobial prophylaxis (the efficacy of which is unproved) for persons who have been bitten by a deer tick is not recommended.

Determining whether a tick is infected, using tests such as the PCR, is not useful clinically, although it may provide important epidemiologic information. The predictive value for infection of humans of either a positive or a negative PCR result is unknown. The test may be positive even if only very few organisms are present. Furthermore, the test provides no information about either the size of the inoculum or the duration of feeding, both of which may be key determinants of the risk of transmission. In addition, false-positive and false-negative test results are quite common.

A more reasonable approach to preventing Lyme disease is to wear appropriate protective clothing (such as lightweight long pants) when entering tick-infested areas and to check for and remove ticks after spending time in such areas. Insect repellents may provide temporary protection, but they may be absorbed from the skin, and if used frequently or in large doses, may produce significant toxicity, especially in children.

Investigators have attempted to develop an effective vaccine against Lyme disease. Antibodies against outer surface protein A (OspA) protect against Lyme disease in animal models. Vaccines employing recombinant OspA proteins have been developed and are being tested in phase III trials in humans. Because the spirochete expresses OspA in ticks and in later stages of human illness but not at the time of initial infection in human skin, it is hypothesized that the vaccine works by the tick ingesting human blood during feeding before it inoculates the spirochete into humans. Presumably antibody-dependent killing of *B burgdorferi* occurs in the tick. Even if the vaccine is found to be efficacious, it likely will be used selectively because the risk of disease is low in most populations and poor outcomes among persons who contract the disease are rare. Vaccines that use other antigens are being developed.

SUGGESTED READING

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PIR QUIZ

1. Which one of the following statements about risk factors for acquiring Lyme disease is *true*?
   A. The bite of an infected tick usually transmits infection.
   B. The incidence of disease is higher in adults than in children.
   C. Lyme disease is transmitted most often by larval-stage ticks.
   D. The risk of infection is appreciable 4 to 6 hours after ticks attach.
   E. Ticks that transmit Lyme disease are found most frequently in fields or lawns near wooded areas.

2. Erythema migrans is a specific sign of Lyme disease. Which one of the following statements about this skin rash is *true*?
   A. Children who have multiple erythema migrans are more likely to be seropositive for *B burgdorferi*.
   B. Most children who have a rash will have a positive serology
   C. Most children will not have a rash with Lyme disease.
   D. Most infants will have the rash on the arms and legs.
   E. The rash rarely persists longer than 48 hours.

3. A 6-year-old child living in a high-prevalence area has a history of tick exposure, multiple erythema migrans lesions, fever, and a positive Western immunoblot for antibodies to *B burgdorferi*. Which one of the following therapies is *most* appropriate?
   A. If the child cannot take amoxicillin, treat with ceftriaxone in a single dose.
   B. In the presence of arthritis, treat with amoxicillin for 14 days.
   C. In the presence of concomitant facial nerve palsy, treat with steroids and amoxicillin for 21 days.
   D. Treat the child with amoxicillin for 21 days.
   E. Treat the child with doxycycline for 21 days.

Lyme Disease

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