Borrelia burgdorferi (Lyme Disease)

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Educational Gaps

1. Although Lyme disease, caused by *Borrelia burgdorferi*, is the most common vector-borne disease in the United States, there is considerable misunderstanding about the clinical manifestations and consequences of this infection. (1)(2)
2. When to perform diagnostic tests and how to interpret the results for antibodies against *B burgdorferi* are common sources of confusion for physicians and patients. (3)(4)(5)
3. Misinformation about chronic Lyme disease on the Internet and in popular media has led to publicity and anxiety about Lyme disease that is out of proportion to the actual morbidity that it causes. (6)(7)(8)

Objectives After completing this article, readers should be able to:

1. Understand the ecology and the epidemiology of Lyme disease.
2. Know when to order and how to interpret serologic tests for the diagnosis of Lyme disease.
3. Understand the clinical manifestations of Lyme disease and appropriate treatment

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ABBREVIATIONS

DEET	N,N-diethyl-meta-toluamide
ELISA	enzyme-linked immunosorbent assay
EM	erythema migrans
STARI	southern tick–associated rash illness

EPIDEMIOLOGY AND ECOLOGY

Lyme disease is the most common vector-borne disease in the United States. In the United States, the spirochete *Borrelia burgdorferi* sensu stricto (hereafter termed *B burgdorferi*) is the only pathogen that causes Lyme disease. However, in Europe and Asia, *Borrelia afzelii*, *Borrelia garinii,* and other related species, in addition to *B burgdorferi*, cause Lyme disease. In the United States, these bacteria are transmitted by hard-bodied ticks, including *Ixodes scapularis* (the black-legged tick, commonly called a deer tick) in the East and Midwest and *Ixodes pacificus* (the western black-legged tick) on the Pacific Coast. *Ixodes ricinus* (the sheep tick) and *Ixodes persulcatus* (the taiga tick) are the vectors in Europe and Asia, respectively.

Lyme disease occurs only in certain geographic areas in which the ecologic conditions are right to support this zoonotic illness. In Europe, most cases occur in the Scandinavian countries and Central Europe, although cases have been

reported throughout Europe. Most cases of Lyme disease in the United States occur in New England, the Mid-Atlantic states, Wisconsin, and Minnesota (Figure 1). It also occurs, although much less frequently, on the Pacific Coast, primarily in Northern California and Oregon. Although the geographic distribution is expanding, more than three-quarters of cases still occur in fewer than 70 counties, an indication of the geographic limitation of the disease. In recent years, the number of reported cases has increased to 25,000 to 30,000 per year. Although the annual number of cases of Lyme disease have been reported to be as high as 300,000, information about the true incidence of the disease is complicated by reliance on passive reporting of cases and the high frequency of misdiagnosis and false-positive serologic test results. In highly endemic areas of the United States, such as Connecticut and Southern New York, the annual incidence is approximately 0.5 cases per 1,000 persons but can be substantially higher in local areas. The reported incidence is highest in children age 5 to 10 years, nearly twice as high as the incidence among adults. Persons with occupational, recreational, or residential exposure to tick-infested fields, yards, or woodlands in endemic areas are at increased risk of developing Lyme disease.

Ixodid ticks have a 2-year, 3-stage life cycle (Figures 2 and 3). The larvae hatch in the early summer and are not infected with *B burgdorferi*. The tick may become infected at any stage of its life cycle by feeding on a host that is a natural reservoir for *B burgdorferi*, such as chipmunks or white-footed mice. The larvae overwinter on the ground and emerge the following spring as nymphs. Nymphal ticks are most likely to transmit the infection because they are small and difficult to see and abundant at times when humans frequent tick-infested areas. Nymphs molt to become adults in the fall. Adult females, which often attach to large animals, such as deer, in the winter (hence the common name deer tick), lay their eggs the following spring before they die, and the 2-year life cycle begins again.

Of course, a tick must be infected to transmit *B burgdorferi*. The proportion of infected ticks varies greatly by geographic area and stage of the tick in its life cycle. Lyme disease is uncommon in the Pacific states because few *I pacificus* ticks are infected with *B burgdorferi*. By contrast, in highly endemic areas of Southern New England, approximate rates of infection of *I scapularis* are 20% to 30% for nymphs and 30% to 50% for adult ticks. On the basis of experimental studies with animals, to transmit *B burgdorferi* an infected nymphal tick generally must feed for at least 36 to 48 hours and an infected adult tick must feed for at least 72 hours before the risk of transmission becomes substantial. These experimental findings were confirmed in a study in humans in which the risk of transmission from ticks (for which the duration of feeding could be assessed) to humans was 25% for nymphal ticks that had fed for at least 72 hours and 0% for nymphal ticks that had fed for less than 72 hours, as well as for all adult and all larval ticks. The bacteria live in the midgut of the tick, which needs to become engorged with blood before the bacteria migrate to the salivary glands and the saliva, through which the organism is injected into the host. Studies indicate that in most instances in which a tick bite is recognized, the tick has fed for less than 48 hours, which in part explains the low risk of Lyme disease (1%–3%) after a recognized

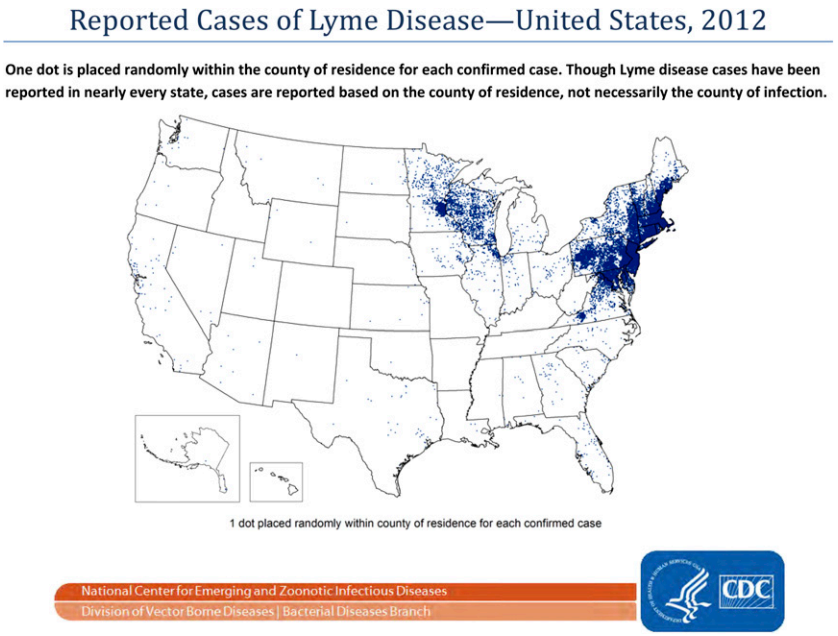

Figure 1. Reported cases of Lyme disease in the United States, 2012

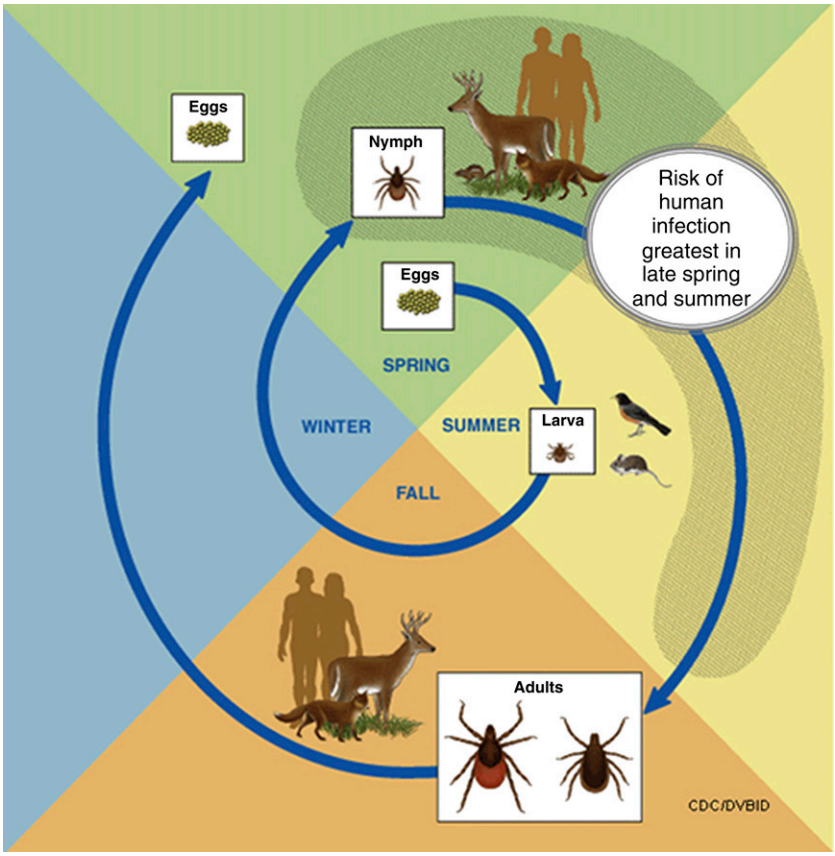

Figure 2. Life cycle of *Ixodes scapularis*.

tick bite in endemic areas. Risk of Lyme disease may be higher from bites that are unrecognized because the tick may feed to repletion and would be more likely to transmit the infection.

CLINICAL ASPECTS

The clinical manifestations of Lyme disease can be classified into stages: early localized disease, early disseminated disease, and late disease. Erythema migrans (EM), the manifestation of early localized disease, appears at the site of the tick bite 3 to 30 days (typically 7 to 14 days) later. The skin lesion begins as a red macule or papule and expands for days to weeks to form an erythematous lesion that can grow to a foot or more in diameter. Most often (two-thirds of the time in the United States), the rash is uniformly erythematous or has enhanced central erythema (Figure 4). Less commonly it may appear as a bull's-eye lesion (Figure 5). Occasionally, EM may have vesicular or necrotic areas in the center. It is often asymptomatic but may be pruritic or painful, and it may be accompanied by systemic symptoms, such as fever, malaise, headache, stiff neck, myalgia, or arthralgia.

Figure 3. *Ixodes scapularis*. From left to right: adult female, adult male, nymph, and larva. The scale is in centimeters.

The most common manifestation of early disseminated Lyme disease in the United States is multiple EM, which is due to spirochetemic dissemination of the organism that may be related to strain-specific characteristics of the bacteria. Multiple EM usually appears 1 to 4 weeks after infection and consists of multiple annular erythematous lesions similar to, but usually smaller than, the primary lesion, which may not be apparent (Figure 6). In the United States, EM (single or multiple) occurs in approximately 90% of patients with Lyme disease. Other common manifestations of early disseminated Lyme disease are cranial nerve palsies, especially facial nerve

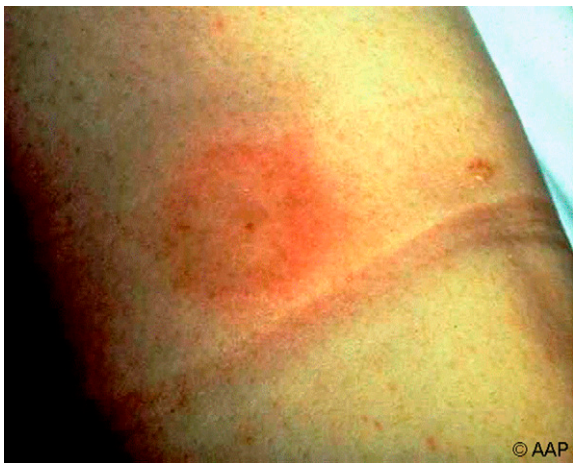

Figure 4. Erythema migrans.

palsy, and meningitis (sometimes accompanied by papilledema and increased intracranial pressure). Systemic symptoms, such as fever, myalgia, arthralgia, headache, or fatigue, are common in this stage of Lyme disease. Carditis, which usually presents with a prolonged PR interval on electrocardiography or, rarely, complete heart block (which may cause syncope), is another manifestation of early, disseminated disease.

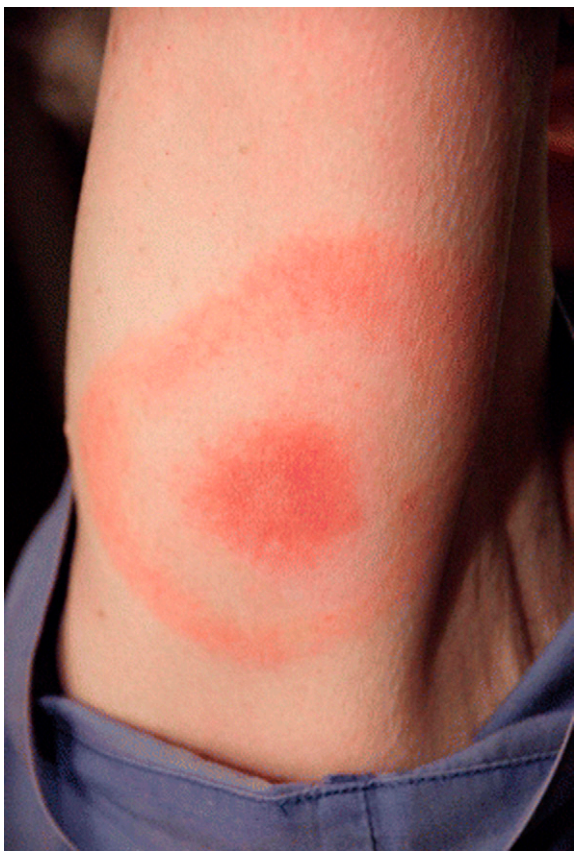

Figure 5. Erythema migrans (bull's-eye appearance).

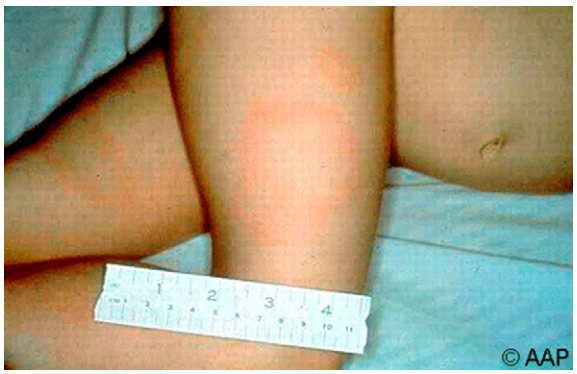

Figure 6. Multiple erythema migrans.

The most common manifestation of late Lyme disease, which occurs weeks to months after the initial infection, is arthritis. The arthritis is usually monoarticular but may be oligoarticular. It primarily affects the large joints, particularly the knee. There is a wide spectrum of acuity that ranges from subacute (there may be weeks or even months of swelling before the patient presents for care) to acute (mimicking acute bacterial arthritis). Although the affected joint is typically swollen and somewhat tender, the exquisite tenderness associated with acute septic arthritis usually is not present. Likewise, the number of leukocytes in joint fluid can range from 15,000 to 100,000 or more. Encephalitis and polyneuropathy are also manifestations of late Lyme disease, but they are extremely rare, especially in children. Table 1 gives the relative frequencies of clinical manifestations of Lyme disease in children from one prospective study.

Several studies designed to assess the potential link between Lyme disease during pregnancy and congenital infection with *B burgdorferi* found no documented *B burgdorferi* infections of the fetus or infant. Additional studies found no difference in birth outcomes between seropositive and seronegative pregnant women. Likewise, a survey of pediatric

TABLE 1. **Frequency of Initial Clinical Manifestations of Lyme Disease (9)**

MANIFESTATION	PATIENTS, *n* (%) (N=201)
Single erythema migrans	132 (66)
Multiple erythema migrans	45 (22)
Arthritis	13 (6)
Facial nerve palsy	6 (3)
Meningitis	4 (2)
Carditis	1 (0.5)

neurologists in endemic areas found no evidence of any credible cases of congenital Lyme disease. Transmission of Lyme disease via breastfeeding has also not been documented.

DIAGNOSIS

The diagnosis of early Lyme disease depends on the presence of EM, the characteristic skin lesion. The rash initially may be confused with nummular eczema, granuloma annulare, an insect bite, ringworm, or cellulitis. The relatively rapid and prolonged (untreated, it lasts for weeks) expansion of EM helps to distinguish it from these other conditions. In addition, EM may be a manifestation of southern tick–associated rash illness (STARI), the cause of which is unknown, so there is no diagnostic test for STARI. Although STARI is associated with the bite of the lone star tick, it may not be due to an infectious agent. Symptoms similar to those that may be associated with early Lyme disease (fatigue, myalgia, and fever) may accompany the EM associated with STARI, but there is no evidence that STARI is associated with any neurologic, cardiac, or joint involvement as there is in disseminated Lyme disease.

The sensitivity of culture for *B burgdorferi* is only fair, and special media are required; moreover, it usually is necessary for patients to undergo an invasive procedure to obtain appropriate tissue or fluid for culture, and it takes weeks before a result is available. Consequently, culture usually is not available and is indicated only in rare circumstances. Concentrations of bacteria in blood and cerebrospinal fluid are low, so sensitivity of polymerase chain reaction assays of these samples also is poor. Sensitivity for samples from joint fluid is much better. Nevertheless, contamination is a potential problem for polymerase chain reaction assays performed in commercial laboratories, and an invasive procedure is still necessary to obtain appropriate material to test. Consequently, the confirmation of Lyme disease by the laboratory usually rests on the demonstration of antibodies to *B burgdorferi* in the patient's serum.

Official recommendations from the Second National Conference on Serologic Diagnosis of Lyme Disease and from the Centers for Disease Control and Prevention are that clinicians should use a 2-tier procedure when ordering antibody tests for Lyme disease. A sensitive screening test, usually an enzyme-linked immunosorbent assay (ELISA), should be performed, and if that result is positive or equivocal, a Western immunoblot is performed to confirm the specificity of the result. The ELISA provides a quantitative estimate of the concentration of antibodies against *B burgdorferi*. The immunoblot provides qualitative information about the specificity of the antibodies; positive bands on the immunoblot mean that antibodies against specific protein antigens of *B burgdorferi* are present. The presence of antibodies against at least either 2 (for IgM) or 5 (for IgG) proteins of *B burgdorferi* are required for the immunoblot result to be considered positive. If the ELISA result is negative, even if the immunoblot result is positive, the test result for Lyme disease should be interpreted as negative. Immunoblots should not be performed without a simultaneous quantitative test, such as an ELISA, for concentrations of antibodies against *B burgdorferi*. Results are uninterpretable when the immunoblot test result is positive without a simultaneous ELISA result.

Newer tests, such as ELISA for antibodies against C6VlsE as a single test for Lyme disease at any stage, has sensitivity and specificity comparable to or better than conventional ELISA. However, its specificity is inferior to that of the 2-tier test. Antibody test results generally are not useful for the diagnosis of early Lyme disease because only a few patients with single EM will have a positive result because the rash usually develops before antibodies are detectable. The antibody test result is often negative in the acute phase even in those with multiple EM. Even in the convalescent phase after antimicrobial treatment, antibody test results are negative in approximately half of those with single EM and a quarter of those with multiple EM. Consequently, follow-up tests for antibody generally are not indicated. Early treatment may prevent the development of antibodies because antimicrobials kill the bacteria, thereby eliminating the antigenic stimulus to produce antibody. The sensitivity of 2-tier testing is far better in patients with early disseminated neurologic or cardiac disease (80%–100%) or in those with late disease (nearly 100% with arthritis). Because of a particularly high rate of false-positive results and the fact that in untreated patients IgG antibodies usually develop within 4 weeks, a diagnosis of Lyme disease should not be based on a positive IgM result alone in patients who have had symptoms for 4 weeks or longer.

MISDIAGNOSIS

It is critically important to understand that the predictive value of antibody test results, even of very accurate tests, is highly dependent on the pretest probability of the infection in the patient who is tested (Table 2). Pretest probability is the probability that the symptoms are due to the disease based on the clinical and epidemiologic history, the physical examination, and any other relevant information available before the test result is known. Antibody tests for Lyme disease should *not* be used as screening tests. Unfortunately, because many laypersons (as well as physicians) have the

erroneous belief that chronic, nonspecific symptoms alone (eg, fatigue or arthralgia) may be manifestations of Lyme disease, patients with only nonspecific symptoms are frequently tested for Lyme disease. Lyme disease will be the cause of the nonspecific symptoms in few such patients, if any. However, because the specificity of even the best antibody tests for Lyme disease is nowhere near 100%, many of the test results in patients without specific signs of Lyme disease will be falsely positive (Table 2). Nevertheless, an erroneous diagnosis of Lyme disease frequently is made, and such patients often are treated with antimicrobials unnecessarily.

Even though a symptomatic patient has a positive serologic test result 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 it is a false-positive result, the patient may have been infected with *B burgdorferi* previously, and the patient's current symptoms may be unrelated to that previous infection. Once serum antibodies to *B burgdorferi* develop, IgG antibodies, IgM antibodies, or both may persist for many years despite adequate treatment and clinical cure of the illness. Performing additional serologic tests after therapy is not indicated. Physicians should not routinely order antibody tests for Lyme disease for patients who have not been in endemic areas or for patients with only nonspecific symptoms.

Ixodes ticks may transmit other pathogens in addition to *B burgdorferi*, including *Babesia microti*, *Anaplasma phagocytophilum*, *Borrelia miyamotoi*, and deer tick virus (a variant of Powassan virus). These agents may be transmitted separately from or simultaneously with *B burgdorferi*. Patients should be evaluated for these organisms if they have findings suggestive of these diseases, such as prolonged fever, neutropenia, thrombocytopenia, severe illness, or failure to respond as expected to standard antimicrobial treatment.

TREATMENT

Guidelines for antimicrobial therapy for different manifestations of Lyme disease have been published by the Infectious Disease Society of America and the Committee on Infectious Diseases of the American Academy of Pediatrics and are given in Tables 3 and 4. Additional treatment with nonsteroidal anti-inflammatory drugs may also provide symptomatic benefit to the patient.

Intravenous therapy with ceftriaxone is often used for Lyme meningitis. Data indicate that doxycycline administered

TABLE 2. **Predictive Value of Serologic Tests**[a]

TEST RESULT	DISEASE PRESENT	DISEASE ABSENT	TOTAL
Patients with 1% pretest probability of disease			
Positive	95	990	1,085
Negative	5	8,910	8,915
Total	100	9,900	10,000
Predictive value	8.8[b]	99.9[c]	
Patients with 10% pretest probability of disease			
Positive	950	900	1,850
Negative	50	8,100	8,150
Total	1,000	9,000	10,000
Predictive value	51.4[b]	99.4[c]	
Patients with 50% pretest probability of disease			
Positive	4,750	500	5,250
Negative	250	4,500	4,750
Total	5,000	5,000	10,000
Predictive value	90.5[b]	94.7[c]	

[a] *Results are for the theoretical population of 10,000 persons and are given as numbers, except for predictive values, which are percentages. In each case, the test is 95% sensitive and 90% specific.*
[b] *Predictive value of a positive test result.*
[c] *Predictive value of a negative test result.*

TABLE 3. **Recommended Routes and Durations of Treatment for Lyme Disease**

CLINICAL MANIFESTATIONS BY DISEASE STAGE	TREATMENT	DURATION, d
Early localized disease		
Erythema migrans	Oral	14–21[a]
Early disseminated disease		
Multiple erythema migrans	Oral	14–21
Isolated cranial nerve palsy	Oral	14–21
Meningitis	Intravenous[b]	10–21
Carditis		
Ambulatory	Oral	14–21
Hospitalized	Intravenous followed by oral[c]	14–21
Late disease		
Arthritis	Oral	28
Recurrent or persistent arthritis after oral therapy	Oral or intravenous	28 14–28
Encephalitis	Intravenous	14–28

[a]*Doxycycline may be administered for 10 days in uncomplicated cases.*
[b]*Doxycycline may be substituted after symptoms have resolved.*
[c]*At the time of discharge, the patient may receive oral medication to complete therapy.*

orally is as effective as ceftriaxone for Lyme meningitis in adults in Europe, although it is not yet recommended as first-line therapy in the United States.

Few clinical trials of treatment for Lyme disease have been conducted in children. Most recommendations for the treatment of children are extrapolated from studies of adults. Doxycycline is preferred when possible because of its excellent penetration into the central nervous system, but it is not recommended for children younger than 8 years because it may cause permanent discoloration of their teeth (although there is scant evidence that a single dose or even a short course of treatment would have that effect). Patients who are treated with doxycycline should be told of the risk of developing dermatitis in sun-exposed areas. Cefuroxime is also effective for the treatment of Lyme disease and is an alternative for persons who cannot take doxycycline and who are allergic to penicillin. Azithromycin is less effective than other oral agents and should only be used when there is a clear contraindication to the preferred antimicrobials. There is little need to use other antimicrobial agents because the results of treatment with amoxicillin or doxycycline have been excellent and strains resistant to recommended antimicrobials have not been reported.

Some patients may develop a Jarisch-Herxheimer reaction within 24 hours after treatment is initiated. The manifestations of this reaction are increased temperature, sweats, and myalgia. These symptoms resolve spontaneously within 1 to 2 days, although administration of nonsteroidal anti-inflammatory drugs may alleviate symptoms. Antimicrobial treatment should not be discontinued.

PREVENTION OF LYME DISEASE

Reducing the risk of tick bites is one obvious strategy to prevent Lyme disease. In endemic areas, clearing brush and trees, removing leaf litter and woodpiles, and keeping grass mowed may reduce exposure to ticks. Application of pesticides to residential properties is effective in suppressing populations of ticks but may be harmful to other wildlife and people.

Tick and insect repellents that contain N,N-diethyl-meta-toluamide (DEET) applied to the skin provide additional protection but require frequent reapplication. Serious neurologic complications in children from frequent or excessive application of DEET-containing repellents have been reported, but they are rare and the risk is low when these products are used according to instructions on the labels. Use of products with concentrations of DEET greater than 30% is not necessary and increases the risk of adverse effects. DEET should be applied sparingly only to exposed skin but not to the face, hands, or skin that is irritated or abraded. After one returns indoors, skin that

TABLE 4. **Recommended Drugs and Doses for Treatment of Lyme Disease**

TREATMENT	ADULT DOSE	PEDIATRIC DOSE
Oral therapy		
Doxycycline (Patients ≥8yrs)	100 mg 2 times per day	4 mg/kg/day Divided 2 times per day (up to 100mg/dose)
Amoxicillin	500 mg 3 times per day	50mg/kg/day Divided 3 times per day (up to 500mg/dose)
Cefuroxime axetil	500 mg 2 times per day	30 mg/kg/day Divided 2 times per day (up to 500mg/dose)
Intravenous therapy		
Ceftriaxone	2g 1 time per day	50-75 mg/kg/day (up to 2g/dose) 1 time per day
Cefotaxime	2g Every 8 hours	150-200 mg/kg/day (up to 2g/dose) Every 8 hours

was treated should be washed with soap and water. Permethrin (a synthetic pyrethroid) is available in a spray for application to clothing only and is particularly effective because it kills ticks on contact.

Because most persons (approximately 75%) who recognize that they were bitten by a tick remove the tick within 48 hours, the risk of Lyme disease from recognized deer tick bites is low (approximately 1%–3% in areas with a high incidence of Lyme disease). Indeed, the risk of Lyme disease likely is higher for unrecognized bites (because such ticks will feed for a longer time). Persons should be taught to inspect themselves and their children's bodies and clothing daily after possible exposure to ticks. An attached tick should be grasped with fine-tipped tweezers as close to the skin as possible and removed by gently pulling the tick straight out. If some of the mouth parts remain embedded in the skin, they should be left alone because they usually are extruded eventually; additional attempts to remove them often result in unnecessary damage to tissue and may increase the risk of local bacterial infection. Analysis of ticks to determine whether they are infected is not indicated because it is unclear how these test results correlate with the probability of human disease. No vaccine for Lyme disease is currently available.

A study of antimicrobial prophylaxis for tick bites among adults found that a single 200-mg dose of doxycycline was 87% effective in preventing Lyme disease, although the 95% confidence interval around this estimate of efficacy was wide (the lower bound was 25% or less, depending on the method used). (10) In that study, the only persons who developed Lyme disease had been bitten by nymphal ticks that were at least partially engorged (10% among recipients of placebo) compared with 0% for bites by all larval and all adult deer ticks. Unfortunately, the expertise to identify the species, stage, and degree of engorgement of a tick, and thereby to assess the degree of risk, is rarely available to persons who are bitten. Routine use of antimicrobial agents to prevent Lyme disease in persons who are bitten by a deer tick, even in highly endemic areas, is not generally recommended because the overall risk of Lyme disease is low (1%–3%), and if Lyme disease develops, treatment is effective. (11-12)

PROGNOSIS AND CHRONIC LYME DISEASE

The long-term prognosis for individuals who are treated appropriately with antimicrobials for Lyme disease, regardless of the stage of the illness, is excellent. The most common reason for a lack of response to appropriate antimicrobial therapy is misdiagnosis (ie, the patient actually does not have Lyme disease). Nonspecific symptoms, such as fatigue, arthralgia, or myalgia, may persist for several weeks even in patients with early Lyme disease who are treated successfully. Their presence should not be regarded as an indication for additional treatment with antimicrobials. These nonspecific symptoms will usually resolve without additional antimicrobial therapy.

There is substantial evidence that there is no such entity as chronic Lyme disease. Indeed, there is not even a case definition for chronic Lyme disease. There are many websites that contain misinformation about Lyme disease that only enhance the already inflated and inaccurate fears about the consequences of Lyme disease of many parents and patients. Many patients labeled as having chronic Lyme disease actually have medically unexplained symptoms. Such patients are best treated symptomatically rather than with prolonged courses of antimicrobial therapy, which have been associated with serious adverse effects and little or no benefit. It is important to acknowledge that the patient has symptoms even if they are not due to Lyme disease. Forming a therapeutic alliance with the patient and instituting a program of exercise and other strategies designed to help the patient cope with the symptoms often is the most productive approach.

Summary

- On the basis of strong evidence from research, approximately 90% of children with Lyme disease have erythema migrans, which often does not have central clearing; most are either uniformly erythematous or have enhanced central erythema.
- On the basis of strong evidence from research, antibody testing of patients with erythema migrans is not indicated routinely because of poor sensitivity in early Lyme disease. By contrast, sensitivity is excellent in patients with infection for 4 weeks or longer.
- On the basis of strong research evidence, treatment of Lyme disease at any stage with antibiotics is safe and highly efficacious.
- On the basis of strong evidence from research, a single 200-mg dose of doxycycline reduces the risk of Lyme disease in persons bitten by *Ixodes scapularis* but is not indicated routinely (because risk of transmission from a tick bite is low).
- There is no evidence that chronic Lyme disease exists. On the basis of strong evidence from research, patients treated for Lyme disease who have persistent, nonspecific symptoms (eg, arthralgia and fatigue) do not have persistent infection; the risks of prolonged treatment with antimicrobials far outweigh benefits, if any.

NOTE: The content of this article is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

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Parent Resources from the AAP at Healthy Children.org

- English: http://www.healthychildren.org/English/health-issues/conditions/from-insects-animals/Pages/Lyme-Disease.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/from-insects-animals/paginas/lyme-disease.aspx

PIR Quiz

1. Which of the following is the most common manifestation of early disseminated Lyme disease in the United States?
    A. Arthritis.
    B. Carditis.
    C. Encephalitis.
    D. Facial nerve palsy.
    E. Multiple erythema migrans.
2. A 15-year-old boy presents to the hospital in mid-August with mild photophobia, headache, a low-grade fever, and malaise for 5 days. He had been visiting relatives on Cape Cod, Massachusetts, earlier in the summer. You are concerned that he may have Lyme disease. Which of the following tests will BEST make the confirmatory diagnosis of Lyme disease?
    A. Antibody testing for *Borrelia burgdorferi* from serum.
    B. Culture of cerebrospinal fluid for *B burgdorferi.*
    C. Culture of serum for *B burgdorferi.*
    D. Polymerase chain reaction of cerebrospinal fluid.
    E. Western immunoblot testing.
3. A mother brings her 6-year-old child to your office because of a new rash. The rash is round with slight central clearing. It is not pruritic or painful. The child has a low-grade temperature of 100.2°F (37.9°C) and some body aches but otherwise has no symptoms. The family lives in coastal Connecticut, and the mother remembers removing a tick in the same area of the rash 2 weeks ago. What is the next BEST step in management for this patient?
    A. Observation only.
    B. Perform polymerase chain reaction testing on blood.
    C. Perform 2-tiered testing for Lyme disease, such as an enzyme-linked immunosorbent assay (ELISA) followed by a Western immunoblot.
    D. Prescribe amoxicillin, 50 mg/kg/d divided 3 times daily for 14 days.
    E. Prescribe doxycycline, 4 mg/kg/d divided twice daily for 14 days.
4. The father of a 5-year-old boy calls your office because he has just pulled off a tick from his son's neck. It is unclear how long the tick was attached, but the father believes the tick to be mildly engorged. What is your next BEST step in management?
    A. Administer a single 200-mg dose of doxycycline orally.
    B. Administer amoxicillin, 50 mg/kg/d divided into 3 doses for 14 days.
    C. Perform an ELISA test for Lyme disease.
    D. Reassure the father that the overall risk of Lyme disease is low.
    E. Wait 2 weeks and then perform 2-tiered testing for Lyme disease.
5. A teenage girl goes to her physician because of malaise, diffuse body pain, and fatigue for 2 months. A complete blood cell count is within normal limits. The physician performed 2-tiered testing for Lyme disease. The ELISA test result was positive, and the Western immunoblot revealed positive IgG and negative IgM test results. She was prescribed doxycycline, 100 mg twice daily. She returns to the physician after 2 weeks because she has had no improvement in her symptoms. What is the next BEST step in management of this patient?
    A. Change the antimicrobial from doxycycline to amoxicillin, 500 mg 3 times daily.
    B. Continue to administer the doxycycline but add nonsteroidal anti-inflammatory agents to her medication regimen.
    C. Discontinue use of the doxycycline and prescribe a regimen of physical therapy and pain control options for the patient.
    D. Perform testing for *Babesia microti.*
    E. Retest the patient with ELISA and Western immunoblot for Lyme disease.

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