CHAPTER 24

Lyme Disease

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In 1977, Steere and co-workers reported on an epidemic of arthritis in the region of Old Lyme, Connecticut. This breakthrough work catalyzed a flurry of studies that soon described *Ixodes* ticks as the vector, identified the spirochete *Borrelia burgdorferi* as the causative infectious pathogen, and characterized the broad clinical manifestations of Lyme disease. Interestingly, several authors had previously described patients in Europe with clinical manifestations similar to patients with Lyme disease, and subsequently European cases were also shown to be caused by infection with *Borrelia* species. Currently, Lyme disease is appreciated as an important vector-borne disease that occurs worldwide and is the most common tick-borne infection in both North America and Europe.

CAUSATIVE ORGANISM

B.burgdorferi is a 0.2 × 25 μm unicellular spirochete bacteria. In different regions of the world, distinct *B. burgdorferi* species exist, based on specific antigenic differences: (1) *B. burgdorferi* sensu stricto, (2) *B. garinii*, (3) *B. afzelii*, and (4) *B. japonica*. In the United States, all isolates to date have been *B. burgdorferi* sensu stricto. In Europe, however, most isolates have been either *B. garinii* or *B. afzelii*. The distinct antigenic strains may explain some of the differences observed in the predominant clinical manifestations in persons infected with *B. burgdorferi* in the United States versus those infected in Europe. In 2016, a new species provisionaly called *B. mayonii* was described in the blood of six patients from the Midwestern US who presented with atypical and severe Lyme Disease; whether this species will emerge as an important pathogen, and whether it should be diagnosed or treated differently from *B. burgdorferi* infection, remains to be seen.

All strains of *B. burgdorferi* have a central protoplasmic cylinder surrounded by an outer envelope that contains important surface proteins. In 1995, Schwan and colleagues reported that *B. burgdorferi* present in unfed ticks is predominantly covered by outer surface protein (Osp)A, but after the tick feeds for several days on a mammal, OspC replaces OspA. The change from spirochete OspA to OspC coating results from increased expression of the OspC gene in response to the increase in tick temperature that takes place during feeding. This change in surface proteins evidently serves as a prerequisite for the spirochete to migrate from the tick's midgut to the tick's salivary gland. Available data suggest that infection of humans involves *B. burgdorferi* coated with OspC, not OspA. More recent work has described two other heat-sensitive *B. burgdorferi* outer surface proteins, known as decorin-binding proteins A and B (DbpA and DbpB); these are lipoproteins that may act as spirochetal adhesins. Mice immunized with DbpA antigen develop antibodies that block *B. burgdorferi* dissemination from the site of cutaneous inoculation, and antiserum from persistently infected mice had cidal activity against both cultured and plasma-derived *B. burgdorferi*. These findings suggest DbpA antibodies may contribute to control of acute and persistent infection.

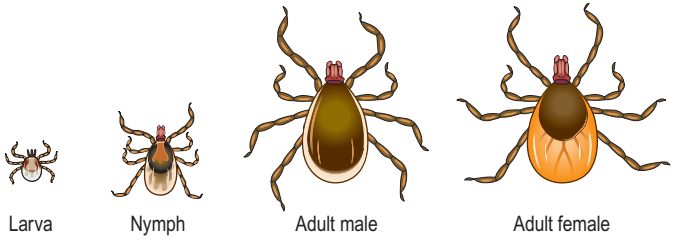

Fig. 24.1 Non-engorged *Ixodes* ticks at different life cycle phases. (To reproduce with permission from University of Rhode Island; TickEncounter Resource Center)

TRANSMISSION

In the United States, *B. burgdorferi* can be potentially transmitted to humans via one of two types of *Ixodes* ticks: *Ixodes scapularis* (formerly known as *Ixodes dammini* and commonly referred to as the deer tick) and *Ixodes pacificus* (commonly referred to as the Western black-legged tick) (**Fig. 24.1**). In the United States, *I. scapularis* ticks are most concentrated in the Northeastern, mid-Atlantic and north-central states, and *I. pacificus* is clustered in West Coast states. In Europe, *Ixodes ricinus* serves as the primary vector, whereas in Asia *Ixodes persulcatus* is the major vector. In the Northeastern and upper north Midwestern United States, the white-footed mouse, *Peromyscus leucopus*, serves as the most common reservoir for *B. burgdorferi*. The white-tailed deer also play a major role, because the adult *I. scapularis* ticks prefer to mate on these animals. In most of the Western United States, the dusky-footed wood rat is the major reservoir for *B. burgdorferi*, but two species of *Ixodes* ticks, *Ixodes neotomae* and *I. pacificus*, are involved in the life cycle of *B. burgdorferi*. In this so-called California bi-cycle, the *I. neotomae* ticks play the role of infecting the wood rat with *B. burgdorferi*, whereas the *I. pacificus* ticks play the role of transmitting *B. burgdorferi* to humans after acquiring *B. burgdorferi* from the wood rat reservoir.

In contrast to many other infections discussed in this book, Lyme disease is *not* typically acquired in the tropics, due to the life cycle of the vector.

The life cycle of these *Ixodes* ticks includes three stages, typically lasting 2 years and requiring a blood meal at each stage in order to mature to the next stage. The cycle begins in the spring when the adult female tick releases her eggs and they hatch as six-legged larvae. During the summer, the larvae take a blood meal, followed by a dormant phase in the fall. In the spring, the ticks molt and enter the second phase of their life cycle as eight-legged nymphal ticks. In the late spring or summer, the nymphal ticks take a blood meal and subsequently molt as eight-legged adults in the fall. The adults then mate and the male dies; the female, however, takes one more blood meal before she lays her eggs and dies. Although ticks at any of these three stages are competent vectors for *B. burgdorferi* transmission to humans, most cases of Lyme disease result from the bite of the 2-3 mm nymphal tick. In the United States, *Ixodes* ticks also serve as the vector for the infectious pathogens that cause babesiosis (*Babesia microti*) and human granulocytic anaplasmosis (*Anaplasma phagocytophilum*), formerly referred to as ehrlichiosis. Thus, a bite from an *I. scapularis* tick may lead to an infection with any one of these agents as a single infection or possibly as a co-infection.

Bites from *Ixodes* ticks are generally painless, and <50% of patients with Lyme disease recall a tick bite. Animal laboratory studies show efficient transmission of *B. burgdorferi* by *I. scapularis* requires a minimum of 36-48 hours of tick attachment, but human cases have apparently occurred after shorter periods of tick attachment. Nevertheless, it does appear that, in general, transmission to humans probably requires at least 8 hours of attachment. The requirement for prolonged attachment correlates with the change in *B. burgdorferi* OspA (non-infectious state) to OspC (infectious state).

EPIDEMIOLOGY

In 1982, following the realization that Lyme disease had emerged as a major vector-borne disease in the United States, the Centers for Disease Control and Prevention (CDC) initiated surveillance for Lyme disease. In 1991 Lyme disease became a reportable disease, with a case defined for surveillance purposes as: (1) physician-diagnosed erythema migrans rash of at least 5 cm or (2) at least one objective late manifestation (i.e., musculoskeletal, cardiovascular, or neurologic) with laboratory evidence of infection with *B. burgdorferi* in a person with possible exposure to infected ticks.

In 2013, CDC reported a total of 27, 203 confirmed cases, yielding a national incidence of 8.6 confirmed cases per 100,000 population. An additional 9,104 probable cases that year would result in a higher case incidence, if included in the calculation. However, Lyme disease happens in a very focal manner: 95% of the cases in 2013 occurred among residents of 14 states where the disease is considered endemic: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, and Wisconsin (**Fig. 24.2**). These highly endemic regions for Lyme disease correlate with the regions that have a high density of *Ixodes* ticks.

From 1982 until the present time, reported cases of Lyme disease have shown a gradual increase, despite the fact that Lyme disease surveillance is subject to both underreporting and overdiagnosis of cases, in addition to probable variation in diagnostic and reporting practices. In August 2013, the CDC shared new, higher estimates of Lyme disease incidence: up to 300,000 cases per year in the United States.

In the United States, most human infections with *B. burgdorferi* occur during the months of May-August, corresponding with the most active feeding period of the *Ixodes* nymphal ticks and maximal human outdoor exposure. The timing of cases in the Western United States is generally several weeks later than in the Eastern United States, mainly because of the later onset of warmer weather. In the 2003-2005 CDC data, 61% of cases were in children aged 5-14, with a male predominance. However, this gender difference diminishes with age, and overall males accounted for 54% of reported cases in that data set.

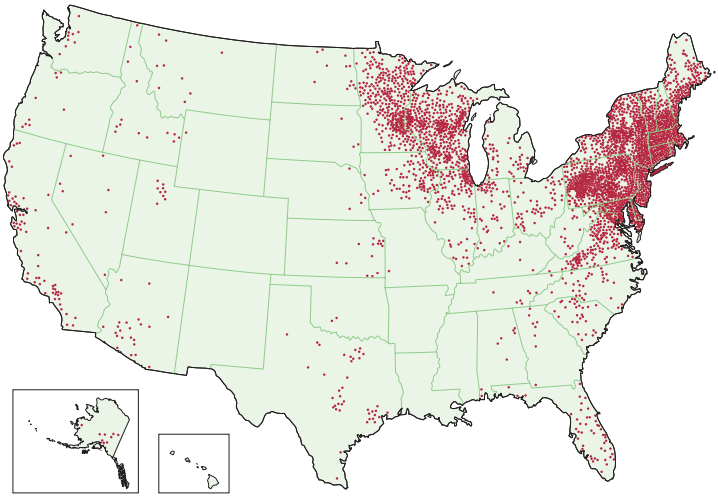

Fig. 24.2 Reported cases of Lyme disease—United States, 2014. One dot was placed randomly within the county of patient residence for each reported case (not necessarily the location of infection). (Source: CDC.gov/lyme.)

Several lines of evidence suggest *B. burgdorferi* can be transmitted transplacentally, but adverse birth outcomes related to maternal Lyme disease appear to be rare.

CLINICAL MANIFESTATIONS

From a conceptual standpoint, Lyme disease can be categorized into three different stages: (1) early-localized (onset days to weeks after infection), (2) early-disseminated (days to months), and (3) late (months to years). From a practical perspective, most patients do not pass through all three phases; the manifestations of the stages can overlap; specific clinical manifestations can occur independently; and some patients develop asymptomatic infection. Clinical features of Lyme disease in the United States differ somewhat from those in Europe; erythema migrans and arthritis occur more frequently among patients in the United States, whereas neurologic and chronic skin conditions are more common in European patients.

The most common clinical manifestation of Lyme disease in the United States is the erythematous macular rash known as erythema migrans. This lesion develops in 60-80% of Lyme disease cases, typically appearing at the site of the tick bite an average of 7 days following the bite (range 3-30 days). Patients often also have concomitant mild to moderate constitutional symptoms, including low-grade fever, headache, fatigue, myalgias, and regional lymphadenopathy. The typical appearance of erythema migrans is a round or oval, well-demarcated, erythematous lesion at least 5 cm in diameter (median, 15 cm). The lesion can appear in one of several forms, including a solid lesion, a bull's-eye pattern, or as multiple rings. If untreated, the erythema migrans lesion gradually expands, typically developing partial central clearing and reaching a diameter of >30 cm. Erythema migrans and associated early symptoms typically persist for 3-4 weeks if left untreated. In some instances, patients and medical providers may confuse erythema migrans with an allergic reaction to an insect bite. An insect bite typically is painful, has its onset within 24 hours of the bite, and usually resolves within several days. Erythema migrans, on the other hand, is usually painless, has a delayed onset of typically 7-10 days, and will persist for weeks if not treated.

Although *B. burgdorferi* infection is initially limited to the primary cutaneous site, dissemination from the site of infection to distant sites can occur within days to a few weeks after initial inoculation. Some patients will show evidence of dissemination early in their course by developing multiple, widespread, secondary annular erythema migrans lesions; these secondary lesions are generally smaller than the initial erythema migrans lesion and can vary in number from one lesion to >50. Years after the initial infection, patients may develop a late-stage cutaneous manifestation known as acrodermatitis chronica atrophicans; this chronic scarring skin lesion can resemble scleroderma and is considerably more common among European patients with Lyme disease than among those in the United States.

Months after the initial infection, approximately 60% of patients with Lyme disease in the United States will develop arthralgias or arthritis. The arthritis typically consists of brief attacks of asymmetric, oligoarticular arthritis involving large joints, interspersed with months of remission. Only about 10% of patients with untreated Lyme disease will develop chronic arthritis, and these patients often have the HLA-DR4 haplotype. In addition, patients with HLA-DR4 often have a poor response to antimicrobial therapy. Even with chronic Lyme arthritis, patients generally have resolution of their active flares within 5-6 years, and most do not develop permanent joint damage. The arthralgias tend to also involve large joints, have intermittent recurrences, and usually resolve within 5-6 years.

Overall, about 20% of patients with Lyme disease have some type of neurologic manifestation. Early in the course of Lyme disease, patients may develop unilateral or bilateral facial palsy. Less frequently, patients may present with a lymphocytic meningitis or meningoencephalitis within months of the initial infection. Later in the course (months to years after infection), patients may develop peripheral neuropathy that can manifest as radiculoneuritis, mononeuritis multiplex, or diffuse peripheral neuropathy. The late-appearing chronic neurologic manifestations pose special difficulty, since many of these symptoms are nonspecific and can overlap with many other diseases. The Lyme-associated chronic neurologic manifestations include subacute encephalopathy, axonal polyneuropathy, and, less

frequently, leukoencephalopathy. Available studies suggest that sub-acute encephalopathy is the most common of these chronic neurologic manifestations; it is characterized by cognitive deficits and disturbances in mood and sleep. Unfortunately, patients with untreated chronic neurologic Lyme disease may have persistence of their symptoms for several years, even longer than 10 years in some cases. However, this rarely happens in current practice, where antibiotics are often given on suspicion of Lyme disease. There is no evidence that patients who have received an appropriate course of treatment (see below) but who still complain of fatigue or cognitive disability have "chronic Lyme disease." Rather, these patients carry a diagnosis of "post-treatment Lyme disease syndrome," an important distinction that emphasizes the fact that further courses of antibiotics will not be of benefit.

Although cardiac manifestations develop in <10% of patients with Lyme disease, they can have potentially fatal consequences. The most common cardiac abnormality is atrioventricular block, occurring in about 5-8% of patients with Lyme disease, typically weeks to months after the initial infection. Although some patients have required a temporary pacemaker for severe atrioventricular conduction disturbances, these abnormalities generally do not necessitate placing a permanent pacemaker if the patient receives appropriate therapy for Lyme disease. Other less common cardiac manifestations include myocarditis, pericarditis, and pancarditis. Rare reports have described cases of chronic cardiomyopathy caused by *B. burgdorferi*. The prevalence of cardiac abnormalities among persons with Lyme disease who have received antibiotic therapy—typically for erythema migrans—is the same as for persons without a history of Lyme disease.

In addition to the cutaneous, joint, neurologic, and cardiac manifestations, rare reports have described involvement of other body sites, which poses a diagnostic challenge for even the most astute clinician.

DIAGNOSIS

As noted earlier, the CDC has generated a case definition for Lyme disease for surveillance purposes. This case definition, however, is not meant to be a rigid guideline for actual clinical decisions regarding who should or should not receive therapy for Lyme disease. Multiple factors play a role in the clinical decision making regarding the clinical diagnosis of Lyme disease. From a clinical perspective, a diagnosis of Lyme disease should initially be based on compatible clinical findings in a patient with a reasonable probability of previous exposure to *Ixodes* ticks; serologic testing for evidence of *B. burgdorferi* infection can then serve as an adjunct to clinical judgment. Most laboratories use the serum enzyme immunoassay (EIA) as a screening test and the serum Western immunoblot as a confirmatory test.

Recommendations for serologic testing of patients with suspected Lyme disease arose from expert groups that convened at the Second National Conference on Serologic Diagnosis of Lyme Disease in 1994; these expert groups included the CDC, the Association of State and Territorial Public Health Laboratory Directors, the Food and Drug Administration (FDA), and the National Institutes of Health. In general, these groups recommended using a two-step diagnostic process for suspected cases, with initial testing consisting of an EIA or an immunofluorescent antibody test (**Fig. 24.3**). If the initial test is positive or equivocal, further "confirmatory" testing should be performed using a standardized Western immunoblot, because the screening tests have less than optimal specificity. If the Western immunoblot is positive, the patient is considered to have laboratory evidence of Lyme disease. Because adequate antibody responses to *B. burgdorferi* may not be generated in the first several weeks of infection, patients with a negative screening test taken <4 weeks after possible infection should undergo follow-up convalescent repeat testing. If, however, the patient has a negative screening test taken after 4 weeks of infection, they do not have laboratory evidence of Lyme disease and would, in general, not need further testing for Lyme disease.

The same expert panel also generated recommendations that standardized the criteria for a positive Western immunoblot serology test. Specifically, they recommended that the Western immunoblot IgM should be considered positive if at least two of the following bands are present: 21/24 kDa (OspC), 39 kDa (BmpA), and 41 kDa (Fla). The

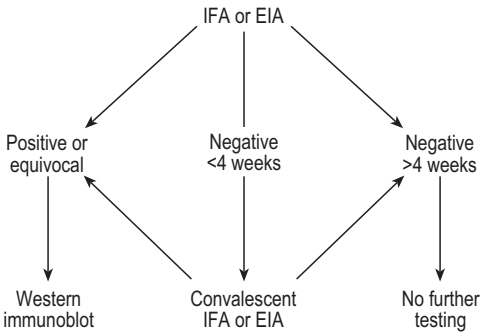

Fig. 24.3 Recommended approach for serologic testing of patients with suspected Lyme disease. *EIA*, Enzyme immunoassay; *IFA*, immunofluorescent antibody test. (Source: Centers for Disease Control and Prevention.)

recommended criteria for a positive Western immunoblot IgG are presence of at least five of the following 10 bands: 18 kDa, 21/24 kDa (OspC), 28 kDa, 30 kDa, 39 kDa (BmpA), 41 kDa (Fla), 45 kDa, 58 kDa (not GroEL), 66 kDa, and 93 kDa. Most commercial laboratories that perform *B. burgdorferi* Western immunoblot assays now incorporate these specific diagnostic criteria into their interpretation of the test.

Although standardization of *B. burgdorferi* Western immunoblotting now exists, several major problems still exist with serologic testing for Lyme disease. First, false-negative antibody tests are common during the initial 4-6 weeks of the patient's illness, a time when patients most often present with the initial erythema migrans rash. Second, antimicrobial treatment of early Lyme disease can blunt antibody responses and thus generate a false-negative test. Third, false-positive results can result from other infectious agents and other diseases, including Epstein-Barr virus, oral treponemes, syphilis, relapsing fever, and rheumatoid arthritis. Fourth, test results vary significantly in different laboratories, a problem compounded by the multitude of laboratories that now perform *B. burgdorferi* serologic testing. Other diagnostic tests, such as culture, antigen detection, polymerase chain reaction (PCR), and measurement of cell-mediated immunity to *B. burgdorferi*, are considered investigational and are not recommended for routine clinical purposes. Among these investigational techniques, PCR-based tests show the most promise, especially for patients for early-stage Lyme disease, as well as those with potential false-negative antibody titers. However, this technique is experimental, and clinical decisions should not be based on PCR results from commercial laboratories. Although several investigators have cultured *B. burgdorferi* from clinical specimens, performing cultures requires a special medium (Barbour-Stoenner-Kelly) that is neither rapid nor widely available. Some reference laboratories perform *B. burgdorferi* cerebrospinal fluid antibody titers, but interpretive criteria are not standardized.

Several studies have shown that significant problems exist with the overdiagnosis of Lyme disease. In particular, two studies both found that only about one-quarter of patients referred to their clinic with suspected active Lyme disease actually had active Lyme disease. One of these studies also reported that among persons referred to their clinic who had not responded to antibiotic therapy for Lyme disease, nearly 80% had not responded because the initial diagnosis of Lyme disease was not warranted. Patients may present with a diagnosis of Lyme made by a self-described "Lyme literate doctor," which is a warning sign that their workup and management may have been incomplete or flawed. Healthcare workers can combat this problem in two ways:

(1) *Blood should be tested for Lyme disease only when clinically appropriate*. Unless there is pre-test suspicion for this infection based on epidemiological risk factors and clinical

manifestations, the reliability of the test falls dramatically, and the odds of a positive test reflecting true infection are greatly reduced. A common error is to test for Lyme during the initial work-up of chronic fatigue syndrome. Instead, a stepwise approach should be pursued, as suggested by the CDC (www.CDC.gov/cfs).

(2) *Use an appropriate laboratory*. The importance of sending specimens to a reputable laboratory cannot be overemphasized. Some laboratories have been outlawed in certain states, due to their questionable business and scientific practices. Ensure that the laboratory you use is certified by the FDA and College of American Pathologists and performs other blood work services for your institution; in general, avoid labs that "specialize" exclusively in Lyme diagnostics and exercise skepticism when reviewing results ordered by a patient before seeking formal medical care.

THERAPY

Patients with early Lyme disease, especially erythema migrans, respond well to antimicrobial therapy. In general, with long delays in the initial diagnosis of Lyme disease, patients have poorer responses to antimicrobial therapy. The following treatment recommendations are based on the Infectious Diseases Society of America (IDSA) clinical practice guideline "The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis" (**Table 24.1**). The primary goal of treating patients with early-stage Lyme disease is to decrease the duration of the acute manifestations (such as erythema migrans), as well as to diminish the likelihood that later sequelae of Lyme disease will develop. More than 90% of patients with erythema migrans respond to a 10- to 21-day course of oral doxycycline (100 mg twice/day), amoxicillin (500 mg three times/day), or cefuroxime axetil (500 mg twice/day). In general, doxycycline should not be used to treat Lyme disease in pregnant women, lactating women, or children ≤8 years old. Either amoxicillin or cefuroxime axetil could be used instead of doxycycline in these individuals. In children, amoxicillin should be dosed at 50 mg/kg per day in three divided doses (maximum of 500 mg/dose), and cefuroxime axetil dosed at 30 mg/kg per day in two divided doses (maximum of 500 mg/dose). In children ≥8 years of age, doxycycline would be dosed at 4 mg/kg per day in two divided doses (maximum of 100 mg/dose). Because the macrolide antibiotics (azithromycin, clarithromycin, erythromycin) have treatment success rates lower than doxycycline or amoxicillin, they are not recommended as first-line therapy for the treatment of Lyme disease.

Treatment with doxycycline provides an advantage over amoxicillin in geographic areas where patients with Lyme disease may have concomitant human granulocytic anaplasmosis because doxycycline effectively treats both of these tick-borne diseases. Doxycycline is not recommended for the treatment of babesiosis (initial therapy for babesiosis consists of a 7- to 10-day course of either atovaquone plus azithromycin or clindamycin plus quinine).

Initial therapy of Lyme arthritis with oral therapy gives response rates similar to those seen with intravenous regimens. Overall response rates are in the range of 50-60%, but lower among those who previously received intra-articular steroids. In addition, responses are often delayed several months. For patients with recurrent arthritis after treatment with an oral regimen, another course of oral therapy for 28 days or a course of intravenous therapy for 14 days may be considered.

For patients with early-stage neurologic Lyme disease that manifests only as a facial palsy, oral therapy is recommended, whereas those with acute meningitis or radiculopathy should receive parenteral therapy. Recommended treatment for late neurologic Lyme disease consists of parenteral therapy. Overall, about 60% of patients with neurologic involvement show significant improvement in their neurologic manifestations, but, similar to patients with Lyme arthritis, improvement may be delayed for several months after therapy. Treatment for neurological infection with antibiotic courses beyond 28 days has not been shown to help patients in carefully constructed randomized trials, and thus the IDSA recommends against this practice.

TABLE 24.1 Preferred Regimens for the Initial Treatment of Lyme Disease in Adults

Manifestation	Therapy	Route	Dose	Duration in Days (Range)
Erythema migrans	Doxycycline	p.o.	100 mg b.i.d.	14 (10-21)
	Amoxicillin	p.o.	500 mg t.i.d.	14 (14-21)
	Cefuroxime axetil	p.o.	500 mg b.i.d.	14 (14-21)
Arthritis (without neurologic disease)	Doxycycline	p.o.	100 mg b.i.d.	28
	Amoxicillin	p.o.	500 mg t.i.d.	28
	Cefuroxime axetil	i.v.	500 mg b.i.d.	28
Cardiac				
Mild (AV block with PR <0.3 s)	Doxycycline	p.o.	100 mg b.i.d.	14 (14-21)
	Amoxicillin	p.o.	500 mg t.i.d.	14 (14-21)
	Cefuroxime axetil	p.o.	500 mg b.i.d.	14 (14-21)
Serious	Ceftriaxone	i.v.	2 g q.d.	14 (10-28)
Early Neurologic				
Meningitis or radiculopathy	Ceftriaxone	i.v.	2 g i.v. q.d.	14 (10-28)
Cranial nerve palsy	Doxycycline	p.o.	100 mg b.i.d.	14 (14-21)
	Amoxicillin	p.o.	500 mg t.i.d.	14 (14-21)
	Cefuroxime axetil	p.o.	500 mg b.i.d.	14 (14-21)
Late neurologic (central or peripheral nervous system disease)	Ceftriaxone	i.v.		14 (14-28)

AV, Atrioventricular; *b.i.d.*, twice per day; *i.v.*, intravenous; *p.o.*, by mouth; *q.d.*, once per day; *t.i.d.*, three times per day.
(Based on recommendations from: Wormser, G.P., Dattwyler, R.J., Shapiro, E.D., et al., 2006. 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. 43, 1089–1134.)

Patients with mild cardiac disease (asymptomatic and PR interval ≤0.3 s) can be treated with oral therapy. For all other patients with cardiac disease, intravenous therapy should be used. In general, patients with cardiac involvement should be observed closely and may require a temporary pacemaker.

Many patients treated for Lyme disease do not improve after therapy. The complex reasons for poor response may include initial misdiagnosis, concomitant chronic illnesses such as fibromyalgia or depression, slowly resolving Lyme disease, permanent tissue damage caused by *B. burgdorferi*, post-Lyme autoimmune disease, persistent tissue infection with *B. burgdorferi*, and sterile inflammation caused by dead organisms. For those patients who do not respond to antibiotics and have no objective evidence of active Lyme disease, repeated courses of antibiotics have no proven benefit but do carry substantial risk of harm and are not recommended. They do not have "chronic Lyme disease" but rather should be diagnosed with "post-treatment Lyme disease syndrome." This condition is very real, and suffering should be validated; optimum treatment is not certain, but antibiotics are clearly not beneficial here and indeed are often harmful. An excellent resource for patients is the website www.CDC.gov/lyme/postlds.

PREVENTION

The three major strategies involved in preventing Lyme disease include avoiding tick bites, administering prophylactic antibiotics in the event a tick bite occurs, and using a vaccine. The vaccine option is no longer available in the United States.

Tick Bite Prevention

The easiest and first step in preventing Lyme disease and other *Ixodes* species-transmitted pathogens involves decreasing the risk of receiving an *Ixodes* tick bite and minimizing the duration of a bite if it does occur. In general, specific preventive measures consist of staying in the middle of trails when walking through wooded areas, avoiding tall grass and shrubs, wearing light-colored clothing to more easily spot any tick that may crawl onto clothing, wearing long pants tucked into socks, wearing shoes or closed-toed sandals, and wearing an effective tick repellent (Chapter 1). Frequent checks for ticks are recommended, because *B. burgdorferi* is usually not transmitted to humans unless a tick has been attached for at least 8 hours. If an attached tick is found, a pair of tweezers should be used to grasp the tick as close to the skin as possible, and then it should be removed by pulling perpendicular to the skin with slow, steady pressure.

Post-Exposure Antibiotic Prophylaxis

Recommendations on whether to give prophylactic antibiotics to persons following an *Ixodes* tick bite have generated controversy over the years. Clinical practice guidelines from the IDSA guidelines state that "a single dose of doxycycline may be offered to adult patients (200 mg dose) and to children ≥8 years of age (4 mg/kg up to a maximum dose of 200 mg) when all of the following circumstances can be met: (a) the attached tick can be reliably identified as an adult or nymphal *I. scapularis* tick that is estimated to have been attached for ≥36 h on the basis of degree of engorgement of the tick with blood or of certainty about the time of exposure to the tick; (b) prophylaxis can be started within 72 h of the time that the tick was removed; (c) ecologic information indicates that the local rate of infection of these ticks with *B. burgdorferi* is ≥20%; and (d) doxycycline treatment is not contraindicated." The guidelines go on to state that "prophylaxis after *I. pacificus* bites is generally not necessary, because rates of infection with *B. burgdorferi* in these ticks are low in almost the entire region in which the tick is endemic."

These IDSA guidelines regarding the use of prophylactic antibiotics after a tick bite are predominantly based on results from a study conducted in a region in New York hyperendemic for Lyme disease. The major findings of this study were that a single 200-mg dose of doxycycline was highly effective for post-exposure prophylaxis if given within 72 hours of the *Ixodes* tick bite and that only those bites involving partially or fully engorged ticks led to clinical disease. Whether or not the person receives prophylactic antibiotics, he or she should receive specific information on the signs and symptoms of early Lyme disease and should promptly return for further evaluation if any signs or symptoms develop that are suggestive of Lyme disease.

Lyme Disease Vaccine

Two recombinant *B. burgdorferi* OspA Lyme disease vaccines have been developed and have undergone large-scale evaluation: LYMErix (SmithKline Beecham) and ImuLyme (Pasteur Merieux Connaught). These vaccines have a novel mechanism of action in that they stimulate human antibodies to OspA, and these antibodies neutralize *B. burgdorferi* in the midgut of the *Ixodes* tick, while the tick takes a blood meal. Because *B. burgdorferi* within the tick changes its outer protein covering from OspA to OspC after prolonged feeding, the human OspA antibodies would not likely provide reliable protection if *B. burgdorferi* entered the human bloodstream. The LYMErix vaccine received FDA approval in the United States in 1999 for immunization of persons aged 15-70 years, but the manufacturer discontinued production in early 2002, citing insufficient consumer demand.

FURTHER READING

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