Lyme Disease: A Review

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Abstract Lyme disease is the most common vector-borne illness in the United States and is also endemic in Europe and Asia. It is caused by the spirochete *Borrelia burgdorferi* and transmitted by the bite of the *Ixodes* (deer) tick. It occurs most frequently during spring and summer and may involve the skin, nervous system, heart, and joints. This article reviews the pathogenesis, epidemiology, clinical manifestations, diagnosis, treatment, and prevention of Lyme disease.

Keywords Lyme disease · *Borrelia burgdorferi* · Infection · Tick-borne illness

Introduction

Lyme disease is a multisystem illness caused by the spirochete *Borrelia burgdorferi* sensu lato. It is the most common vector-borne illness in the United States, with more than 19,000 cases reported to the Centers for Disease Control and Prevention in 2006 [1]. Lyme disease was first described in the late-1970s during an investigation of an unusual epidemic of what appeared to be juvenile rheumatoid arthritis in Lyme, Connecticut [2]; however, manifestations of Lyme disease were evident in Europe as early as the beginning of the 20th century. The causative agent was isolated from *Ixodes* ticks in 1982 [3], marking the start of a new era in the understanding of this disease.

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The Organism and Pathogenesis

The genus *Borrelia* is a member of the family Spirochaetaceae, which also includes *Leptospira* and *Treponema*. Spirochetes have a wavelike body and flagella enclosed between the outer and inner membranes. Three genospecies of *B. burgdorferi* cause most human disease: *B. burgdorferi* sensu stricto, *B. garinii*, and *B. afzelii*. *B. burgdorferi* sensu stricto is the only genospecies associated with human disease in the United States, whereas all three genospecies occur in Europe, and *B. garinii* and *B. afzelii* occur in Asia. *B. garinii* and *B. afzelii* are antigenically distinct from *B. burgdorferi* sensu stricto, and these differences may account for the variation in clinical presentation in different geographic regions.

The genomes of *B. burgdorferi* sensu stricto strain B31, *B. garinii* strain PBi, and *B. afzelii* strain PKo, have been sequenced. These genomes include a linear chromosome and multiple linear and circular plasmids. The number of plasmids and their sizes vary substantially among strains and species [4], and they encode many of the factors necessary for survival during the organism's complex life cycle [5]. The chromosomal genes code for proteins needed for replication, energy metabolism, and transport of nutrients. Interestingly, no genes for cellular biosynthetic reactions and no classically defined virulence factors have been found in *B. burgdorferi*.

Lipoproteins play an important role in the life cycle of *B. burgdorferi* and account for a significant part of the *B. burgdorferi* genome. Lipoproteins have differential expression in culture, in the tick, and in the mammalian host. For example, outer surface protein A (OspA) and outer surface protein B (OspB) are expressed abundantly in culture. OspA also is expressed in the tick gut, where it mediates spirochete attachment [6]. As an infected tick begins to feed on a mammal, the synthesis of OspA is repressed and that of outer surface protein C (OspC) is induced [7]. OspC is important in the transmission of the spirochete from tick to

mammal, and it is required early in mammalian infection [8]. OspC is very diverse, and OspC alleles have been linked to both infectivity and invasiveness [9, 10]. The lipoprotein variable major protein-like sequence, expressed (VlsE) is required for persistence of infection in the immunocompetent mammalian host [11] and plays a major role in immune evasion in Lyme borreliosis [12].

The immune system plays an important role in the pathogenesis of Lyme disease. *B. burgdorferi* lipoproteins are potent activators of the innate immune system and have been shown to activate Toll-like receptors (TLRs) 1 and 2 in a CD14-dependent manner [13, 14], and mice deficient in TLR2 or myeloid differentiation antigen 88 (MyD88) have higher spirochete loads [15]. *B. burgdorferi* also induces type I interferon production in mice and human cells [16, 17]. The adaptive immune response, particularly humoral response, is important in controlling the severity of Lyme disease in mice, but the bacteria can survive despite eliciting a strong antibody response, possibly because of immune evasion by modulating gene expression. In mice, a stronger initial T-helper type 1 (Th1) response seems to be important for controlling the infection [18, 19]. Interestingly, *Ixodes* tick saliva has been shown to induce a Th2 response that facilitates infection [18, 20].

Epidemiology

Borrelia burgdorferi is transmitted to humans by *Ixodes* ticks. These small, dark-colored ticks have a 2-year life cycle made up of four developmental stages: egg, larva, nymph, and adult. Eggs are laid in spring and hatch into larvae during the late summer. Larvae feed on small animals (usually mice) and can acquire *B. burgdorferi* infection at this stage. The larvae then molt into nymphs, which feed again the following spring to early summer (and may transmit the infection to the new host). Nymphs molt into adult ticks in mid-October and early-November, when the adult female ticks feed again, mainly on large animals. Small mammals are important in the transmission cycle of *B. burgdorferi*, as some, particularly the white-footed mouse, may remain infected but asymptomatic and therefore serve as reservoirs for the organism. Some avian species also may serve as reservoirs for *B. burgdorferi*. Deer also are important because they are the principal hosts for the adult ticks, although they are not reservoir competent for *B. burgdorferi*.

The risk for acquiring Lyme disease in the United States varies with the distribution, density, and prevalence of infection in vector ticks. Most cases of Lyme disease occur in the northeastern and north-central states [1]. Lyme disease also is endemic in several regions in Europe and Asia. Most Lyme disease cases result from bites by infected nymphs, as their small size (about the size of a poppy seed) allow them to easily go unnoticed. Most infections occur during the months of May through August, when both the nymph ticks' activity and human outdoor activity are at their peak. Adult ticks also can transmit the disease, but because they are larger (the size of a sesame seed), they are more easily recognized. Laboratory studies indicate that efficient transmission of *B. burgdorferi* by the ticks requires a minimum of 36 to 48 hours of attachment [21].

Clinical Features

For clinical purposes, Lyme disease is divided into early and late disease. Lyme disease usually begins with the characteristic skin lesion, erythema migrans (Fig. 1), at the site of the tick bite. The incubation period from infection to onset of erythema migrans typically is 7 to 14 days but may be as short as a day and as long as 30 days. Because of the small size of the ticks, most patients do not remember the preceding tick bite. Classically, erythema migrans starts as a red papule at the site of the bite, which gradually expands to an annular lesion with red borders and partial central clearing; however, fewer than 35% of patients in the United States have lesions with central clearing. Less commonly, the center of the lesion may appear vesicular or necrotic [22, 23]. Constitutional symptoms, arthralgias, myalgias, and severe fatigue are common, and regional lymphadenopathy also may occur. Erythema migrans may be absent in about 10% of patients with early Lyme disease, and patients may have asymptomatic infection or only nonspecific symptoms [24].

Fig. 1 Erythema migrans

After several days or weeks, the spirochete may spread hematogenously, and patients may develop multiple erythema migrans lesions. These secondary lesions are similar in appearance to the primary lesion. Fever, headache, mild neck stiffness, migratory musculoskeletal pain, arthralgias, and profound malaise and fatigue are common; these symptoms may be intermittent. Patients also may develop neurologic, cardiac, and rheumatologic involvement. Neurologic abnormalities occur in 15% to 20% of untreated patients. The most common neurologic manifestations are cranial neuropathy, particularly facial palsy (which may be bilateral), lymphocytic meningitis, and motor or sensory radiculoneuritis. Cardiac involvement occurs in 4% to 8% of untreated patients, the most common feature being a fluctuating atrioventricular block. *Borrelia* lymphocytoma is a firm, painless, bluish-red nodular lesion usually localized on the earlobe or nipple. It occurs almost exclusively in Europe and is associated with *B. afzelii* and *B. garinii* infection. These early signs may resolve even if the patient is untreated.

Asymmetric oligoarticular arthritis, especially involving the knees, occurs in about 60% of untreated patients at a mean of 6 months from the onset of the disease. Typically, the joint effusions are large, and synovial fluid findings suggest an inflammatory process with leukocyte counts averaging 25,000/mm^3, with most being polymorphonuclear leukocytes. Chronic arthritis typically involves one or two large joints, with preference for the knees, and occurs in 11% of untreated patients with erythema migrans. If untreated, the arthritis may persist or resolve spontaneously [25]. A few of these patients will have persistent arthritis after antibiotic therapy, classified as antibiotic-refractory Lyme arthritis. Antibiotic-refractory Lyme arthritis is associated with certain HLA-DR molecules and T-cell reactivity against OspA [26]. An autoimmune reaction as a result of molecular mimicry between OspA of *B. burgdorferi* and human leukocyte function-associated antigen 1 (hLFA-1) was proposed as a mechanism of this persistent arthritis [27, 28], although further work has not confirmed hLFA-1 as a relevant autoantigen [29]. Current hypotheses to explain this condition include bystander activation of autoreactive T cells due to an increased inflammatory response [30–32].

Late neurologic Lyme disease may present as a subacute mild encephalopathy affecting memory and concentration. Patients also may present with chronic mild axonal polyneuropathy manifested as distal paresthesias and, less commonly, as radicular pain [33, 34]. Rarely, an encephalomyelitis or leukoencephalitis may occur. An autoimmune mechanism may play a role in certain cases of chronic neurologic disease [35]. Acrodermatitis chronica atrophicans, a chronic skin disease that occurs in Europe and Asia, is associated primarily with *B. afzelii* infection.

The skin lesions usually are found on the extensor surfaces of the extremities. They begin insidiously as an inflammatory infiltrate that subsequently becomes indurated with reddish violaceous discoloration and progress to atrophy of the skin over a period of years. Patients may have an associated sensory neuropathy.

Chronic Lyme disease is a confusing term used to describe vastly different patient populations, including patients with late Lyme disease, those with post-Lyme disease syndrome, and those who have no evidence of Lyme disease [36]. *Post-Lyme disease syndrome* describes patients with an episode of well-documented Lyme disease who have nonspecific symptoms of fatigue, sleep disorders, headache, memory and concentration difficulties, myalgias, and arthralgias after receiving adequate antibiotic therapy. The cause of this syndrome currently is unknown, but it likely is multifactorial, including part of the expected resolution of symptoms after therapy, postinfective fatigue syndrome, and intercurrent conditions [37].

Lyme disease is a reportable disease in the United States; for surveillance purposes, it is defined as 1) physician-diagnosed erythema migrans greater than 5 cm in diameter or 2) one or more objective late manifestations of Lyme disease with laboratory evidence of infection with *B. burgdorferi* (ie, isolation of the organism or positive serologic testing) in an individual with possible exposure to infected ticks [1, 38].

Laboratory Evaluation

Most laboratory evaluation methods supporting the diagnosis of Lyme disease are indirect, based on serologic assays because of the difficulty in demonstrating *B. burgdorferi* by direct techniques (culture and polymerase chain reaction [PCR]). Direct detection of antigens is not reliable [39].

Culture

Although culture of *B. burgdorferi* from clinical samples has been instrumental in expanding our knowledge regarding subspecies [40–42], as well as clearly documenting infection in clinical studies, its use in clinical practice is very limited because of its special requirements and the lack of sensitivity of culture outside skin samples from patients with erythema migrans, in whom there is little need for laboratory diagnosis. Culture of *B. burgdorferi* requires special enriched bacteriologic media, the most commonly used being Barbour-Stoenner-Kelly (BSK) or modified Kelly-Pettenkofer (MKP), as well as a prolonged period of observation (up to 12 weeks) because of the slow multiplication of the bacterium. *B. burgdorferi* can be

cultured from 20% to 90% (usually 50%) of biopsy specimens taken from untreated erythema migrans lesions [43–45]. Large-volume (9-mL) plasma cultures have a yield of about 40% in blood samples from patients with early disease who have not received antibiotics [43]. Culture of cerebrospinal fluid (CSF) has a yield of less than 10% [41], and it is extremely rare to isolate the spirochete from joint fluid.

Polymerase Chain Reaction

PCR has been used to amplify genomic DNA of *B. burgdorferi* in skin, blood, CSF, and synovial fluid. It seems to be most useful in patients with Lyme arthritis. *B. burgdorferi* DNA has been detected in synovial fluid samples from 85% of patients [46]. However, the sensitivity of PCR determinations in CSF from patients with neuroborreliosis has been much lower (<40% in patients with acute neuroborreliosis) [47, 48]. In skin biopsies from erythema migrans lesions, PCR sensitivity varies from 25% to 90% and is similar to culture [43, 49]. The sensitivity of PCR for acrodermatitis chronica atrophicans lesions varies from 20% to 90%. PCR of urine samples has been used with variable results.

Serology

Serologic testing, the most commonly used corroborative laboratory test for Lyme disease, can provide helpful information in patients with clinical findings indicating later-stage disseminated Lyme disease. As expected for a test that depends on antibody production, the sensitivity of the test increases with the duration of the infection, and patients who present very early in their illness are more likely to have a negative result. This is most important in patients with erythema migrans lesions, in whom the diagnosis should be based on clinical findings, as fewer than 50% of these patients will have positive serologic results at presentation [40, 50]. A major shortcoming of current serologic assays is that they do not distinguish between active and inactive infection, and patients may continue to be seropositive for years, even after adequate antibiotic treatment [51, 52]. Also, serologic tests commonly are used by physicians to determine whether otherwise unexplained symptoms are the result of Lyme disease in cases in which the pretest probability for the illness is low, increasing the chance of a false-positive result [53]. Finally, the use of commercial laboratories offering nonvalidated Lyme diagnostic tests is discouraged [39, 54, 55].

Most enzyme-linked immunosorbent assays (ELISA) and indirect fluorescent-antibody (IFA) assays are made of whole-cell sonicate of *B. burgdorferi* and have a significant number of false-positive results because of the presence of cross-reactive antigens such as the flagellar and heat-shock proteins. To increase specificity, Western blotting is used as a second step. The current recommendations for serodiagnosis of Lyme disease consist of a two-test approach: a sensitive ELISA or IFA assay, followed by Western blotting when results are indeterminate or positive. The Western blot is interpreted using standardized criteria, requiring at least two of three bands for a positive IgM Western blot, and 5 of 10 bands for a positive IgG Western blot. The IgM Western blot is used only within the first 4 weeks of the illness [56].

The use of recombinant antigens, principally VlsE lipoprotein of *B. burgdorferi*, and the C6 peptide, which reproduces the invariable region 6 of VlsE, has been a major advance in Lyme disease serodiagnosis. The C6 peptide ELISA has excellent sensitivity for acute-, convalescent-, and late-phase specimens, as well as excellent specificity [40, 50, 57–59]. A commercially available C6 ELISA currently is approved by the US Food and Drug Administration (FDA) as a first-tier test and may in the future be approved as a single-tier test.

Intrathecal Antibody Production

The concomitant analysis of serum and CSF is used to demonstrate local synthesis of anti-*Borrelia* antibodies. The tests available in the United States use two main techniques to measure *B. burgdorferi*-specific antibody; one method uses an antibody-capture immunoassay, whereas in the other method, the serum and CSF are diluted so that the final immunoglobulin concentrations are similar. None of these tests has been approved by the FDA. Intrathecal antibody production is considered present if the antibody titer in the CSF exceeds the titer in the serum, that is, the "CSF index" is greater than 1. Presence of intrathecal antibody production is considered by some as a requirement for the diagnosis of neuroborreliosis. However, although this test is frequently positive in European patients [60], it is positive more frequently in neuroborreliosis caused by *B. garinii* infection [41]. There are few data regarding the sensitivity of intrathecal borrelial antibody production in diagnosing neuroborreliosis in the United States. Intrathecal borrelial antibody production may be detected for several months or years after treatment.

Coinfection

Ixodes ticks are also vectors for human granulocytic anaplasmosis (HGA) and babesiosis, and in Europe and Asia, they also transmit tick-borne encephalitis virus. HGA ranges in severity from asymptomatic seroconversion to a severe febrile illness that may be fatal. Patients present with

fever, headache, and myalgias; laboratory findings may include leukopenia, lymphopenia, thrombocytopenia, and elevated liver enzymes [61]. Babesiosis, an infection by intraerythrocytic protozoans from the genus *Babesia*, can cause disease ranging from an apparently silent infection to a fulminant, malaria-like illness. Concurrent infection should be considered in a patient with unusually severe or atypical features of Lyme disease [62, 63].

Southern Tick-Associated Rash Illness

Southern tick-associated rash illness (STARI; or Masters disease), a condition similar to erythema migrans, is associated with the bite of the Lone Star tick, *Amblyomma americanum*. Lesions occur 2 to 15 days after a tick bite and, compared with those seen in Lyme disease, tend to be smaller, have central clearing more often, and occur as multiple lesions less commonly [64]. The cause of STARI is unknown, as it is the natural course of the disease. Lone Star ticks are found throughout the southeastern and south-central states, as well as along the coastal areas as far north as Maine.

Treatment

In most cases, Lyme disease is treated successfully with antimicrobial therapy (Tables 1 and 2). Oral therapy is recommended for early and uncomplicated infection, including isolated facial nerve palsy. Doxycycline and amoxicillin are the drugs of choice. Doxycycline has the advantage of being effective against HGA, but it is contraindicated in children younger than 8 years of age and in pregnant or lactating women. During doxycycline

therapy, patients should be advised to wear sunscreen and avoid sun exposure, as the drug may cause photosensitivity. Amoxicillin is the drug of choice for children younger than 8 years of age and pregnant or lactating women. Cefuroxime axetil is a second-line alternative because of its slighter higher cost. Oral macrolides are considered third-line alternatives, as their clinical efficacy has been less than that of the β-lactams and tetracyclines.

The recommended duration of therapy varies from 14 to 28 days. Parenteral antibiotics generally are recommended for treating neurologic Lyme disease and for the initial therapy of patients with more severe cardiac disease (ie, those with symptoms, second- or third-degree atrioventricular block, or first-degree block with a PR interval ≥0.3 seconds). Patients with more severe cardiac disease require hospitalization for cardiac monitoring because the degree of blocking may fluctuate and worsen rapidly and may require a temporary pacemaker.

The antibiotic course may be completed with oral therapy. Intravenous (IV) ceftriaxone is the most commonly used parenteral therapy, but IV cefotaxime or IV penicillin G also may be used. For adult patients who cannot receive cephalosporins or penicillins, doxycycline is an alternative. Patients with Lyme encephalopathy have gradual improvement in their symptoms, usually starting a few months after completion of therapy, and continue to improve slowly for up to 1 to 2 years. For patients with Lyme arthritis (with no neurologic involvement), initial therapy usually is with oral antibiotics for 28 days. A course of oral therapy may be repeated if the patient has persistent joint swelling. Patients who do not respond may receive IV therapy for 2 to 4 weeks. For patients with antibiotic-refractory Lyme arthritis, treatment with anti-inflammatory agents is recommended.

Table 1 Lyme disease: recommendations for therapy

Clinical manifestation	Treatment regimen[a]	Duration, *d (range)*
Erythema migrans (single or multiple)	Oral	14 (14–21)
Isolated facial nerve palsy	Oral	14 (14–21)
Meningitis, radiculoneuritis	IV	14 (10–28)
Mild cardiac disease	Oral	14 (14–21)
More severe cardiac disease[b]	IV (may complete regimen with oral therapy)	14 (14–21)
Late neuroborreliosis[c]	IV	14 (14–28)
Arthritis	Initial therapy with oral regimen. May repeat oral therapy or give IV therapy if response is not satisfactory. Patients who do not respond may have antibiotic-refractory Lyme arthritis.	Oral regimen: 28 IV therapy: 14 (14–28)

[a] Failures occurred rarely with all these regimens

[b] More severe cardiac disease (patients with symptoms, second- or third-degree atrioventricular block, or first-degree block with a PR interval ≥0.3 seconds) requires hospitalization for cardiac monitoring

[c] In late disease, the response to therapy may be delayed for several weeks to months

IV—intravenous

Table 2 Antibiotics used for the treatment of Lyme disease

Oral agents		Adult dosage	Pediatric dosage	Comments
Preferred	Doxycycline	100 mg twice/d	Children >8 y old: 4 mg/kg/d divided in 2 doses (maximum 100 mg/dose)	Active against HGA. Contraindicated in pregnancy, actation, and children younger than 8 y
	Amoxicillin	500 mg every 8 h	50 mg/kg/d divided in 3 doses (maximum 500 mg/dose)	–
	Cefuroxime axetil	500 mg twice/d	30 mg/kg/d divided in 2 doses (maximum 500 mg/dose)	Useful when cellulitis cannot be ruled out. More expensive.
Alternative	Azithromycin	500 mg/d	10 mg/kg/d (maximum 500 mg/d)	Patients treated with macrolides should be observed closely because of the risk of failure. In 1 trial, adults with erythema migrans were more likely to fail therapy if treated with azithromycin for 7 d than if treated with amoxicillin.
	Clarithromycin	500 mg twice/d	7.5 mg/kg twice/d (maximum 500 mg/dose)	
	Erythromycin	500 mg 4 times/d	12.5 mg/kg 4 times/d (maximum 500 mg/dose)	
Intravenous agents				
Preferred	Ceftriaxone	2 g/d IV	50–75 mg/kg/d (maximum 2 g/d)	Easy to administer and largest experience in Lyme disease. It can cause biliary complications.
Alternative	Cefotaxime[a]	2 g IV every 8 h	150–200 mg/kg/d IV divided into 3 or 4 doses (maximum dose 6 g/d)	Efficacy possibly same as that of ceftriaxone but requires more frequent administration.
	Penicillin G[a]	18–24 MU/d IV divided every 4 h	200,000–400,000 U/kg/d divided every 4 h (maximum dose 18–24 MU/d)	More frequent administration. May be less effective than ceftriaxone.

[a] Needs adjustment for renal impairment

HGA—human granulocytic anaplasmosis; IV—intravenous

Four randomized, placebo-controlled studies demonstrated that antibiotic therapy offers no sustained benefit to patients with post-Lyme disease syndrome. The Infectious Diseases Society of America recently issued practice guidelines for the treatment of Lyme disease [63].

Prevention

Patients should be instructed in measures that help avoid ticks, including walking in the center of a path, avoiding brushy areas, and wearing appropriate clothing (ie, light-colored clothing, which facilitates spotting of the ticks, long-sleeved shirts, and pants tucked into socks or boot tops). Other measures, such as applying insect repellent, checking for ticks daily, and removing them promptly if found, will help prevent infection because transmission of *B. burgdorferi* from an infected tick increases with time of attachment. Postexposure antimicrobial prophylaxis for *Ixodes scapularis* bites with a single 200-mg dose of oral doxycycline may be considered for patients (who have no contraindications to the drug) when 1) the incidence of *B. burgdorferi* infection is at least 20% in ticks in the patient's area, 2) the tick was attached for at least 36 h, and 3) prophylaxis can be started within 72 h after the tick was removed. Serologic testing of patients who present with a tick bite and testing the ticks for infection with *B. burgdorferi* are not helpful. All patients should be moni-

tored closely for up to 30 days for signs and symptoms of tick-borne diseases [63]. An OspA-based vaccine for preventing Lyme disease in humans was approved by the FDA in 1998 but removed from the market in 2002 because of poor sales and theoretic concerns about triggering autoimmune arthritis [65, 66].

Conclusions

Since Lyme disease was first described in 1977, our understanding of it has greatly advanced. In this period, investigators were able to isolate and culture the organism, develop diagnostic tests, describe the disease's main characteristics, conduct therapeutic trials, and sequence the *B. burgdorferi* genome. It is hoped that the coming years will bring further advances in our understanding of the immune system's role in the pathogenesis of Lyme disease as well as the interactions among the spirochete, the tick, and the mammalian host. This knowledge should bring new insights leading to the development of new diagnostic, therapeutic, and preventive approaches.

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