

Lyme Disease

Lyme Borreliosis,
Lyme Arthritis,
Erythema Migrans with
Polyarthritits

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Cooperation in Animal Biologics**
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Etiology

Lyme disease results from infection by four closely related, microaerophilic spirochetes in the family Spirochaetaceae: *Borrelia burgdorferi* sensu stricto, *B. garinii*, *B. afzelii*, and *B. japonica*. These four species are part of the *Borrelia burgdorferi* sensu lato complex. The species appear to cause somewhat different patterns of disease in humans. Arthritis and meningitis are associated most often with *B. burgdorferi* sensu stricto infections. Meningopolyneuritis is associated most often with *B. garinii*. Dermatitis and chronic arthritis are seen more often in *B. afzelii* infections.

Geographic Distribution

Lyme disease has been reported throughout the United States but the major endemic foci are localized in the northeastern and mid-Atlantic states, along the Pacific coast and in the upper Midwest. The geographic range of this disease appears to be expanding within the U.S. It also occurs in Europe, Australia, China, Japan, parts of the former Soviet Union, and Ontario, Canada.

In the U.S., Lyme disease results from infection by *B. burgdorferi* sensu stricto. In Europe, Lyme disease is caused by *B. garinii*, *B. burgdorferi* sensu stricto and *B. afzelii*. In Asia, Lyme disease is caused by *B. garinii* and *B. afzelii*.

Ixodes ticks, the vectors for Lyme disease, are usually found in temperate climates, in areas where the relative humidity is high at ground level. In the eastern U.S., these ticks are found most often in deciduous forests and other habitats that contain leaf litter. In the north-central states, *I. scapularis* is usually associated with heavily wooded areas, often surrounded by cleared agricultural lands. On the Pacific coast, *I. pacificus* can be found in a diverse variety of habitats, including forest, north coastal scrub, high brush, and open grasslands.

Transmission

B. burgdorferi is transmitted by 3-host ticks in the genus *Ixodes*. The major vectors for mammals are *Ixodes scapularis* (*I. dammini*) in the eastern and midwestern U.S., *I. pacificus* on the Pacific coast, *I. ricinus* in Europe, *I. persulcatus* in Asia, and possibly *I. holocyclus* in Australia. The incidence of disease is seasonal and depends on the life cycle of the vector; in the Northern Hemisphere, most cases are seen from late spring to summer. Other insects such as flies, mosquitoes and fleas could be involved in transmission but there is little evidence that they are important vectors.

In endemic regions, the infection cycles between the tick vectors and wild animals. Adult ticks may transmit *B. burgdorferi* transovarially to a very small percentage of the eggs, but the agent diminishes or disappears as they develop into larvae and nymphs. Larvae and nymphs become infected (or reinfected) when they feed on small mammals; adult *I. scapularis* prefer to feed on deer. Domestic animals and humans become infected when they are bitten by infected ticks. Transmission is unlikely to occur before the tick has been attached for at least 24 hours. During the 24 to 48 hour lag phase, the surface proteins on the spirochete become adapted to the vertebrate host, in response to signals from the tick host and the blood meal. Although all stages of the tick can transmit the disease, humans usually become infected by nymphs, which are very small and may be overlooked. Larvae rarely carry *B. burgdorferi* before feeding, and adult ticks are likely to be noticed and removed within a few hours.

Borrelia burgdorferi can survive for 28 to 35 days in guinea pig blood at room temperature, for up to 48 days in human blood processed for transfusion and held at 4°C, and for short periods in urine. However, there are no known cases of Lyme disease resulting from a blood transfusion or contact with infected blood or urine in humans. In dogs, a single case of horizontal transmission has been reported, from an experimentally infected to a control animal.

Disinfection

Borrelia burgdorferi can be inactivated by 1% sodium hypochlorite and 70% ethanol. It is also sensitive to heat and ultraviolet light.

Infections in Humans

Incubation Period

The incubation period in humans is typically 7 to 14 days, but can vary from 3 to 36 days.

Clinical Signs

Both asymptomatic and symptomatic infections are seen in people. The first symptom in humans is a characteristic skin lesion, called erythema migrans; a macule or papule widens and develops into a red, slowly expanding “bull’s-eye” rash with central clearing. The skin lesion may be associated with malaise, fatigue, fever, headache, a stiff neck, myalgia, arthralgia or lymphadenopathy. Secondary cutaneous lesions may appear in other regions. These initial symptoms usually last a few weeks and may recur. Approximately 20-30% of infected people do not develop a rash; some may have no early symptoms while others develop only nonspecific signs.

In the second stage, seen weeks or months later, some patients develop disseminated disease. The most common sign is intermittent pain of one or a few joints, with or without swelling; large, weight-bearing joints such as the knee are most often affected. The arthritis may become chronic and recur for several years. Meningoencephalitis and neuropathies including cranial neuropathy (particularly facial nerve palsy) and radiculoneuritis are less common. Cardiac signs such as myocarditis and transient atrioventricular block, of varying severity, are rare. Multiple erythema migrans lesions may also be seen.

After months or years, some patients enter a third, chronic stage, which may include acrodermatitis chronica atrophicans, neurological abnormalities or chronic arthritis. Severe, disabling disease is infrequent but does occur.

Communicability

There is no evidence that *B. burgdorferi* is a communicable disease in humans. Infection has never been documented after transfusion with infected blood or contact with infected blood or urine. However, laboratory-acquired infections have been reported for the related organisms *B. recurrentis* and *B. duttoni*, and caution is warranted when working with infected clinical specimens and ticks.

Diagnostic Tests

A diagnosis may be made based on clinical signs and epidemiology. Isolation of *B. burgdorferi* in culture (BSK medium) is possible, but often impractical; prolonged observation of cultures is necessary and, in one study, the agent was isolated from only three of 56 patients. *B. burgdorferi* is easier to isolate from skin lesions than blood; the agent was cultured from 80% or more of early skin lesions in some studies. Cerebrospinal fluid has also been positive in some cases.

Serology is often used for diagnosis. Serologic tests include IFA, ELISA and immunoblotting. Cross-reactions with other spirochetes may be seen in some tests. PCR has been used to detect *B. burgdorferi* antigens in skin, blood, CSF and synovial fluid but this technique has not been standardized for routine diagnosis.

Treatment

Early treatment with antibiotics reduces the duration of erythema migrans and may prevent or decrease the severity of the later stages of disease. Later stages of disease may require prolonged treatment with intravenous antibiotics, and treatment may need to be repeated if the symptoms recur. *B. burgdorferi* infections may persist in spite of antibiotics.

Prevention

Lyme disease can be prevented by avoiding endemic areas, and preventing tick bites with protective footwear, clothing, and insect repellents. Ticks may be more visible on light-colored clothing. People who enter tick habitats should check frequently for ticks and remove them as soon as possible; gloves are recommended during tick removal.

In the eastern U.S., habitat modification can decrease the population of *I. scapularis* around homes. Studies have shown that tick populations can be decreased by 72-100% if leaf litter is removed.

A human vaccine was licensed for use in the U.S. in 1998 but was withdrawn from the market by the manufacturer in 2002 after reports of limited efficacy in the field. Previous exposure or infection does not necessarily prevent reinfection; repeated infections have been reported.

Morbidity and Mortality

In 2002, approximately 23,000 cases of Lyme disease were reported in the U.S., with 90% of the cases in 12 states. This figure is likely to underestimate the true incidence of disease, as this disease is considered to be greatly underreported. The overall incidence is approximately 7 per 100,000 population but, in a few regions, the morbidity rate may be as high as 1 to 3% per year. Both genders and all ages are susceptible to Lyme disease but most infections occur in children up to 14 years, and adults 30 years of age and older.

An estimated 5-50% of infected people develop symptomatic disease. All patients with the initial skin lesions do not develop the symptoms of the second stage; in one study, 61% of patients with erythema migrans later developed neurological, articular or cardiac symptoms. Fatal disease is rare and severe chronic disease uncommon.

Infections in Animals

Species Affected

The reservoir hosts appear to be small rodents and other wild mammals, including the white-footed mouse (*Peromyscus leucopus*) in the eastern U.S., and the rodents *Apodemus sylvaticus* and *Clethrionomys* spp. in Europe. Dogs may be able to serve as reservoir hosts. Naturally occurring Lyme disease has been reported in dogs, horses and cattle. Serologic evidence of infection has been seen in cats. Dogs, horses, cats, rabbits, mice, hamsters, gerbils and guinea pigs can be infected experimentally. Wild mammals with evidence of infection include white-tailed deer, white-footed mice, eastern chipmunks, gray squirrels, opossums, and raccoons.

Incubation Period

The incubation period is 2 to 5 months in experimentally infected dogs. The incubation period for natural infections in animals is unknown.

Clinical Signs

Lyme disease has been reported in dogs, horses, cattle, cats and rabbits. Many infections appear to be asymptomatic.

Dogs

The main symptoms in dogs are lameness and arthritis, particularly in the carpal and tarsal joints. The lameness can be intermittent or shift from leg to leg. It may or may not be accompanied by swollen, painful joints. Fever, anorexia, fatigue or lymphadenitis, particularly in the prescapular or popliteal nodes, may be seen concurrently. The arthritis is usually self-limiting but may become chronic or intermittent.

Kidney disease is seen less frequently. This form, which is generally fatal, is characterized by a severe protein-losing nephropathy, uremia, hyperphosphatemia and often peripheral edema.

A rare cardiac form, characterized by conduction abnormalities with bradycardia, and a neurologic form, with facial paralysis, seizures or aggression, have also been reported.

The classic skin lesion seen in humans, erythema migrans, is not seen in dogs; however, in endemic regions expanding skin lesions on the abdomen or other relatively hairless regions, may suggest Lyme disease.

Cats

Although 5-36% of cats are seropositive in surveys, cases of naturally occurring disease have not been published. Conflicting results have been seen in experimental infections: in one study, cats remained asymptomatic while, in another, they developed fever, lethargy, stiffness and arthritis.

Horses

The most common symptoms attributed to *B. burgdorferi* infection are low-grade fever, stiffness or lameness in

multiple limbs, hyperesthesia, muscle tenderness, behavioral changes, and, rarely, swollen joints. Encephalitis, uveitis, dermatitis, edema of the limbs, and abortion have also been reported. Lymphohistiocytic nodules in the dermis have been seen in experimentally infected ponies. Cause and effect have been difficult to document in this species.

Cattle

In cattle, high titers to *B. burgdorferi* in serum or joint fluid have been associated with arthritis and lameness. Cattle appear to be relatively resistant to experimental infection.

Rabbits

Erythema migrans skin lesions, polyarthritis and carditis have been reported in experimentally infected rabbits.

Communicability

There is no evidence that *B. burgdorferi* is communicable to other animals or humans under natural conditions. There is one report of transmission from an experimentally infected dog that excreted spirochetes in its urine to a control animal.

Diagnostic Tests

A diagnosis of Lyme disease is usually based on the clinical signs, epidemiology, elimination of other diseases, laboratory data and response to antibiotics. The CBC, blood chemistry, autoimmune panels and radiographs are generally normal with the exception of results associated with the affected system(s). The joint fluid in chronically affected dogs usually consists of a purulent exudate, with neutrophils the most abundant cell, and rarely contains spirochetes. In acute cases, the volume of joint fluid is often too small to sample.

Serology is useful as an adjunct for the clinical diagnosis. Antibodies can be detected by ELISA, indirect immunofluorescence (IFA) or immunoblotting (Western blotting). Antibodies generally take 4-6 weeks to develop in dogs and horses; immunoblots may not become positive until 10-12 weeks in horses. Either immunoblotting or the C₆ ELISA can differentiate antibody responses to the pathogen from vaccine responses. Serologic diagnosis is complicated by the long incubation period, presence of asymptomatic infections, cross-reactions with other spirochetes, and persistence of titers for months or years. After treatment, titers do not decrease in the IFA, whole cell ELISA or immunoblot tests; however, in experimentally infected dogs, titers in the C₆ ELISA appear to decrease, either from clearance of the organism or sequestration of the organism in immune privileged sites.

Isolation of *B. burgdorferi* is possible but may be difficult; in one human study, the agent was isolated from only three of 56 patients. Organisms may be isolated from joints, periarticular tissue, cerebrospinal fluid (CSF), lymph nodes, skin or other sources, including cardiac tissue in heart disease and renal tissue in kidney disease. *B. burgdorferi* is rarely found in the blood. Barbour, Stoener, Kelly (BSK)

medium is used for isolation and prolonged observation of cultures is necessary. Polymerase chain reaction (PCR) techniques to detect antigens in tissues have been reported in the literature.

Treatment

Treatment with penicillins or tetracyclines usually results in a rapid clinical response in dogs with joint disease; however, incomplete or transient improvement occurs in a significant number of animals. Symptomatic treatment, directed toward the affected organ system, may also be necessary. Cardiac disease may require a pacemaker. *B. burgdorferi* infections can persist in spite of antibiotic treatment.

Prevention

Acaricides can be used to help prevent tick bites. Animals should also be checked frequently for ticks, which should be removed as soon as possible. Both an inactivated, whole cell bacterin and a recombinant Osp A vaccine directed against a surface protein are available for dogs.

Permethrin-treated cotton balls have been used to decrease tick populations on rodent reservoir hosts in the wild; mice use the cotton as nesting material. Rodent bait boxes using fipronil, and amitraz-impregnated posts for deer have also been tried.

Morbidity and Mortality

High rates of exposure are seen in animals in endemic foci. In eastern Connecticut, 50% of gray squirrels, 27% of white-tailed deer, 24% of dogs, 23% of raccoons, 17% of eastern chipmunks and opossums, and 10% of white-footed mice are seropositive. In some parts of the Northeast, antibodies have been found in approximately 50% of adult horses.

Many infections appear to be subclinical. Clinical disease has rarely been reported in horses. Most seropositive dogs also appear to be asymptomatic. In one study, only 14% of dogs with naturally-occurring, *Borrelia*-specific IgG had any symptoms consistent with Lyme disease. In endemic regions, epidemiologic studies suggest that approximately 5% of all infected dogs develop clinical disease. However, approximately 75% of dogs develop arthritis in experimental infections.

The mortality rate varies with the form of the disease. The most common form of Lyme disease in dogs is arthritis, which is not life-threatening. The rare renal form is usually fatal and the cardiac form can cause a life-threatening conduction block. Approximately 15-25% of treated dogs with arthritis develop recurring or chronic infection.

Post-Mortem Lesions

Dogs

In dogs with the kidney form, the kidney cortices may be diffusely light tan or red-brown, and the cortical surface

may contain pinpoint red foci. The medulla often bulges on cut surface. Subcutaneous, mesenteric, perirenal or retroperitoneal edema and ascites may be seen. Pleural effusion and pulmonary edema are also common. Less common lesions include bilateral parathyroid hyperplasia and changes associated with uremia, including mineralization of the pleura or left atrium, pulmonary mineralization, hemorrhages or mineralization of the gastric mucosa or serosa, and bilateral glossal ulcers. Pulmonary artery thrombi and acute myocardial necrosis have also been reported. Microscopically, the kidney lesions are characterized by glomerulonephritis, tubular necrosis and diffuse interstitial lymphoplasmacytic inflammation. Nonerosive arthritis may be seen in dogs with lameness.

Cats

In one study, experimentally infected cats had hepatic degeneration, splenic hyperplasia, plasmacytosis of the regional lymph nodes and pneumonitis. Cats in another study remained asymptomatic.

Horses

In experimentally infected ponies, lesions included lymphohistiocytic nodules in the dermis, particularly near the sites of tick attachment, enlargement of the prescapular lymph nodes, and perivascular and perineural lymphocytic reactions particularly in the skin, fascia and perisynovial membranes.

Internet Resources

Centers for Disease Control and Prevention (CDC)

<http://www.cdc.gov/ncidod/dvbid/lyme/index.htm>

Lyme Disease Network

<http://www.lymenet.org/>

Material Safety Data Sheets – Canadian Laboratory

Center for Disease Control

<http://www.hc-sc.gc.ca/pphb-dgsp/msds-ftss/index.html#menu>

Medical Microbiology

<http://www.gsbs.utmb.edu/microbook>

The Merck Manual

<http://www.merck.com/pubs/mmanual/>

The Merck Veterinary Manual

<http://www.merckvetmanual.com/mvm/index.jsp>

Recent Advances in Canine Infectious Diseases

http://www.ivis.org/advances/Infect_Dis_Carmichael/toc.asp

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