# Lyme Disease

*Lyme Borreliosis,*
*Lyme Arthritis,*
*Erythema Migrans*
*with Polyarthritis*

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## Importance

Lyme disease is a tickborne illness that results from infection with members of the *Borrelia burgdorferi* sensu lato complex. These organisms are maintained in wild animals, but they can affect humans and some species of domesticated animals. Lyme disease was first recognized in the 1970s, when a cluster of juvenile arthritis cases was investigated in the U.S., but its symptoms can be found in European historical records as far back as the early 20th century. This disease has also been detected in Australia, parts of Asia, the province of Ontario, Canada, and recently, the Amazon region of Brazil. Lyme disease in people is readily cured with antibiotics during the initial stage of the illness, when an unusual rash often aids disease recognition. However, people whose infections remain untreated sometimes develop chronic arthritis, neurological signs and other syndromes. Lyme disease in domesticated animals is still poorly understood, and no distinctive rash seems to occur. The illness is best characterized in the dog, where arthritis and nephropathy appear to be the most common sequelae. Clinical signs attributed to Lyme disease have also been reported in other species including horses and cattle.

## Etiology

Lyme disease results from infection by members of the *Borrelia burgdorferi* sensu lato complex, in the family Spirochaetaceae. There are more than a dozen recognized genospecies (genomic groups) in this complex, but some of them do not seem to be pathogenic in people or domesticated animals. Genospecies known to cause Lyme disease in humans include *B. burgdorferi* sensu stricto, *B. garinii*, *B. afzelii* and the recently recognized species *B. spielmanii*. *B. bissettii*, *B. lusitaniae* and *B. valaisiana* may also be pathogenic, based on their isolation from Lyme disease patients in Europe or Asia, and/or studies in laboratory animals. Each genospecies in the *B. burgdorferi* sensu lato complex may cause a somewhat different syndrome. In some genospecies, a few genetic groups appear to be associated with disseminated forms of the illness, while others are associated only with skin lesions. *B. garinii*, which circulates in both mammalian and avian reservoir hosts, is sometimes divided into "bird related" and "mammal or human related strains." However, the isolate found in seabird ticks is nearly identical to some isolates from humans with Lyme disease, and the validity of this division has been questioned.

*B. burgdorferi* s.l. has also been divided into eight serotypes, with *B. burgdorferi* sensu stricto corresponding to serotype 1, *B. afzelii* corresponding to serotype 2, and *B. garinii* containing serotypes 3 to 8.

Genospecies in the *B. burgdorferi* s.l. complex that are not known to cause illness include *B. andersonii*, *B. carolinensis* and *B. americana*, which occur in North America, and *B. japonica*, *B. tanukii*, *B. turdi* and *B. sinica* in Asia. Several new genospecies (including *B. carolinensis* and *B. americana*) were identified recently in wild animals. Other species of *Borrelia*, which cause relapsing fever and other conditions, can cross-react with *B. burgdorferi* s.l. in serological tests.

## Geographic Distribution

Lyme disease has been reported in North America, Europe, Australia and parts of Asia. Until recently, the organism was not thought to be endemic in South or Central America, although there have been isolated reports of human illness from Brazil, Mexico and Colombia. However, *B. burgdorferi* s.l. was recently confirmed to cause endemic cases of Lyme disease in the Amazon region of Brazil. Most of the organisms that cause Lyme disease occur in temperate regions because their vectors, *Ixodes* ticks, can survive only in these climates. *B. garinii*, which can infect both mammalian ticks and the seabird tick *I. uriae*, is an exception. *I. uriae* has a wide distribution that includes both polar and temperate regions in the Northern and Southern Hemispheres, and *B. garinii* has been detected in Alaska, the Antarctic, the Faroe Islands and Iceland. One study reported the occurrence of this genospecies in seabird ticks from Gull Island, Newfoundland, but not at other North American seabird nesting sites (Maine, Newfoundland and Labrador) on the Atlantic coast. Whether organisms in seabird ticks can be transmitted to people is still uncertain.

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Each genospecies varies in its distribution. In North America, Lyme disease results from infection by *B. burgdorferi* sensu stricto. Although Lyme disease has been reported throughout the U.S., the major endemic foci are in the northeastern and mid-Atlantic states, along the Pacific coast and in the north-central U.S. *B. burgdorferi* s.l. is also endemic in Ontario, Canada. *B. bissettii*, which has been linked uncommonly to Lyme disease in Europe, occurs in North America, but it has not been associated with Lyme disease in this location.

In Europe, several genospecies can cause Lyme disease. *B. afzelii* is the most common species in northern Europe, while *B. burgdorferi* s.s. has been reported mainly in western Europe. *B. lusitaniae* occurs in the Mediterranean basin, and seems to be more common than other genospecies in this region. A low prevalence of this organism may be found focally in other countries. *B. spielmanii* has been detected in Germany, France, the Netherlands, Hungary, Slovenia, Ukraine and other countries. *B. valaisiana* has been detected in a number of countries in mainland Europe and in the U.K., as well as in Russia.

In Asia, Lyme disease is mainly caused by *B. garinii* and *B. afzelii*. *B. burgdorferi* s.s. has been detected in Taiwan. *B. bissettii*, *B. valaisiana* and *B. lusitaniae* have also been found in Asian countries.

Within endemic areas, the prevalence of the infection in ticks, humans and animals can be highly focal. For example, one study detected antibodies to *B. burgdorferi* s.l. in 100% of the dogs in one small area of Maine, but in only 2% of the dogs in a nearby region. Migratory songbirds can distribute infected tick vectors during their spring migration, sometimes spreading the organisms beyond their usual geographic range.

## Transmission

Members of the *B. burgdorferi* s.l. complex cycle between tick vectors and wild animal reservoir hosts in endemic areas. The organisms in this complex are transmitted by 3-host hard ticks in the genus *Ixodes*. *B. burgdorferi* s.s. is transmitted mainly by *Ixodes scapularis* (the deer tick; formerly *I. dammini*) in the eastern and midwestern U.S., and by *I. pacificus* (the Western black-legged tick) on the Pacific coast. Other important vectors for the *B. burgdorferi* s.l. complex include *I. ricinus* (the sheep tick or forest tick) in Europe, and *I. persulcatus* (the taiga tick) in Asia and parts of Europe. *B. garinii*, which is transmitted by *I. ricinus* and *I. persulcatus*, can also be transmitted between seabirds by *I. uriae*, the seabird tick. *I. uriae* has occasionally been found on seals, river otters, humans and other mammals. *B. burgdorferi* s.l. also occurs in some ticks that, due to their preferred ecological niche, rarely bite humans. For example, this organism is found in some ticks, known as nidiculous ticks, which live mainly in the burrows, nests or caves of their hosts. Many genospecies of *Borrelia* can circulate in a region, and ticks can have mixed infections. Other insects such as flies, mosquitoes and fleas could be involved in spreading the organism via blood, but there is no evidence that these arthropods are important vectors.

*Ixodes* ticks are widely distributed and feed on a variety of large and small mammals, birds and reptiles. These ticks are usually found in areas where the relative humidity is high at ground level. Reservoir hosts for *B. burgdorferi* s.l. are defined as those animals that can infect a significant number of the ticks that feed on them, Depending on the genospecies of *Borrelia*, they may include small mammals, birds and even some reptiles. Deer are not competent reservoir hosts, but they are important in maintaining tick populations by supplying a blood meal. Reservoir hosts are critical in maintaining Lyme disease in an area. Adult ticks may transmit *B. burgdorferi* transovarially to a very small percentage of the eggs, but the agent diminishes or disappears as the eggs develop into larvae and nymphs. For this reason, ticks must become infected (or reinfected) from a vertebrate reservoir host, and larvae (which have not yet fed) are rarely infected. However, transstadial transmission does occur. Before a tick can transmit the organism to a new host, it must remain attached for some time. During this 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. Transmission is always more likely with longer attachment, but the lag period seems to vary with the genospecies. *B. burgdorferi* s.s. is not usually transmitted before the tick has been attached for 48 hours, while *B. afzelii* can be acquired with an attachment period of less than 24 hours. The minimum attachment period is unknown for some genospecies. Domesticated animals and humans are incidental hosts, and become infected when they are bitten by ticks. Humans in the U.S. usually become infected by nymphs, which are very small (the size of a poppy seed) and may be overlooked long enough to transmit the organism. Dogs are more likely to be infected by adult ticks.

*B. burgdorferi* s.l. is not thought to be transmitted via body fluids or the environment, although it has been reported occasionally in blood, urine, the breast milk of humans with erythema migrans, and colostrum or milk from cattle. This organism has been reported to 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. There are no known cases of Lyme disease resulting from a blood transfusion or contact with infected blood or urine in humans, although transfusion-acquired disease is theoretically possible: *B. burgdorferi* s.s. can be transmitted by blood transfusion in experimentally infected mice. In dogs, one case of horizontal transmission was reported from an experimentally infected to a control animal. In another study, seroconversion was not reported when uninfected and infected dogs were co-housed for a year.

## Disinfection

*Borrelia burgdorferi* s.l. can be inactivated by 1% sodium hypochlorite and 70% ethanol. It is also sensitive to heat and ultraviolet light. This organism does not survive well outside the body.

## Infections in Animals

## Species Affected

### *Reservoir hosts*

Reservoir hosts for *B. burgdorferi* s.l. are considered to be those animals that infect a significant number of the ticks that feed on them. The white-footed mouse (*Peromyscus leucopus*) is the main reservoir host for *B. burgdorferi* s.s. in the eastern U.S. Short-tailed shrews (*Blarina brevicauda*) are also efficient reservoir hosts, and eastern chipmunks (*Tamias striatus*) seem to be important in some states. Rodents that have been implicated as reservoir hosts in the western U.S. include the white-footed mouse (*Peromyscus maniculatus)*, the brush mouse (*Peromyscus boylii)* the western gray squirrel (*Sciurus griseus*), the duskyfooted wood rat (*Neotoma fuscipes)*; and the California kangaroo rat (*Dipodomys californicus*); however, a recent molecular analysis suggests that most of the *Borrelia* species carried by the latter two rodents are uncharacterized species and only a minority is *B. burgdorferi* s.l.. Additional species of rodents, birds and other vertebrates might also be able to act as vectors, especially where the main reservoir hosts are absent.

Animals that have been implicated as reservoir hosts in Europe include yellow-necked mice (*Apodemus flavicollis*), striped field mice (*A. agrarius*) and wood mice (*A. sylvaticus*), and the voles *Clethrionomys glareolus* and *Microtus agrestis*. *Apodemus* spp. mice develop persistent, low level infections and are efficient in transmitting the infection to ticks. *Clethrionomys* spp. can also transmit the infection, but they develop an immune reaction that prevents ticks from feeding completely and molting successfully. Other species implicated as reservoir hosts include shrews, rats, squirrels, dormice, European hedgehogs (*Erinaceus europaeus*), and lagomorphs, particularly the brown hare (*Lepus europaeus*) and the varying hare (*L. timidus*). The reservoir hosts vary with the genospecies. *B. spielmanii* has been associated with dormice, and *B. afzelii*, and *B. burgdorferi* s.s. are found in rodents, but *B. garinii* and *B. valaisiana* can also be detected in birds.

The role of birds as reservoirs for Lyme disease has been controversial. However, pheasants (*Phasianus colchicus*), and some passerine birds including European blackbirds (*Turdus merula*) and song thrushes (*Turdus philomelos*) in Europe, and *Emberiza* spp. (a genus in the bunting family) and *Turdus* spp. in Asia are now considered to be maintenance hosts for *B. garinii* in Eurasia and/or *B. valaisiana* in Europe. *B. garinii* is also linked with seabirds. Pheasants do not seem to be infected by B. *burgdorferi* s.s. in significant numbers. In one study, American robins (*Turdus migratorius*), song sparrows (*Melospiza melodia*) and Northern cardinals (*Cardinalis cardinalis*) were competent reservoir hosts for *B. burgdorferi* s.s. in the laboratory, but Eastern towhees (*Pipilo erythrophthalmus*) and brown thrashers (*Toxostoma rufum*) were not. Gray catbirds (*Dumatella carolinensis*) had some reservoir competence for *B. burgdorferi* s.s. in this experiment, but not in another study.

The role of lizards appears to vary with the species and area. The complement proteins in the blood of many lizards are highly lytic for *B. burgdorferi* s.l., and ticks are less likely to carry the organism after feeding on these lizards; this phenomenon is called zooprophylaxis. In contrast, *B. lusitaniae* seems to be maintained in reptiles in the Mediterranean region. Ticks containing this organism may be spread by birds, but whether birds can also be competent reservoir hosts for *B. lusitaniae* is unknown. .

### *Incidental hosts*

Dogs and wild carnivores may occasionally transmit *B. burgdorferi* s.l. to ticks, but they are not considered to be reservoir hosts. A number of cervid species that have been investigated, including white-tailed deer (*Odocoileus virginianus*), Columbian black-tailed deer (*O. hemionus columbianus*) and other 'mule deer,' roe deer (*Capreolus capreolus*), elk/ red deer (*Cervus elaphus*), fallow deer (*Dama dama*) and moose (*Alces alces)* do not transmit the bacteria to ticks, although they can be important in providing blood meals to adult ticks. Co-feeding, a phenomenon where bacteria are transmitted between ticks feeding on a host even if the host is not infected, has been demonstrated in sheep.

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.

## Incubation Period

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

## Clinical Signs

The syndromes caused by *B. burgdorferi* s.l. in animals are poorly characterized. Many infections appear to be asymptomatic.

### *Dogs*

It has been difficult to reproduce Lyme disease in experimentally infected dogs. In one study, puppies developed transient fever, anorexia and arthritis, sometimes accompanied by lymphadenopathy, with the clinical signs resolving on their own in 4 days. Some puppies had a few recurrent self-limiting episodes of arthritis in the same leg or

a different leg. Susceptibility seems to decrease with age; older puppies were affected less often and the illness resolved in 1–2 days, while adult beagles seroconverted asymptomatically. Syndromes that have been attributed to *B. burgdorferi* in naturally infected dogs include arthritis, kidney disease (Lyme nephritis), cardiac dysfunction and neurological signs. With the exception of transient arthritis, these syndromes have not been reproducible in the laboratory. However, *Borrelia* antigens have been detected in the kidney in cases of kidney disease, and the agent was detected in urine culture from at least one dog. One recent study suggests that Lyme nephritis may be immune complex related.

The most commonly described syndrome in dogs is lameness and arthritis, particularly of the carpal joints. One or a few joints may be involved, and the lameness can be intermittent or shift from leg to leg. It may or may not be accompanied by swollen, painful joints. Fever, anorexia, lethargy/fatigue or lymphadenitis, particularly of the prescapular or popliteal nodes, may be seen concurrently. The arthritis is usually self-limiting but may become chronic or intermittent.

*B. burgdorferi* s.l. has also been associated with a form of kidney disease called Lyme nephritis or Lyme nephropathy. This syndrome is characterized by protein-losing nephropathy and a unique pathology consisting of immune-mediated glomerulonephritis, lymphocytic-plasmacytic interstitial nephritis and diffuse tubular necrosis with regeneration. Some dogs have a history of Lyme arthritis or lameness, but this condition also occurs in a significant number of dogs that were vaccinated for Lyme disease. The clinical signs may be acute or chronic. Most dogs have signs of renal failure, which may include dehydration, anorexia, lethargy, vomiting, polyuria and polydipsia of varying degrees, and weight loss. Vasculitis may cause edema or effusions. Hypertension, thromboemboli and neurological signs can also be seen. Lyme nephritis usually progresses rapidly and is fatal, but a few dogs may live for months. A syndrome of glomerulonephritis and interstitial nephritis has also been reported in Bernese Mountain Dogs, most of which were seropositive for *B. burgdorferi* s.l..

A rare cardiac form, characterized by conduction abnormalities with bradycardia, and a neurologic form, with facial paralysis, seizures or aggression, have also been attributed to Lyme disease. Erythema migrans rashes are not known to occur. Dogs that are referred to specialists with nonresponsive Lyme disease often have other illnesses.

### *Cats*

Very little is known about the consequences of infection in cats. Although 5-47% 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*

In horses, the description of Lyme disease has been based mainly on published case reports. Many horses in endemic areas are seropositive, and most cases are probably subclinical. Clinical signs that have been attributed to *B. burgdorferi* s.l. infection include low-grade fever, arthritis with intermittent or shifting lameness and swollen joints, myalgia, chronic weight loss and myalgia. Neurological signs and skin lesions, as well as rare eye signs (uveitis), cardiac disease, hepatitis, laminitis 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*

Clinical signs that have been attributed to acute Lyme disease in cattle include fever, lameness/ stiffness, with or without joint swelling, and decreased milk production in the acute stage. Erythema, warmth, swelling and hypersensitivity of the skin on the ventral udder were reported as the first signs in two cows. These skin lesions healed with dark sloughing scabs within a few weeks. Laminitis, chronic weight loss, uveitis and abortions have also been reported. The illness is said to occur most often in first calving heifers. Cattle appear to be relatively resistant to experimental infection. In one recent study, calves inoculated with the three European genospecies (10 different Finnish strains) remained asymptomatic.

## Rabbits

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

## Communicability

There is little or no evidence that *B. burgdorferi* s.l. is communicable to other animals or humans under natural conditions. There is one report of transmission from an experimentally infected dog, which excreted spirochetes in its urine, to a control animal. However, another study reported that susceptible dogs co-housed with infected dogs for a year did not seroconvert.

## Diagnostic Tests

A diagnosis of Lyme disease is usually based on the clinical signs, epidemiology (i.e., a history of exposure to ticks in an endemic area), elimination of other diseases, laboratory data and response to antibiotics. The diagnosis is usually presumptive rather than definitive: in most cases, laboratory confirmation is by serology, and many seropositive animals never develop clinical signs. 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 in supporting the clinical diagnosis. Antibodies usually appear in 3-6 weeks in dogs and horses; immunoblots may not become diagnostic until 10-12 weeks in horses. Because the animal usually seroconverts much earlier than the clinical signs appear, paired titers are not generally useful. In the past, a two-tier system that consisted of screening with ELISA or IFA followed by confirmation with immunoblotting was used. In many cases, a single C6-peptide-based assay has replaced the two-tier serologic testing in dogs. An in-house C6 ELISA test, as well as quantified C6 antibody testing from diagnostic laboratories, are available. The C6 test can also be used in horses, with one study reporting sensitivity of 63% and specificity of 100% in recently infected horses. Both the C6 test and immunoblotting can distinguish vaccinated dogs from dogs that have been infected. Antibodies to the C6 antigen occur only during natural exposure. 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, titers in the C6 ELISA decrease in experimentally infected dogs, either from clearance of the organism or sequestration in immune privileged sites.

Isolation of *B. burgdorferi* s.l., detection of nucleic acids by PCR or antigens by immunohistochemistry, or cytology may be possible in some animals, but it is difficult to find the organism with any test. Lack of detection does not mean that the animal is not infected. Organisms may be detected occasionally in the joints (especially synovium), periarticular tissue, muscle, CSF, adrenal tissues, lymph nodes, skin, milk (cattle) or other sources, including cardiac tissue in heart disease and renal tissue in kidney disease. They are rarely found in the blood or urine. *B. burgdorferi* s.l. is fastidious and microaerophilic, and must be cultured on enriched bacteriologic media such as Barbour-Stoenner-Kelly (BSK) or modified Kelly-Pettenkofer (MKP) media. Isolation may take up to 12 weeks, although most cultures may be positive at 1 week. *B. burgdorferi* is a Gram negative spirochete, with a length of 10 to 30 µm and a width of 0.2 to 0.5 µm. Spirochetes from cultures are motile in freshly prepared slides. Organisms can be visualized using dark-field or phase-contrast microscopy, immunofluorescent microscopy, silver staining, Giemsa, or acridine orange stains. They can be confirmed as *B. burgdorferi* sensu lato with specific monoclonal antibodies or by detecting nucleic acids with PCR. PCR can also be used to identify the genospecies. The diagnostic sensitivity of PCR has been reported to be comparable to culture in experimentally infected animals. Postmortem diagnosis can be made, especially in cases of Lyme nephritis, by identifying characteristic lesions and by detecting antigens with immunohistochemistry. However, other dogs with glomerulonephritis may also have positive results in this test.

## Treatment

Dogs with acute Lyme arthritis usually respond rapidly to antibiotics such as amoxicillin or tetracycline derivatives (e.g., doxycycline). Acute cases have generally been treated for 2 weeks, while dogs with chronic intermittent arthritis are usually treated for 4 weeks; however, the optimum period and dose have not been established by clinical trials. Dogs with chronic arthritis that is not responsive to antibiotics may have immune-mediated polyarthropathy, and tend to respond to steroids. Longer term antibiotics may be used for Lyme nephropathy in dogs. Antibiotics or combined antibiotics and anti-inflammatory agents have been used for the treatment of Lyme disease in horses. Symptomatic treatment, directed toward the affected organ system, may also be necessary. Adjunct treatment in canine Lyme nephropathy may include angiotensin-converting enzyme inhibitors, low-dose aspirin, omega-3 fatty acids, dietary therapy, anti-hypertensive drugs, fluids and immunomodulators, but the optimal treatment is still unknown. Whether the organism may persist after treatment is controversial, but persistent infections, based mainly on PCR but also occasionally on skin biopsies, have been reported in experimentally infected dogs.

One author treats Lyme positive dogs that have early signs of Lyme nephropathy but appear outwardly healthy with doxycycline, angiotensin converting enzyme [ACE] inhibitor and low-dose aspirin. These dogs may be stable for longer, although it is not certain that this is due to the treatment. Some clinicians may monitor seropositive dogs for proteinuria as a sign of early Lyme nephropathy.

## Prevention

Acaricides and tick repellents can be used to help prevent tick bites. Animals should also be checked frequently (at least daily) for ticks, which should be removed as soon as possible. Avoidance of tick habitats, such as the woods, reduces exposure. Ticks can especially be found in leaf litter, vegetation, overhanging branches, and brushy or overgrown lawns. Environmental modifications, such as excluding deer from areas near the home, can be helpful as for the prevention of Lyme disease in people.

Several different types of Lyme disease vaccines are currently available for dogs. The use of these vaccines is controversial. Studies of their efficacy are hampered by the difficulty in establishing a definitive diagnosis of Lyme disease, and uncertainty about the prevalence of the various syndromes in seropositive animals. Estimates of vaccine efficacy vary from 50% to 85%. The potential contribution of autoimmunity to Lyme nephritis raise concerns about sensitization from vaccines. Immunity to *B. burgdorferi* s.l.

does not persist for long, and annual boosters are recommended if vaccines are given.

## Morbidity and Mortality

Many animals in endemic regions are seropositive. Antibodies to Lyme disease can be detected in 25% to 90% of healthy dogs in endemic areas, as well as 5% to 47% of cats. In the U.S., 14–25% of horses are reported to be seropositive in the Northeast, with some studies reporting rates as high as 50% in adult horses, and 6–35% in the western states. Studies in horses also report seroprevalence rates of approximately 26% in Poland, 3-5% in Japan, 8% in the Czech Republic, and 49% in Eastern Slovakia. In cattle, studies have demonstrated increased numbers of seropositive animals after exposure to ticks in the field: reported seroprevalence rates were 38% in the spring and 50% in the summer in Minnesota and Wisconsin; 21% to 40% when at pasture, and 36% to 64% after pasturing in Slovenia; and 21-40% when going out to pasture and 37-64% when coming in from pasture in Slovakia. In addition, 27% of Polish cattle with clinical signs were seropositive, and 6% to 34% of cattle in Slovakia had titers, with higher seroprevalence rates in older cows and cattle that were lame or had swollen joints. One study reported that 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 were seropositive in eastern Connecticut. Within an endemic area, the prevalence of the infection can be highly focal. For example, one study reported that the seroprevalence was 100% in dogs in one small area of Maine, but only 2% in a nearby region.

Many infections in animals appear to be subclinical. Although approximately 75% of young puppies develop transient arthritis in laboratory studies, epidemiologic studies in endemic areas suggest that approximately 5% or less of all infected dogs develop Lyme disease. In one study, only 14% of dogs with naturally-occurring, *Borrelia*-specific IgG had any clinical signs that could be consistent with Lyme disease. It is not known how many dogs that become ill have self-limited illness. Private practitioners who use vaccines, as well as those who do not, both report they are seeing fewer cases of Lyme disease. It is possible that fewer naive dogs are being exposed. There is relatively little information on the long-term outcome of infections in dogs, and the incidence of Lyme nephritis is unknown. Whether breed, genetic predisposition or other predisposing factors are involved is unknown. Bernese Mountain dogs might be more susceptible to Lyme disease, but there was no increase in the incidence of lameness or signs of renal disease in seropositive Bernese Mountain dogs followed for 2.5 to 3.0 years. The incidence of Lyme disease in horses is unknown. In a survey of veterinary practitioners in Germany, approximately half reported that they had seen Lyme disease in horses, with 1-10 cases seen each year on average.

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 cardiac disease has been reported to cause a life-threatening conduction block. Approximately 15-25% of treated dogs with arthritis develop recurring or chronic signs.

## Post Mortem Lesions

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### *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.

# Infections in Humans

## Incubation Period

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

## Clinical Signs

Both asymptomatic and symptomatic infections are seen in people. Each genospecies tends to be associated with particular syndromes, and somewhat different clinical presentations may occur in different geographic areas. The disease is more variable in Europe, where several pathogenic genospecies can be found, than in North America.

In clinical cases, the first sign is usually a characteristic skin lesion called erythema migrans. In erythema migrans, a macule or papule widens and develops into a red or bluish-red rash that expands over days or weeks. Its borders are usually distinct and often intensely colored (e.g., bright red), but not raised. The rash often, but not always, takes the form of a "bull's-eye" with central clearing. Occasionally there may be vesicular or necrotic lesions in the center. Erythema migrans is ordinarily painless, but itching is possible. Secondary erythema migrans lesions sometimes appear in other areas. A small number of patients infected with *B. afzelii* or *B. garinii* develop a *Borrelia* lymphocytoma at the site of the tick bite. This lesion appears as a painless bluish-red or reddish-purple nodule or plaque, most often on the ear, nipple, or scrotum, but also on the nose, arms or other areas. It often occurs concurrently with erythema migrans, and is more common in children than adults. *Borrelia* lymphocytoma is very rare in North America. Lyme disease skin lesions may be accompanied by a flu-like illness with malaise, fatigue, fever, headache, a stiff neck, myalgia, arthralgia and/or regional lymph-adenopathy. Approximately 10-20% of infected people do not develop erythema migrans; some may have no early symptoms while others develop only nonspecific systemic signs. The initial symptoms of Lyme disease usually last a few weeks (*Borrelia* lymphocytoma can persist for months) and may recur. These signs eventually disappear even without treatment.

Weeks or months later, some people may develop additional symptoms. The frequency of the various syndromes varies with the organism. Arthritis is especially common in *B. burgdorferi* s.s. infections, and it is seen more often in North American than Europe. It usually occurs as intermittent pain of one or a few joints, with or without swelling; large, weight-bearing joints such as the knee are most often affected. Arthritis may be recurrent or long lasting; it may persist for months or possibly years if not treated. Neurologic signs can be seen with all organisms, but especially *B. garinii*. They may include meningitis, facial palsy, radiculitis (pain or discomfort associated with nerve inflammation) or lymphocytic meningoradiculitis with or without paresis, as well as less common or rare syndromes such as myelitis, cranial neuritis, chorea or encephalitis. The specific neurological signs vary with the organism. Acute symptoms such as facial nerve palsy are usually self-limiting, but some signs can persist for months and sequelae are possible. Cardiac signs. with palpitations, lightheadedness and chest pain may be seen in 4-8% of patients in the U.S. but are uncommon (1% of patients) in Europe. The most frequent cardiac abnormality is transient atrioventricular block, of varying severity, but other arrhythmias, myocarditis, endomyocarditis or pericarditis can also occur.. Rarely, there may be ocular signs including conjunctivitis during the early stages, and uveitis, keratitis, optic neuritis and other conditions late.

After months or years, some patients enter a third, chronic stage, which may include acrodermatitis chronica atrophicans, neurological abnormalities or chronic arthritis. Acrodermatitis chronica atrophicans is a skin condition associated with *B. afzelii* and seen most often on the limbs. It usually occurs six months to several years after the initial signs. It begins as red or bluish-red discoloration of the skin, often accompanied by doughy swelling, followed by slow, progressive skin atrophy in affected areas, with the skin becoming parchment-like and the veins becoming more prominent. Pain, pruritus, hyperesthesia or paresthesia, and altered pigmentation are possible. Acrodermatitis chronica atrophicans almost always occurs in adults, especially women. Late stage neurological complications in Europe may include chronic progressive meningoencephalitis (in less than 5% of those with neurological signs) and multifocal cerebral vasculitis. Severe neurological disease is uncommon in North America. Chronic cardiac signs have also been associated with Lyme disease, but this condition is unproven. Lyme disease does not seem to affect pregnancy or cause congenital infections.

Treatment failures are rare with the currently recommended antibiotic regimens; however, patients treated later may respond more slowly and recovery can take weeks or months. A small proportion (less than 10%) of patients with arthritis do not respond to antibiotic treatment by resolution of the arthritic signs, and have a more prolonged course, with persistence for months or years. Antibiotic-refractory Lyme arthritis is thought to be caused by an autoimmune reaction. A small number of patients with neurological signs, arthritis or acrodermatitis chronica atrophicans may have residual deficits, especially if treatment is delayed until the signs are advanced. Severe, disabling disease is infrequent. Only one human death has ever been attributed to Lyme disease.

Co-infection with another tick-borne disease, especially human granulocytic anaplasmosis (formerly human granulocytic ehrlichiosis) or babesiosis, can alter the clinical signs and response to treatment.

### *Chronic Lyme disease and post-Lyme disease syndrome*

"Chronic Lyme disease" can be a confusing term, because it has been used to describe several different groups of patients, including those with persistent objective signs of Lyme disease such as arthritis or neurological signs; those with nonspecific signs diagnosed as Lyme disease; and those with post-Lyme disease syndrome. Patients with post-Lyme disease syndrome complain of persistent or relapsing nonspecific symptoms such as fatigue, headache, sleep disorders, myalgia, arthralgia, paresthesias, or difficulty with memory or concentration after they have been treated for Lyme disease. The cause of post-Lyme syndrome is not known. There is no clear evidence that the organism persists in

this syndrome, and limited numbers of double-blind studies have shown no benefit to prolonged antibiotic treatment in these patients. Possible causes of post-Lyme disease syndrome may include slow resolution after treatment, persistent undetected infections, autoimmune reactions, post-infective fatigue syndrome (which also occurs after a variety of other infections), and concurrent diseases or conditions. The number of patients reporting symptoms of post-Lyme disease syndrome decreases over time.

## Communicability

There is no evidence that Lyme disease is a communicable disease in humans. There are also no reports of infections after transfusion with infected blood or contact with infected tissues. However, *B. burgdorferi* s.l. can be spread by transfusion in experimentally infected rodents, suggesting that this route is at least theoretically possible. Laboratory-acquired infections have been reported for the related organisms *B. recurrentis* and *B. duttoni*, and infection control precautions are warranted when working with clinical specimens and ticks.

## Diagnostic Tests

Lyme disease is diagnosed by the clinical signs, particularly erythema migrans lesions, in conjunction with epidemiology (e.g., exposure to ticks) and laboratory testing.

Serology is used most often for diagnosis, but the results must be interpreted with caution and in conjunction with clinical signs. The serological diagnosis of Lyme disease in many cases of tiredness and vague ill health without erythema migrans is controversial. The most commonly used screening tests are indirect immunofluorescent-antibody (IFA) assays and enzyme immunoassays including enzyme-linked immunosorbent assay (ELISA) and enzyme-linked fluorescent assay (ELFA). EIA, which can be automated, has in many cases replaced the IFA test. Because cross-reactions occur in screening tests, immunoblotting (Western blotting) is used as a confirmatory test with indeterminate or positive samples. This two-tier process significantly reduces but does not entirely eliminate false positives. A newer test based on the C6 portion of the vlsE protein of *B. burgdorferi* is promising. The C6 ELISA may become accepted as a one-step test in human medicine in North America, but the presence of more than one genospecies may limit its utility in Europe. The CSF/serum antibody index(AI), used together with signs of inflammation in the CSF, is especially helpful in the diagnosis of neurological disease caused by *B. garinii*. The AI response, but not the signs of inflammation, can persist for years after recovery.

Relatively few organisms are found by direct examination of clinical specimens. The use of culture in diagnostic testing is limited because the procedure is labor-intensive, the organism is fastidious, and the sensitivity is greatest in untreated patients with erythema migrans, who can usually be diagnosed by the clinical signs and serology. *B. burgdorferi* s.l. is fastidious and microaerophilic, and it must be cultured on enriched bacteriologic media such as Barbour-Stoenner-Kelly (BSK) or modified Kelly-Pettenkofer (MKP) media. Isolation may take up to 12 weeks, although most cultures may be positive at 1 week. *B. burgdorferi* is a Gram negative spirochete, with a length of 10 to 30 µm and a width of 0.2 to 0.5 µm. Spirochetes from cultures are motile in freshly prepared slides. Organisms can be visualized using dark-field or phase-contrast microscopy, immunofluorescent microscopy, silver staining, Giemsa or acridine orange. They can be confirmed as *B. burgdorferi* sensu lato with specific monoclonal antibodies or by detecting nucleic acids with polymerase chain reaction (PCR) assays. PCR can also be used to identify the genospecies. Culture is most successful early in the course of the disease, in patients with erythema migrans or early neuroborreliosis. On average, *B. burgdorferi* s.l. can be cultured from 50% of erythema migrans lesions, with a range of 20% to 90%. In early studies, the organism could be detected in less than 5% of blood samples from infected patients, but success rates as high as 40% have been reported with high volume plasma culture. It is found in less than 10% of CSF samples, and it is detected in only 1% of joint fluid samples from patients with Lyme arthritis.

PCR protocols have been developed, and can be successfully used on skin biopsies and other samples. The sensitivity is highest for erythema migrans and acrodermatitis chronica atrophicans lesions, as well as for synovial fluid in untreated or partially treated Lyme arthritis. The sensitivity of PCR is low for blood or plasma, but nucleic acids are sometimes found in the CSF, especially early. PCR can be positive if residual nucleic acids from nonviable organisms are present.

## Treatment

Early treatment with antibiotics such as doxycycline or amoxicillin reduces the duration of erythema migrans and prevents late stage complications. Doxycycline is used most often, since it also is effective for human granulocytic ehrlichiosis. Different antibiotics and/or parenteral treatment may be recommended for patients with neurological signs or cardiac involvement. Treatment failures are rare with the currently recommended regiments; however, patients treated later in the course of the disease may recover more slowly. Anti-inflammatory drugs are used in antibiotic-refractory Lyme arthritis. There have been only limited studies on the use of antibiotics for post-Lyme disease syndrome; however, there was no benefit to continuing antibiotics in the studies that have been conducted. Whether the organism can persist after antibiotic treatment is uncertain.

## Prevention

Lyme disease prevention consists of avoiding tick-infested locations in endemic areas, and preventing tick

bites with protective footwear, clothing (e.g., long pants tucked into the boots, and shirts tucked into the trousers), 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.

Environmental modification to decrease tick exposure is more common in North America, where people are often exposed around their homes, than in Europe, where exposure tends to be occupational or recreational. Acaricides and habitat modification, such as the removal of leaf litter and brush, can reduce the population of ticks around the home. Other approaches in development include the use of biological controls such as entomopathogenic fungi (e.g., *Beauveria bassiana* and *Metarhizium anisopliae*), which destroy ticks. Reducing the number of deer in the area (e.g. with deer fencing) can be helpful, because deer support adult ticks by providing blood meals. Studies have also been conducted in treating rodent reservoirs or deer with acaricides, or supplying wild rodents with permethrin-treated cotton balls, which are used as nesting material.

Postexposure antimicrobial prophylaxis (a single dose of doxycycline within 72 hrs) is sometimes given in areas where the risk of infection is high and the tick has been attached for at least 36 hours. Prophylactic treatment is controversial. It is not usually used in Europe.

A human vaccine was licensed for use in the U.S. in 1998 but was withdrawn from the market by the manufacturer in 2002. Problems included poor demand, high cost, the need for a series of 3 vaccinations and boosters to maintain high titers, insufficient titers in approximately 5% of recipients, and theoretical concerns that vaccination might increase the risk of autoimmune arthritis. A 2nd-generation vaccine is being studied.

## Morbidity and Mortality

The incidence of Lyme disease is seasonal and varies with vector activity; in the Northern Hemisphere, most cases are seen from late spring to summer. The prevalence of Lyme disease can be influenced by the ecological niches preferred by the tick vectors. For example, Lyme disease is common in the eastern and midwestern U.S., but uncommon in the Southeast, despite the presence of the vector *I. scapularis* in the latter location. In the Southeast, *I. scapularis* nymphs are much less active in the summer, and the nymphs and larvae are also more likely to feed on lizards, which are not usually competent reservoir hosts for *B. burgdorferi* s.s.

Lyme disease in people is reportable in the U.S., and roughly 20,000 cases are reported each year to the Centers for Disease Control and Prevention (CDC). Residential exposure is common in the U.S., and most cases occur in the Northeast, upper Midwest and West Coast. Incidence rates of 7 to 9.7 per 100,000 population have been reported. However, some authors suggest that difficulty in the interpretation of serological tests leads to overdiagnosis and confusion with other conditions. A significant number of patients with chronic conditions seen at Lyme disease referral centers do not have this disease.

In Europe, exposure tends to be the result of occupational exposure to ticks or recreation in tick habitats, rather than exposure to ticks around the home. Lyme disease is not reportable in most European countries. The estimated incidence varies from 0.7 cases per 100,000 population in the UK and 0.6 cases per 100,000 population in Ireland to 155 cases per 100,000 population in Slovenia, and 100 to 150 cases per 100,000 population in Germany. Many cases may not be reported.

An estimated 5-50% of people infected with *B. burgdorferi* s.l. become ill. In Europe, the seroconversion rate is estimated to be 3% to 6% after a tick bite, with overt clinical signs in 0.3% to 1.4%. Only some patients with erythema migrans and early signs develop late symptoms such as Lyme arthritis. In one study, 61% of patients with erythema migrans developed neurological, articular or cardiac symptoms. Fatal disease is rare, with only one human death attributed to Lyme disease, and severe chronic disease is uncommon. People can become reinfected, usually with a different strain, after approximately 1.5 years.

## Internet Resources

Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov/ncidod/dvbid/lyme/index.htm

Material Safety Data Sheets – Canadian Laboratory Center for Disease Control
http://www.hc-sc.gc.ca/pphb-dgspsp/msds-ftss/index.html#menu

The Merck Manual
http://www.merck.com/pubs/mmanual/

The Merck Veterinary Manual
http://www.merckvetmanual.com/

Recent Advances in Canine Infectious Diseases
http://www.ivis.org/advances/Infect_Dis_Carmichael/toc.asp

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*Link defunct