Lyme disease

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Summary
Lyme disease is among the most frequently diagnosed zoonotic tick-borne diseases worldwide. The number of human cases has been on the increase since the first recognition of its aetiological agent. Lyme disease is caused by spirochete bacteria belonging to the genus *Borrelia*, with *B. burgdorferi* sensu stricto (s.s.) found in the Americas, and *B. afzelii* and *B. garinii*, in addition to *B. burgdorferi* s.s., in Europe and Asia. Environmental factors, such as human encroachment onto habitats favourable to ticks and their hosts, reduced deforestation, increased human outdoor activities, and climatic factors favouring a wider distribution of tick vectors, have enhanced the impact of the disease on both humans and animals. Clinical manifestations in humans include, in the early phases, erythema migrans, followed several weeks later by neuro-borreliosis (meningo-radiculitis, meningitis or meningo-encephalitis), Lyme arthritis and/or *Borrelia* lymphocytoma. In dogs, acute signs include fever, general malaise, lameness, lymph node enlargement and polyarthritis, as well as neuro-borreliosis in the chronic form. Diagnosis is mainly serological in both humans and animals, based on either a two-tier approach (an immunoenzymatic test followed by a Western blot confirmatory test) in humans or C₆ peptide, only in dogs. Early treatment with antibiotics, such as doxycycline or amoxicillin, for three weeks usually reduces the risk of chronic disease. Tick control, including the use of tick repellents for both humans and animals, particularly dogs, is highly reliable in preventing transmission. Vaccines are not available to prevent human infection, whereas several vaccines are available to reduce transmission and the clinical manifestations of infection in dogs.

Keywords

Introduction
Lyme disease (LD), also known as Lyme borreliosis, is certainly among the most frequently diagnosed zoonotic tick-borne diseases worldwide (1). The number of human cases has progressively increased since the first recognition of its aetiological agent (2). The disease is named after the towns of Lyme and Old Lyme, in Connecticut, the United States (USA), where a cluster of arthritis cases was identified in 1975 and tick transmission of the spirochete was identified. Though the name Lyme disease was new, the syndrome was soon recognised to be similar to erythema chronicum migrans and acrodermatitis chronica atrophicans, disease entities recognised in Europe as early as 1883 (3).

Aetiological agent
Lyme disease is caused by spirochete bacteria belonging to the genus *Borrelia*, with *B. burgdorferi* sensu stricto (s.s.) found mainly in the Americas, and *B. afzelii* and *B. garinii* and other species – in addition to *B. burgdorferi* s.s. – reported in Europe and Asia (4). *Borrelia valaisiana* and *B. bissetti* have more recently been proposed as agents of LD. These *B. burgdorferi* sensu lato (s.l.) bacteria are mainly transmitted by *Ixodes* ticks. In fact, the *B. burgdorferi* s.l. complex is a diverse group of bacteria which are distributed worldwide and includes 18 named spirochete species and an as-yet un-named genospecies (5). Of these, 11 species were identified in and are strictly associated with Eurasia (*B. afzelii*, *B. bavariensis*, *B. garinii*, *B. japonica*, *B. lusitaniae*, ...)
Transmission occurs primarily via the deer tick, also known as the black-legged tick (*Ixodes*). In the eastern and north-central USA, *B. burgdorferi* s.s. are endemic. Several ticks of the genus *Ixodes* infect humans or domestic animals (7). Rather, maintenance of *B. burgdorferi* in the environment is dependent on a wildlife reservoir and a transmission vector. *Borrelia burgdorferi* is exceptional among *Borrelia* species in that it is capable of infecting a wide range of tick and vertebrate hosts. Thus, various animals and vectors are responsible for perpetuating *B. burgdorferi* in the different geographic regions in which LD is endemic. Several ticks of the genus *Ixodes* are competent in transmitting LD. In the eastern and north-central USA, the deer tick, also known as the black-legged tick (*Ixodes scapularis*), is the main vector (infection rate > 50%), while in the Pacific states transmission occurs primarily via *I. pacificus*, the Western black-legged tick (infection rate: 1–6%). Transovarial passage of *B. burgdorferi* in *Ixodes* ticks was reported to possibly occur in 1–5% of the ticks (8), suggesting that ticks act as vectors rather than as reservoirs for the spirochete. However, recent data tend to support the theory that transovarial transmission by *B. burgdorferi* does not occur and that *B. miyamotoi* is most probably responsible for early reports of such transmission by *I. scapularis* (9). In the north-eastern USA, the white-footed mouse, *Peromyscus leucopus*, is the primary reservoir of *B. burgdorferi* (3, 7). Mice generally become infected when fed upon by nymphal *I. scapularis* ticks, which acquire spirochetes during their larval feeding on small mammals such as *P. leucopus* (10). Adult *I. scapularis* feed primarily on white-tailed deer (*Odocoileus virginianus*). In northern California, the life cycle of *B. burgdorferi* often involves two tick species. *Ixodes neotomae* is responsible for maintaining the spirochete in the dusky-footed wood rat (*Neotoma fuscipes*), the primary reservoir in that region (8). However, the host range of *I. neotomae* is narrow, so *I. pacificus* is the vector responsible for spreading *B. burgdorferi* infection to other species, including humans and dogs. All three tick stages can be found on humans and domestic animals (11). In California, the Western fence lizard, *Sceloporus occidentalis*, is naturally and experimentally refractory to *B. burgdorferi* s.s. infection. This lizard is also experimentally refractory to *B. bissetti*, which is distributed widely throughout North America and has been implicated as a human pathogen in southern Europe. The complement system of *S. occidentalis* typically destroys *B. burgdorferi* s.l. spirochetes present in the tissues of attached and feeding *I. pacificus* nymphs, thus potentially reducing the probability of transmission of these bacteria to humans or other animals by the resulting adult ticks (12). In Europe, the castor bean tick, *I. ricinus*, is the main vector (8, 13), with an infection rate which varies from 4% to up to 40% (10).

**North America**

Lyme disease is one of the major vector-borne zoonoses to affect humans in the USA and Canada, with approximately 30,000 reported cases and an estimated 300,000 human cases occurring annually in the USA (14). Between 1992 and 2006, a total of 248,074 cases of LD were reported to the Centers for Disease Control by health departments in the 50 US states, the District of Columbia, and US territories (15). The annual count increased 101%, from 9,908 cases in 1992 to 19,931 cases in 2006. During this 15-year period, 93% of cases were reported from only ten states (mainly in the north-east and northern Midwest). The incidence was highest among children aged five to 14 years, and 53% of all reported cases occurred among males. More than 65% of patients with erythema migrans experienced the onset of their illness in June and July, compared with 37% of patients with arthritis. In 2012, 95% of the cases were reported from 13 states: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Vermont, Virginia and Wisconsin (www.cdc.gov/lyme/stats/index.html).

As white-tailed deer serve as an important host for adult black-legged ticks, reducing the deer population may also reduce the tick population and reduce the number of human cases of LD. For this reason, an evaluation of the degree of association between deer density, tick abundance and human cases of LD was carried out in one Connecticut community over a 13-year period (16). After deer hunts were initiated, the number and frequency of deer observations in the community were greatly reduced, as was the number of LD resident-reported cases per 100 households, which was strongly correlated to deer density in the community.
Reducing deer density to 5.1 deer per km² resulted in a 76% reduction in tick abundance, a 70% reduction in the entomological risk index and an 80% reduction in LD resident-reported cases in the community after the deer hunts were carried out.

The geographical distribution of the disease in dogs in the USA matches the distribution in humans. The percentage of positive results for B. burgdorferi antibodies was higher in the north-east (13.3%) than in the three other regions (the Midwest, south-east and West) and was higher in the Midwest (4.4%) than in the south-east (2.5%) or West (1.4%) (17). Furthermore, the percentage of dogs testing positive for B. burgdorferi antibodies and the number of reported human LD cases by state were positively associated, although, in some states, the number of reported human cases was higher (Delaware and New Hampshire) or lower (Rhode Island and South Dakota) than expected, based on canine testing. Therefore, dogs appear to be very good sentinels for B. burgdorferi prevalence (18).

Concerns have been raised about climate changes and their impact on vector-borne diseases (19, 20). An evaluation of the impact of latitude on the rate of change in the incidence of LD in the USA was performed by Tuine et al. (20). State-level, year-on-year incidence rate ratios (IRRs) for LD for the period from 1993 to 2007 were estimated using Poisson regression methods, and between-state heterogeneity in IRRs by using a random-effects meta-analytic approach. Over all, the incidence of LD increased by about 80% between 1993 and 2007. There was marked between-state heterogeneity in the average incidence of LD, ranging from 0.008 per 10⁵ person-years in Colorado to 7.5 per 10⁵ in Connecticut, and significant between-state heterogeneity in temporal trends (p < 0.001). In multivariable meta-regression models, the increasing incidence showed a linear association with state latitude and population density. Similarly, in a recent Canadian study, the rate of spread for black-legged ticks was relatively faster across a larger geographic area along the northern shore of Lake Ontario/ the St. Lawrence River, compared with a slower spread from isolated populations along the northern shore of Lake Erie (21).

Borrelia burgdorferi prevalence in I. scapularis increased in Ontario over the study period from 8.4% in 2008 to 19.1% in 2012. The prevalence of B. burgdorferi-positive black-legged ticks increased yearly during the surveillance period and, while increases were not uniform across all regions, the increases were greatest in the central west region, followed by the eastern and south-west regions.

Central and South America

Lyme disease has been suspected in patients in Mexico (22), as four patients who had received tick bites while visiting forests in Mexico developed skin lesions that met the case definition of erythema migrans, or borrelial lymphocytoma. The disease is probably present and under-reported in Central America. Borrelia burgdorferi antibodies have also been detected in Mexican individuals (23) and B. burgdorferi s.s. was detected in ticks (24), confirming the presence of LD in this country.

In South America, the presence of B. burgdorferi s.l. has been detected in ticks of the I. ricinus complex in both Uruguay (25) and Chile (26). In Chile, the proposed B. chilensis bacterium is carried by endemic I. stilesi ticks, collected from environmental vegetation, and long-tailed rice rats (Oligoryzomys longicaudatus).

Europe

Lyme disease is the most prevalent arthropod-borne disease in the temperate regions of the Northern Hemisphere, with approximately 65,500 patients reported annually in Europe (1). The disease occurs across Europe, with a distribution closely matching that of the vector I. ricinus (1). This tick species can be infected with Borrelia throughout its wide latitudinal range, from northern Turkey and the Atlas Mountains of Tunisia to northern Sweden. Infected-tick density decreases with increasing altitude, although the ticks are now found at up to 1,300 metres. Consequently, the incidence of LD decreases from the endemic areas of central Europe towards the southern and northern limits. In France, for instance, the yearly LD incidence rate averaged 42 cases per 100,000 inhabitants (95% confidence interval [CI]: 37–48), ranging from 0 to 184 per 100,000, depending on region. The annual hospitalisation rate due to LD averaged 1.55 per 100,000 inhabitants (95% CI: 1.42–1.70). Both rates peaked during the summer and autumn and had a bimodal age distribution (5–10 years and 50–70 years) (27).

Asia and other parts of the world

Lyme disease may be an emerging infectious disease in Australia, as four patients who were examined at a medical office over a one-year period from mid-2010 to mid-2011 presented positive polymerase chain reaction (PCR) results from central tissue biopsies of erythema migrans lesions (28). Three sequences were identified as B. burgdorferi s.s. One of the three sequences, though, may have had some similarity to B. bissettii. The fourth sequence was more appropriately placed in the s.l. group and appeared to be similar, but not identical, to a B. valaisiana-type isolate. However, such results still need confirmation by isolation of the spirochetes.
Lyme disease is also present in most of China (29). It was first reported in China in 1985, in a forest region in Hailin County, Heilongjiang Province. The peak of incidence of LD appears to occur from June to August. Its major vectors are I. persulcatus in northern China and I. granulatus and I. sinensis in southern China. Haemaphysalis bispinosa ticks may also act as a vector in southern China. Human cases of LD have been confirmed in 29 provinces/municipalities. The major endemic areas in China are forests in the north-east and north-west. In Heilongjiang, Jilin, Liaoning and Inner Mongolia, over three million people suffer tick bites annually. Of these, approximately 30,000 people become infected with LD and 10% of these new cases may turn into chronic infections without early treatment (29).

### Symptoms and clinical signs

#### Humans

Several days or weeks after a tick bite, if *Borrelia* infection occurs, 60–80% of LD cases develop erythema migrans (a rash or patch on the skin about 10 cm across that may expand peripherally as a palpable band, and may or may not be itchy), although early infection may be completely asymptomatic (1). Other early symptoms include influenza-like symptoms, fever, fatigue, headaches and muscle or joint pain.

Several weeks or months after tick transmission (with or without a previous history of erythema migrans), neuroborreliosis (noted in 10–20% of symptomatic patients in the USA) may occur, in the form of meningo-radiculoitis, meningitis or meningo-encephalitis. Lyme arthritis is more frequent than neuroborreliosis in the USA; whereas the latter is more common in Europe. Borrelial lymphocytoma may occur. Less frequently, multiple erythema migrans or carditis may be diagnosed. Months or even years after *Borrelia* infection, acrodermatitis chronica atrophicans, lymphocytoma, chronic arthritis (fairly rare in Europe), encephalomyelitis or chronic neuro-borreliosis (very rare in Europe) may be observed.

#### Domestic animals

##### Dogs and cats

The dog seems to be the most likely domestic animal to develop the disease, and serves as a sentinel and an appropriate animal model to investigate human LD (30). The first clinical signs are non-specific and do not develop in all dogs; acute signs can be fever, general malaise, lameness, and swelling of the local lymph nodes. Dogs are susceptible to infection with *B. burgdorferi*, but the clinical disease is generally milder, narrower in scope, and less frequent than in humans. Only about 5–10% of dogs exposed to infected ticks develop clinical borreliosis. Clinical borreliosis manifests chiefly as polyarthritis approximately two to six months after exposure and is typically self-limiting. A small percentage of dogs, particularly retrievers, can develop a protein-losing glomerulopathy.

No clinical case of a cat that has been naturally infected with *B. burgdorferi* has been described so far (30). Nevertheless, experimental infections via spirochete inoculation have resulted in short-lived bacteraemia and serological studies have documented immunological evidence of borreliosis in cats (31).

#### Horses and ruminants

Clinical signs of LD in horses may include chronic weight loss, sporadic lameness, laminitis, low-grade fever, swollen joints, muscle tenderness and anterior uveitis (32). In addition, neurological signs such as depression, behavioural changes, dysphagia, head tilt and encephalitis can be seen in chronic cases. Although a broad spectrum of clinical signs has been attributed to *B. burgdorferi* infections in horses, indisputable cases of equine LD are extremely rare so far, if they exist at all (33).

Lyme disease may occur in cattle, usually as a herd problem, but is uncommon. In acute LD, cattle show a fever, stiffness, swollen joints and decreased milk production. Chronic weight loss, laminitis and abortion are also possible outcomes of LD in cattle (32).

#### Diagnosis

The diagnosis of LD in humans and animals is mainly based on serological assays. A ‘two-step approach’ has been widely adopted in human medicine and has improved diagnostic specificity (1). It employs an enzyme immunoassay or indirect immunofluorescence assay, followed by an immunoblotting assay (Western blot). In humans, the detection of immunoglobulin M (IgM) is investigated in early stages of the infection, but has a low specificity. The detection of IgM is not commonly performed for dogs (30). A commercial C6 enzyme-linked immunosorbent assay (ELISA) is available for dogs to document successful treatment approximately four to six months after therapy. C6 positive results from maternal antibodies. The treatment of C6-positive dogs, independent of the presence of illness, should be considered carefully. The use of C6 antibody-testing in veterinary practice is recommended to clarify whether lameness seen in dogs is the result of an infection.
with *B. burgdorferi*, or by other tick-transmitted organisms, such as *Anaplasma phagocytophilum* (30). Co-infections by other tick-borne pathogens should be considered with LD patients (humans or dogs) who present with severe or prolonged manifestations of infection or have anaemia, leukopenia, thrombocytopenia or persistent fever (34).

**Treatment**

Lyme disease is resolved in most human patients with a 10-to-21-day course of treatment with doxycycline (100 mg every 12 h) or amoxicillin (2 g every 8 h) orally. Intravenous ceftriaxone (2 g every 24 h for two to three weeks) may be indicated if the infection is not detected in the early stages or appears refractory to initial treatment protocols (3, 35). For reasons that are poorly understood, some individuals are unable to recover after *B. burgdorferi* infection. These patients may experience chronic peripheral nervous system and central nervous system abnormalities, including depression, fatigue, sleep disorders and memory loss, for months to years after the initial infection (13).

In dogs with LD, contrary to the case in humans, the time of infection cannot be pinpointed as erythema migrans is not observed in most animals. Most cases that the veterinarian decides to treat are in a phase in which the spirochetes have already disseminated into various tissues (30). Treatment of 30 days of doxycycline (10 mg/kg every 12 h) or amoxicillin (20 mg/kg every 8 hr) orally is usually prescribed for symptomatic dogs.

**Prevention**

The prevention of LD in humans and domestic animals relies largely on minimising their exposure to ticks. Tick-infested areas should be avoided whenever possible. When travelling in areas of high tick density, exposure can be minimised by wearing long-sleeved shirts and long trousers tucked into one's socks. Tick repellents and acaricides are available for human and animal use, respectively. Humans should inspect themselves and their pets regularly for ticks, and carefully remove ticks as soon as possible after contact (11, 13). Removal of ticks before 48 h of attachment significantly decreases the likelihood of transmission of *B. burgdorferi* from an infected tick (36).

Concern about immune-mediated adverse reactions has precluded the development of whole-cell vaccines for human use (13). Several vaccines are available for use in dogs. In the USA, these include inactivated whole-organism bacterins or recombinant OspA protein vaccines (3). In Europe, lysate vaccines produced with *B. burgdorferi* s.s. or with *B. garinii* and *B. afzelii* are on the market. Again, the European situation is more complicated as more pathogenic species are present in ticks and complete cross-reactive protection of the vaccine-induced antibodies is not documented.

This mode of prevention is unique, because antibodies induced by vaccination do not fight *Borrelia* in the dog but in the tick (30). Vaccine-induced OspA-specific antibodies circulate in the dog's blood, and are ingested by the tick via the blood meal. OspA antibodies can bind to the OspA-expressing *Borrelia* in the tick, prevent their migration to the salivary glands and thus reduce their growth in the tick. Vaccination must induce high antibody levels in the dog before tick exposure, and the spirochete transfer from ticks to dogs is prevented only during phases with high OspA antibody levels. Hence, frequent revaccination is essential. For most vaccines, primary immunisation is based on two vaccinations given three to four weeks apart. It is recommended that vaccination be repeated six months later and again in another six months' time (one year, in total, after vaccination was initiated). From then on, annual revaccination is sufficient to sustain protective OspA antibody levels.

**Conclusion**

Lyme disease is certainly among the most common vector-borne (tick-borne) diseases in humans and is also quite common in dogs. The fragmented habitat of the *Ixodes* ticks and the expansion of their mammalian hosts have favoured the increase in animal and human cases. Clinical and laboratory diagnostic testing can be challenging and prevention still relies heavily on tick population control and limiting tick infestation. Several veterinary vaccines are available to reduce the risk of clinical disease in pets, but no vaccine is commercially available at present to prevent human infection.
La maladie de Lyme

B. Chomel

Résumé
La maladie de Lyme est l’une des maladies zoonotiques à transmission vectorielle les plus diagnostiquées dans le monde. Le nombre de cas humains n’a cessé de croître depuis la première description de l’agent étiologique. La maladie de Lyme est causée par des bactéries spirochètes appartenant au genre Borrelia: B. burgdorferi sensu stricto (s.s.) est présente dans les Amériques, B. afzelii et B. garinii (en plus de B. burgdorferi s.s.) en Europe et en Asie. L’impact croissant de cette maladie chez l’homme et les animaux est dû à des facteurs environnementaux tels que l’empiètement humain sur les habitats propices aux tiques et à leurs hôtes, le recul de la déforestation et l’accroissement des activités humaines de plein air, ainsi qu’à des facteurs climatiques qui favorisent l’expansion de la distribution des tiques vectrices. Chez l’homme, les manifestations cliniques sont d’abord, en phase initiale, l’apparition d’un érythème migrant suivi quelques semaines plus tard d’une atteinte neurologique ou neuroborréliose (méningo-radiculite, méningite ou méningo-encéphalite), d’une arthrite de Lyme et/ou d’un lymphocytome borrélien. Chez le chien, les signes d’infection aiguë sont une fièvre, un malaise général, une boiterie, un gonflement des ganglions lymphatiques et une polyarthrite, ainsi qu’une neuroborréliose dans les formes chroniques. Chez l’homme comme chez l’animal, le diagnostic repose principalement sur la sérologie : méthode en deux étapes chez l’homme (test immunoenzymatique suivi d’une confirmation par Western blot), détection des anticorps dirigés contre le peptide C6 chez le chien. Une antibiothérapie précoce (doxycycline ou amoxicilline pendant trois semaines) parvient généralement à réduire le risque d’installation chronique de la maladie. Le contrôle des tiques, notamment au moyen de produits répulsifs utilisés chez l’homme et chez l’animal, en particulier le chien, constitue une approche fructueuse pour prévenir la transmission. Il n’existe pas de vaccin contre l’infection humaine ; en revanche, plusieurs vaccins sont disponibles pour réduire les risques de transmission et les manifestations cliniques chez le chien.

Mots-clés

Enfermedad de Lyme

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Resumen
La enfermedad de Lyme figura entre las enfermedades zoonóticas transmitidas por garrapatas que con más frecuencia se diagnostican en todo el mundo. El número de casos humanos no ha cesado de aumentar desde que se describió por primera vez el agente etiológico, que son las bacterias espiroquetas del género Borrelia: B. burgdorferi sensu stricto (s.s.) en el continente americano;
La enfermedad tiene un impacto creciente en el hombre y los animales debido a la influencia combinada de factores ambientales (como la intrusión del hombre en hábitats propios a las garrapatas y sus hospedadores), la menor deforestación, el aumento de las actividades humanas al aire libre y factores climáticos que favorecen una distribución más extensa de las garrapatas. Sus manifestaciones clínicas en el ser humano son, en las primeras fases, un eritema migratorio, seguido, varias semanas después, de neuroborreliosis (meningorradiculitis, meningitis o meningoencefalitis), artritis de Lyme y/o linfocitoma por *Borrelia*.

En el perro, los signos agudos son fiebre, malestar general, cojera, inflamación de los ganglios linfáticos y poliartritis, así como neuroborreliosis en la forma crónica de la enfermedad. Tanto en humanos como en animales el diagnóstico es principalmente serológico, con empleo de un método en dos etapas (ensayo inmunoenzimático seguido de una prueba de confirmación por Western blot) en el caso del hombre o bien la detección del péptido C6, solo en el caso del perro. En general, un tratamiento precoz con antibióticos como la doxiciclina o la amoxicilina durante tres semanas reduce el riesgo de cronicidad. Un medio muy fiable para prevenir la transmisión consiste en luchar contra las garrapatas, en particular aplicando productos repelentes tanto a personas como a animales, sobre todo a los perros. No hay vacuna alguna que sirva para prevenir la infección humana, pero existen varias que reducen la transmisión y las manifestaciones clínicas de la infección en el perro.

**Palabras clave**


### References


