



# Lyme disease/borreliosis as a systemic disease



Virendra N. Sehgal, MD<sup>a,\*</sup>, Ananta Khurana, MD<sup>b</sup>

<sup>a</sup>*Dermato-Venereology (Skin/VD) Center, Sehgal Nursing Home, A/6 Panchwati, Delhi, 110 033, India*

<sup>b</sup>*Department of Dermatology, 1 Dr RML Hospital and Postgraduate Institute of Medical Education and research (PGIMER), New Delhi*

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**Abstract** Lyme disease/borreliosis (LD) is a well-known arthropod-transmitted entity in the northern hemisphere. The incidence of LD is reportedly rising throughout the world, although better diagnostic facilities may be contributory. The disease distribution is expanding in Europe, with its presence being now documented at higher altitudes and latitudes. *Borrelia burgdorferi sensu lato* is the most important genospecies leading to LD, although newer ones continue to be discovered. The variations in clinical spectrum with genospecies involved are an interesting feature. The alteration in gene expression while the organism cycles between two very different hosts is intriguing and has been described. The disease presents in three stages—namely, the early localized, early disseminated, and late stage. Erythema chronicum migrans is the pathognomic early lesion, and its diagnosis is purely clinical; however, laboratory diagnosis is essential for later manifestations. Two-tier serologic testing using an enzyme-linked immunosorbent assay (ELISA) as the first tier and immunoglobulin M (IgM) and IgG immunoblot as the second, if ELISA is positive or equivocal, is the mainstay of diagnosis. Doxycycline is the cornerstone of treatment, whereas parenteral therapy, mainly with ceftriaxone, is indicated in a few specific scenarios.

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Lyme disease (LD) is an infection, an acute inflammatory disease that is caused by a spirochete, *Borrelia burgdorferi*, transmitted by tick bite<sup>1</sup>.

The disease has a wide distribution across North America, Europe, and parts of Asia, covering more than 70 countries of the world. Its horizon has been on the increase, acquiring the global reckoning.<sup>2</sup> Initially, LD presents with cutaneous features at the site of the tick bite, which may ultimately lead to neurologic and cardiac disorders and involvement of the joints; thus, it is best described as a

multisystem disease in which the initial expression is on the skin, at the site of a tick bite.

## Epidemiology

LD is one of the most common arthropod-borne diseases in the northern hemisphere.<sup>3</sup> The disease was named after Lyme, a small town in New London County, Connecticut, where it was first recognized and described in 1975.<sup>4</sup>

The incidence of LD seems to have been increasing worldwide, although its reporting is sporadic. The role of improved diagnostics, greater awareness, and misdiagnosis cannot be overlooked.<sup>5</sup> The Centers for Disease Control and

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\* Corresponding author. Tel.: +91 11 27675363; fax: +91 11 2767 0373.  
 E-mail addresses: [drsehgal@ndf.vsnl.net.in](mailto:drsehgal@ndf.vsnl.net.in), [sehgalvn@yahoo.co.in](mailto:sehgalvn@yahoo.co.in)  
 (V.N. Sehgal).

Prevention (CDC) has estimated that the annual incidence of LD in the United States (US) is about 300,000.<sup>6</sup>

Its incidence is highest in the northeast, the mid- and south Atlantic regions, and the upper Midwest regions of the United States.<sup>6</sup> The states most affected include Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Wisconsin.<sup>7</sup> The corresponding figure for Europe is around 65,500/year.<sup>8</sup> Although its incidence seems to be stabilizing in Europe, LD geographic distribution is still expanding due to the current presence of vector at higher altitudes and latitudes.<sup>9</sup> LD is also widely distributed in China, with an average infection rate of 5.06% in the human population.<sup>10</sup> Infection rates among forest people in the northeast area, inner Mongolia, and Xinjiang Uygur Autonomous Region of China stand even higher at more than 10%.<sup>10</sup> The disease is of public health significance in Russia as well, where it is the most common tick-borne infection.<sup>11</sup> The incidence has been stable in Japan for more than a decade now.<sup>12</sup> The disease does not have much presence in the Indian subcontinent, with only a few scattered reports.<sup>13,14</sup>

## Etiology

The causative organism of LD, the spirochetes belonging to the genus *Borrelia*, was isolated by Willy Burgdorfer, from the mid-guts of *Ixodes* ticks, in 1982.<sup>15</sup> Subsequently, it was given the name *Borrelia burgdorferi*. The spirochete is a thin, spiral-shaped bacterium with unique corkscrew motility. The later is conferred by the presence of two endoflagella within the periplasmic space, the space that lies between a semi rigid peptidoglycan helix and a multilayer, flexible outer membrane sheath. The organism has a linear chromosome and 21 plasmids that are extrachromosomal strands of DNA and allow *Borrelia* to adapt very rapidly to changes in the environment.<sup>16</sup>

Various genospecies of the organism have since been isolated. The three most well established and common are *Borrelia burgdorferi sensu stricto*, *B. afzelli*, and *B. garinii*. They together have been termed *Borrelia burgdorferi sensu lato*.<sup>16</sup> *B. burgdorferi sensu stricto* is the only pathogenic genospecies in North America, but all three are etiologic agents of LD in Europe. *B. Garinii* is the most common genospecies reported from Asia.<sup>17</sup> In addition, seven other genospecies were described in the 1990s, including *B. japonica*, *B. turdi*, and *B. tanukii* from Asia, *B. andersonii* from North America, *B. lusitaniae* and *B. valaisiana* from Europe, and *B. bissettii* from both Europe and Asia<sup>18</sup>; furthermore, eight species—namely *B. sinica* (Asia), *B. spielmanii* (Europe), *B. yangtze* (Asia), *B. californiensis*, *B. americana*, *B. carolinensis* (North America), *B. bavariensis* (Europe), and *B. kurtenbachii* (North America)—were delineated in the years up to 2010.<sup>18–25</sup> Of these 18 genomic

species, *B. afzelli*, *B. burgdorferi*, and *B. garinii* are the established agents of localized and disseminated manifestations of LD, whereas *B. lusitaniae*, *B. bissettii*, and *B. valaisiana* have been detected in specimens from occasional cases only.<sup>17,21,22,25</sup>

The clinical presentations of LD may vary according to the genospecies involved. Although all pathogenic genospecies may cause erythema migrans, different genospecies are also associated with other clinical manifestations of the disease.<sup>9</sup> *B. afzelli* is mostly associated with chronic skin manifestations, *B. garinii* is the most neurotropic, and *B. burgdorferi sensu stricto* seems to be the most arthritogenic<sup>26</sup>; thus the disease has more diverse clinical presentations in Europe, where a larger number of genospecies produce the disease, than in North America, where *B. burgdorferi sensu stricto* is the predominant genospecies implicated.

Hard ticks of *Ixodes* species are the arthropod vectors of LD. *Ixodes ricinus* is the main vector in Europe, *I. persulcatus* in Asia, *I. scapularis* (deer tick) in northeastern and upper Midwestern United States, and *I. pacificus* in the western United States.<sup>17,27</sup>

The *Ixodes* ticks have a three-stage life cycle consisting of larva, nymph, and adult, each lasting 1 to 2 years. The tick feeds only once during each stage, with each blood meal lasting for a few days—about 3 days for larvae, 5 for nymph, and 7 for adult female.<sup>17</sup> In between the meals, the tick lies on the ground in leaf litter for months, while completing its moult.<sup>28</sup> The adult female lays a batch of eggs in litter and then dies. The total life cycle is completed in 2 to 6 years, depending on the climate, host availability, and the effects of development delaying diapause mechanisms.<sup>29</sup> A minimum relative humidity of 80% is required for their survival in soil surface.<sup>30,31</sup>

The typical habitat usually consists of deciduous or mixed woodland, occasionally coniferous, with a substantial understory and a layer of decaying vegetation on the ground.<sup>17</sup> Ticks acquire *Borrelia* while feeding on an infective host, or when feeding close to an infected tick on the same, even uninfected host (transmission by cofeeding) or while feeding from a site where an infected tick has recently finished feeding (localized extended cofeeding).<sup>9</sup>

The major natural reservoirs for *B. burgdorferi* (and source of the organisms for ticks) are mice, chipmunks and other small mammals, and birds.<sup>32,33</sup> Some degree of reservoir host preference has been reported for the different genospecies (eg, association of *B. afzelli* with rodents and *B. garinii* with birds).<sup>34</sup> Deers are not competent hosts but are important in sustaining the life cycle of vector ticks. Deer ticks (*I. scapularis*) are important vectors for LD in the northeastern and upper Midwestern United States, as mentioned earlier (vide supra). Similarly cattle are also incompetent hosts.

Ticks transmit the *Borrelia* to humans when they enter its natural habitats for occupational or recreational purposes. The seasonality of the activity of ticks and of recreational use

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