REVIEW ARTICLE

Lyme Disease: An Emerging Threat

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Abstract

Lyme disease (LD) is a multisystem inflammatory zoonosis affecting the skin, heart, nervous system, and joints, transmitted by ticks and caused by infection with species of the *Borrelia burgdorferi sensu lato* (*B. burgdorferi s.l.*) complex. It is the most common emerging vector-borne disease in the United States. The Centers for Disease Control and Prevention (CDC) estimated the annual occurrence of 3,29,000 cases of LD in the United States during 2005–2010, and it increased to 4,76,000 during 2010–2018. The incidence of various clinical manifestations of LD differs among countries or regions based on the prevalent genospecies of the *B. burgdorferi s.l.* complex responsible for infection. Ticks of *Ixodes* spp. are the main vectors involved in the transmission of LD, which occurs mainly during the spring season. However, in North America and Europe, there is a rise in temperature due to global warming, leading to the extension of tick habitats toward northern areas. These ticks now stay active for an extended period of the year, increasing the chances of transmission to humans, and it is postulated to be one of the reasons responsible for the rising cases of LD. Early diagnosis and treatment with appropriate antibiotics can resolve the early manifestations of LD and prevent subsequent complications, which are known to occur if not treated appropriately.

The disease is most common in rural areas and is difficult to differentiate clinically from other tropical infections such as rickettsial infections. The literature on LD in India is limited; however, LD has been reported from at least 12 states of India. A recently concluded study by the Indian Council of Medical Research (ICMR) has documented the seroprevalence of this disease in eight sites situated in areas of North (Himachal Pradesh and Haryana) and Northeast India (Meghalaya, Assam, Mizoram, and Tripura). LD remains grossly underdiagnosed in India. The lack of awareness among clinicians regarding the prevalence of LD and the limited availability of diagnostic investigations may have contributed toward it. LD should no longer be confined to textbooks, but it should find a place in the list of differential diagnoses in clinical practice. This review is an endeavor to sensitize physicians regarding LD and its impending rise worldwide due to global warming.

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Introduction

The diseases transmitted by ticks are the most common emerging vector-borne diseases and are currently identified as a major public health threat to humans in many countries. Lyme disease (LD) or Lyme borreliosis is caused due to infection by spirochetes [*Borrelia burgdorferi sensu lato* (*B. burgdorferi s.l.*) or Lyme borrelia] transmitted by specific species of *Ixodes* ticks (Fig. 1). LD is the most common tick-borne infectious disease in areas of North America and Eurasia with moderate climates. It has attained the status of being a disease of public health importance in those regions.[1]

Lyme disease was first described in 1977 in children living in Old Lyme, Connecticut, by Steere et al. while investigating a cluster of patients suffering from arthritis.[2] The spirochete (*B. burgdorferi*) responsible for LD was identified in 1981 from the nymph form of the tick *Ixodes scapularis*. Although LD as a clinical entity has been described recently, however, in the United States, spirochete-specific DNA sequences were identified by polymerase chain reaction (PCR) from tick specimens preserved in museums, which were collected in the early 1900s. Since 1977, the reported cases of LD have increased from various geographical areas.[2,3]

Lyme disease is a multisystem inflammatory zoonosis affecting primarily the skin, nervous system, heart, and joints. Recently, the magnitude of tick-borne diseases has increased and expanded worldwide.[1] The Centers for Disease Control and Prevention (CDC) estimated the annual occurrence of 3,29,000 cases of LD in the United States during 2005–2010, and it increased to 4,76,000 during 2010–2018.[4] The incidence of various clinical manifestations of LD differs among regions due to the fact that the prevalent genospecies of B. *burgdorferi s.l.* complex causing infection differs in different areas. *B. burgdorferi s.l.* complex is a diverse group of spirochete genospecies distributed worldwide. Of these genospecies, three commonly and four occasionally infect humans, causing Lyme borreliosis.[5] Early diagnosis and appropriate antibiotic treatment can resolve the early manifestations of LD and prevent subsequent complications, which are known to occur if not treated appropriately.[6]

Lyme Disease in India

In India, there is a paucity of epidemiological data on LD; however, in 1990, Patial et al. reported the first case of LD from Shimla, Himachal Pradesh.[7] Now, new cases of LD are being increasingly reported, which are suspected clinically and diagnosed mainly by enzyme-linked immunosorbent assay (ELISA) due to the nonavailability of confirmatory assays. A study by Sharma et al. conducted in Nilgiri hills, Tamil Nadu, during 1992, has reported serologically positive cases of LD.[8] A study by Praharaj et al. revealed a 13% prevalence of LD among military personnel in Northeast India.[9] The samples from Nagarhole to Bandipur forest ranges in the Western Ghats of Karnataka reported a seroprevalence of 19.9% by ELISA, and 15.6% of these seropositive samples confirmed LD by Western blot.[10] During the period from 1990 to 2019, the presence of LD has been documented in the eastern (Assam, Arunachal Pradesh, Nagaland, Meghalaya, Manipur, and Bihar), northern (Himachal Pradesh, Uttarakhand, Haryana, and New Delhi), and southern (Kerala and Karnataka) parts of India.[11] The reported numbers of LD may be an underestimate of actual cases due to the nonavailability of community-based data and the lack of laboratory diagnostic tests. A recently concluded study by the Indian Council of Medical Research (ICMR) has documented the seroprevalence of LD in eight sites situated in the states of North (Haryana and Himachal Pradesh) and Northeast India (Meghalaya, Assam, Mizoram, and Tripura).[12]

Ecology

Lyme disease has been primarily documented in areas where ticks of the *Ixodes* species are prevalent. The small animals maintain a low level of spirochetemia and act as the reservoir of infection. The disease is most

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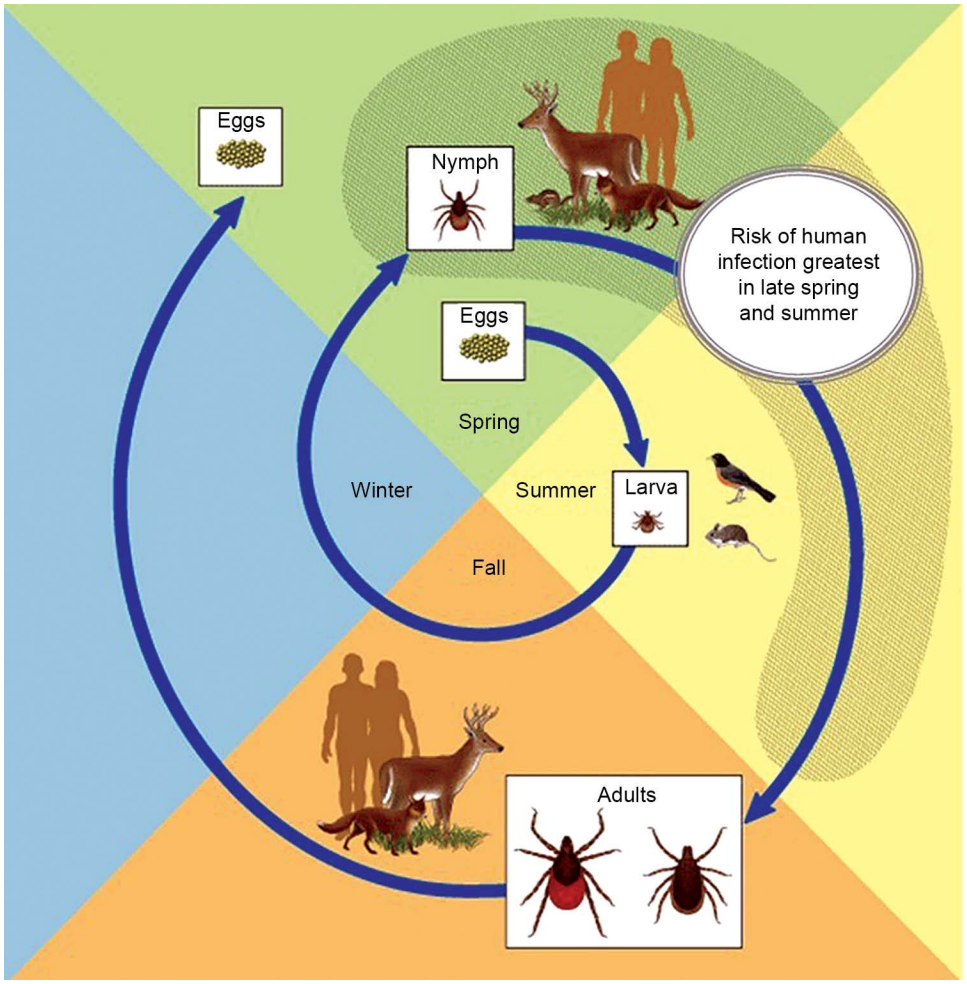

Fig. 1: Life cycle of tick and transmission of LD (*source*: https://www.cdc.gov/lyme/index.html)

common in rural areas and is difficult to differentiate clinically from other tropical infections such as rickettsial infections.[1] There is a lack of coordinated multicentric studies and significant gaps in knowledge on the local distribution and etiological agents causing LD in the Indian subcontinent.

In North America, *B. burgdorferi sensu stricto* remains the single species of Lyme borrelia pathogenic to humans. *Borrelia afzelii*, *Borrelia garinii*, *B. burgdorferi*, *Borrelia spielmanii*, and *Borrelia bavariensis* are known to cause the disease in Europe and are responsible for more diverse clinical manifestations of LD in European regions than in North American areas.[13]

In Europe, *B. afzelii* and *B. garinii* infections are responsible for the majority of cases of LD, whereas *B. garinii* is more common in Asia. *B. afzelii* is commonly reported with skin manifestations; neurological involvement is most common with *B. garinii* infection, whereas arthritis is most common with B. *burgdorferi*.[14]

The main vector for LD is ticks of the *Ixodes* species.[15] Of the total 20 known genospecies of *B. burgdorferi s.l.* species complex, currently six are pathogenic to humans. The transmission of *B. burgdorferi s.l.* is closely related to the life cycle of *Ixodes* ticks. The lifecycle of the tick consists of four stages: (1) egg, (2) larva, (3) nymph, and (4) adult. The tick needs to feed only once during every active stage. The unfed (flat) tick is present in the soil, which attaches to the skin of a host animal passing through vegetation. It drops off to the soil again after feeding, where it may take several months for development into the next stage.[16]

The spirochetes are transmitted during feeding *via* the injection of saliva of the tick. During the process of feeding of a tick on a (reservoir) host, the transmission of spirochetes can occur from an infected tick to a host or vice versa (systemic transmission). This route is mainly responsible for the transmission of spirochetes from an infected host to ticks, and the larval form of the ticks is not important as a vector of LD, as transovarial transmission of spirochetes is rare.

The nymphs are mainly involved in the transmission of *B. burgdorferi s.l.* to new hosts; the adult ticks feed on hosts like deer.[16] The recreational activities and forestry around peri-urban areas or rural areas cause the transmission of LD. Small mammals such as rabbit, rodents, and some bird species are the main vertebrate reservoirs for LD borrelia. Humans are infected inadvertently. In the life cycle of the tick, the role of deer is essential because of their ability to sustain adult ticks in large numbers in the habitat; however, deer are not said to be competent reservoirs for the spirochetes.[16]

Pathogenesis

The spirochetes are deposited by an infected tick into the skin of a host animal during feeding, which subsequently get disseminated through blood or tissue planes from the bite site to other sites of the human body. The capacity of hematogenous dissemination of *B. burgdorferi* is strain-dependent.[17] In order to transmit *B. burgdorferi* to humans, the tick requires a prolonged feeding time period of 36 hours or more.[18]

After feeding on a reservoir host, spirochetes acquired by the tick are carried

in the midgut of the tick for spirochetes multiplication and the expression of outer surface protein C (OspC). The expression of OspC allows spirochetes to invade the salivary glands of the host tick. This process of expression of OspC is essential for transmission and establishment of infection in a mammalian host, and this process takes several days; however, the exact mechanism is still unknown. The time taken for the expression of OspC can explain the delayed transmission of spirochetes to the next host.[19]

After acquiring infection, the spirochetes are killed by the human body by expression of adaptive and innate immune responses. However, Lyme borrelia are said to persist despite a robust cellular and humoral immunological response of the human body.[16] *B. burgdorferi* is postulated to evade immune system-mediated destruction by binding to host complement regulators and inhibiting the activation of the complement cascade. A newly described mechanism of pathogenesis of LD has described that complement regulator-acquiring surface proteins (CRASPs) block the activity of complement.[18] This pathway might be responsible for favoring spirochete transmission to the vertebrate host and determining the preference of host reservoirs of *B. burgdorferi* genospecies. The tissue damage in LD is postulated to be due to host inflammatory reactions, as spirochetes do not produce toxins, and the severity of the inflammatory response is determined by the genospecies of *Borrelia* causing infection.[14]

Clinical Manifestations

As per the European definition adopted in 1995, in Serock, at the World Health Organization (WHO) conference, LD is suspected in a patient with a previous history of exposure to ticks followed by the development of the typical signs and symptoms consistent with Lyme borreliosis involving mainly the skin, musculoskeletal system, nervous system, and heart. As per Asbrink and Hovmark, LD can be defined as early LD and late LD.[20,21] Gerber et al. have described LD as an early localized form, early disseminated disease, and late LD.[22] As per a review published in 2015, LD starts as typical erythema migrans (EM); 45–60% of patients develop arthritis, 11% will show neurologic disease, and about 4–8% of patients manifest with cardiac disease.[23]

Early Lyme Disease

It often manifests as localized EM (Fig. 2), a single skin lesion. About 70–80% of infected persons will develop this at the site of a tick bite. It usually starts appearing on average 7 days (from 3 to 30 days) after a tick bite. The area of lesion (>5 cm in diameter) is round, flat, or slightly raised, with erythema expanding in diameter over days to weeks. There can be an area of central clearing (classic target lesion), but its appearance can vary widely, and the classic target lesion may not always appear. The lesion is rarely itchy or painful, but may feel warm to touch. The systemic symptoms such as fever, headache, chills, fatigue, malaise, arthralgias or myalgias, and regional lymphadenopathy may accompany EM; however, the systemic symptoms and lymphadenopathy may occur without a rash.[21–25]

Early Disseminated Lyme Disease

Early disseminated LD includes patients with multiple EM,[21–25] isolated cranial nerve palsy, meningoradiculoneuritis, meningitis, and carditis.[24] In a cross-sectional study of 213 adults with untreated EM, the formation of multiple EM occurred in 2–18%, which was associated with spirochetemia and systemic symptoms, including fever and chills.

Neurological Symptoms

The neurological symptoms may arise in about 10% of patients concurrently with skin findings or weeks after the skin lesion. In adults, the disease typically presents as unilateral or bilateral painful meningoradiculoneuritis (Garin–Bujadoux–Bannwarth syndrome) and facial palsy. These manifestations are known to occur in isolation or in association with each other. The radiculitic pain can be severe, and following treatment with appropriate antibiotics, the pain decreases rapidly. LD is known to involve the VI cranial nerve, and the involvement of IV or III cranial nerve is less frequent. Plexopathy, mononeuropathy, mononeuropathy multiplex, acute inflammatory demyelinating polyneuropathy are other manifestations described. In the initial stages, meningitis due to LD is limited to the base of the brain with headaches of moderate intensity; however, features typical of meningitis are less frequently observed.[21–25]

Lyme Carditis

It typically arises in about 4–10% of untreated patients within about 1 month (averaging 21 days) after exposure to a tick. The manifestations include atrioventricular (AV) block and/or myopericarditis. The patient may present with dyspnea, palpitations, edema, lightheadedness, syncope, and chest pain.[21–25]

Borrelial Lymphocytoma

It is a rare cutaneous manifestation which occurs ranging from weeks extending up to months after the initial infection.

A solitary bluish-red plaque, papule, or nodule of a few centimeters in size, most commonly located on the earlobe, and less commonly on the nipple or scrotum. It is more common in children and is caused mainly by *B. afzelii* in Europe.[25]

Late Lyme Disease

It usually includes arthritis, acrodermatitis chronica atrophicans (ACA), and other rare features of neurological involvement. The commonly described division of LD into different stages of disease is theoretical, and various clinical findings may not always follow this pattern.

Lyme Arthritis

The involvement of the musculoskeletal system is typical for LD. Lyme arthritis can develop following the tick bite after a period ranging from several weeks up to years, but commonly after 6 months. In the initial weeks after acquiring infection, about 60% of patients develop migratory pain in large joints, bone, periarticular soft tissues and muscles, which can be recurrent in a few patients. The symptoms commonly present unilaterally, which can subside spontaneously or can manifest into full-blown arthritis.[21]

During the course of LD, the manifestation of arthritis is a late development. It usually manifests after months of a tick bite or EM. The patient may not recall the tick bite. Patients can present with swelling of one or more large joints, and the knee joint is most commonly affected. The joint involvement can be persistent or intermittent, lasting for months to several years, with minimal systemic symptoms.[21]

A study was conducted on 55 antibiotic-untreated patients with EM followed prospectively through the period of arthritis. The development of arthritis varied from 4

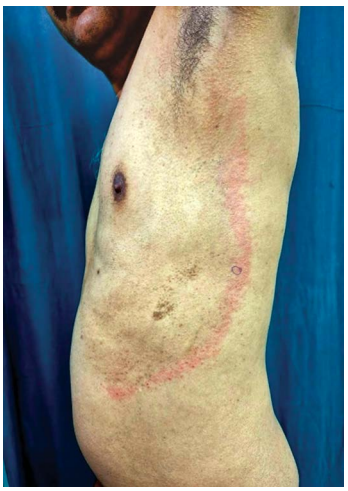

Fig. 2: Erythema migrans (*courtesy*: Dr G Verma)

days up to 2 years after the onset of EM. The intermittent/persistent arthritis involved primarily the knee joint and lasted for several years. However, during earlier episodes, there was involvement of periarticular sites and other small or large joints, including the temporomandibular joint, with involvement of less than five joints at one time. There is often swelling of the knee joint, and rupture of Baker's cysts was commonly observed. Fever and other constitutional symptoms were not common with arthritis.[26]

On examination, monoarthritis of the knee or oligoarthritis affecting the knees was most common, but other small or large joints such as wrist, elbow, shoulder, and ankle were also involved. The knee joints showed very large effusions and were not painful on weight bearing or with movements involving range of motion.[26]

Acrodermatitis Chronica Atrophicans

It is a late and chronic manifestation of LD. ACA mainly involves the distal parts of the extremities, characterized by chronic cutaneous atrophy that does not resolve spontaneously. During the initial inflammatory phase of the disease, it includes focal hyperpigmentation and edema with a bluish-red discoloration of the skin. It can be accompanied by pruritus, pain, or paresthesias of the involved skin. If not treated at this stage, ACA may progress to the atrophic phase, with thinning of the epidermis and dilated veins becoming visible with a shiny appearance or "cigarette paper skin." ACA may be accompanied by inflammatory changes of neighbouring joints and peripheral neuropathy. The bilateral extensor surfaces of the limb are primarily affected, and bony prominences in the ulnar or tibial regions may develop fibroid nodules. This late-stage of LD is more resistant to treatment, and due to the delayed presentation of ACA, the majority of patients may not recall being bitten by a tick.[21,27]

Late Lyme Neuroborreliosis

The features of late Lyme neuroborreliosis are less common and are more frequently reported in Europeans than in patients from the United States. A monophasic, slowly progressive encephalomyelitis, involving white matter mainly, is the severest of neurological presentation. Chronic encephalitis and/or myelitis of neuroborreliosis are less frequent. Chronic encephalomyelitis may have an irregular course and can mimic cerebral ischemic attacks, manifesting as paresis of limb, abnormalities of speech, cerebellar involvement, seizures, visual field defects, progressive dementia, and lethargy. The manifestation of neuroborreliosis in isolation and/or in combination with joint symptoms is common in Europeans than in patients from the United States.[25,28] Cerebrospinal fluid (CSF) examination may reveal slightly raised protein levels with lymphocytic pleocytosis, and glucose concentration is normal with intrathecal production of antibodies against Lyme borrelia.[29] More than half of patients with a long-lasting ACA skin lesion can present with features of peripheral neuropathy of the involved limb.[28]

Lyme Encephalopathy

A mild chronic encephalopathy in patients with late-stage LD may be a common neurologic symptom. The typical symptoms are nonspecific, for example, fatigue, sleep disturbances, depression, and diffuse memory loss. A study compared patients with LD having normal CSF with those having CSF abnormalities and normal controls. The memory test scores in patients with abnormal CSF were lower than normal controls. The presence of fatigue and depression was significantly more common in patients in the LD group than in controls, irrespective of CSF findings. The presence of active neurologic disease, the possibility of residual neurologic deficits from past infection, and the psychological consequences of chronic illness are different factors postulated for cognitive dysfunction in patients with LD.[29]

Post-Lyme Disease Syndrome

Few (about 10%) patients with LD may continue to experience cognitive dysfunction and musculoskeletal pain even after completing the antibiotic treatment prescribed as per recommendations.[4,30] This is called post-Lyme disease syndrome (PLDS) or posttreatment Lyme disease syndrome (PTLD). Persistent inappropriate immune activation and inflammation, persistence of antigenic debris, persistent infection, or the presence of these factors in combination are postulated hypotheses for PLDS/PTLD. The presence of PLDS/PTLD appears to correlate with more severe illness at presentation, delayed antibiotic treatment, and the presence of disseminated disease, but the duration of the initial antibiotic treatment does not appear to be related to PLDS/PTLD.

In 2006, Wormser et al. proposed the following criteria of PLDS:

- A patient with a documented episode of early or late LD fulfilling the case definition of the Centers for Disease Control and Prevention.
- After recommended treatment of the episode of LD, there is resolution or stabilization of the objective manifestation(s) of LD.
- Onset of any of the following subjective symptoms within 6 months of the diagnosis of LD and persistence of continuous or relapsing symptoms for at least a 6-month period after completion of antibiotic therapy: fatigue, widespread musculoskeletal pain, complaints of cognitive difficulties, and sleep disturbances.

Diagnosis

The presence of clinical features consistent with LD, along with assessment of the risk of exposure to ticks, is most important for the diagnosis of LD. The characteristic appearance of EM with a potential exposure of the individual to ticks in an endemic area forms the mainstay of clinical diagnosis of LD; however, the laboratory confirmation remains essential in view of the fact that clinical manifestations of LD are nonspecific. The hematological investigations—hemoglobin, platelet, and total leukocyte counts—are usually normal with a slightly raised erythrocyte sedimentation rate (ESR) in all stages of LD. In early localized LD and early disseminated LD, particularly in patients having EM, mild transaminitis can be observed in 20–35% of patients.

In neuroborreliosis due to LD, CSF examination typically shows slightly increased protein levels, pleocytosis with >90% lymphocytes, and normal glucose concentration. In Lyme arthritis, the synovial fluid examination may show 500–100000 white blood cells (WBCs)/mm^3, predominantly polymorphonucleocytes.[31]

Serology

The detection of characteristic EM remains the mainstay for a clinical diagnosis, and serological tests for the demonstration of antibodies to LD are rarely positive at this stage. The serological assays are indicated in atypical cases only. It takes 2–4 weeks for the appearance of immunoglobulin M (IgM) antibodies after the appearance of EM; the titers peak after 6–8 weeks, and then, after 4–6 months of onset of symptoms, levels gradually decline to low levels. The appearance of immunoglobulin G (IgG) antibodies takes 4–6 weeks after EM, peaks at 6–8 weeks, and remains detectable for years, even after appropriate treatment. In disseminated or late-stage LD nearly all patients will show IgG antibodies against *B. burgdorferi*. The IgG antibodies can be detected by immunoblot in patients who remain symptomatic for a period of 4 weeks or more.[32,33]

For patients with LD presenting without EM, the CDC currently recommends a two-step test for the diagnosis of LD. The first step consists of a sensitive enzyme immunoassay (EIA) or immunofluorescence assay; those who test positive or show equivocal results are confirmed by a second Western immunoblot assay (Fig. 3).[34] The immunoblot assay provides the specificity of the antibodies, and the presence of positive "bands" denotes the presence of antibodies against specific protein antigens of *B. burgdorferi*. The presence of antibodies against at least either two IgM antibodies or five IgG antibodies specific to *B. burgdorferi* proteins by immunoblot is accepted as positive for the diagnosis of LD by most authorities.[24] However, in 2019, the Food Drug and Administration (FDA) cleared a modified methodology for the diagnosis of LD and recommended the use of a second EIA instead of the Western immunoblot assay.[34]

In highly endemic areas with background seropositivity, the additional testing of PCR in synovial fluid for suspected Lyme arthritis, testing of intrathecal antibody in CSF in patients suspected of neuroborreliosis due to LD, or obtaining skin biopsies for suspected ACA or borrelial lymphocytoma might contribute toward increasing the chances of the diagnosis of LD. Due to the fact that IgM/IgG antibodies remain persistent for years even after successful treatment, a positive serological test does not always indicate active LD, and the routine use of serology is not recommended for following up patients after treatment.[35]

False Results

The ELISA test can be falsely positive for LD in patients suffering from other spirochetal diseases (e.g., syphilis), rheumatic diseases, and some bacterial infections (e.g., bacterial endocarditis).[36]

Culture

For the diagnosis of LD in routine clinical practice, the culture of *B. burgdorferi* is not recommended. It requires expert manpower, long incubation on special media with lower sensitivity.[37]

Polymerase Chain Reaction

The detection of DNA of *B. burgdorferi* by PCR from patients with EM is positive, and the majority of pretreatment synovial fluid samples from patients with Lyme arthritis also yield positive PCR results.[38]

Intrathecal Antibody Production

The use of CSF and serum has been done to demonstrate selective central nervous system (CNS) production of anti-*B. burgdorferi* antibodies. The evidence of intrathecal antibody production is specific for the diagnosis of neuroborreliosis due to LD.[25] In Europe, the detection of intrathecal antibodies against *B. burgdorferi* forms the mainstay of the diagnosis of neuroborreliosis due to LD. The demonstration of these antibodies in CSF was reported to precede antibody detection in serum in some European patients, and these antibodies are known to persist for years even after recommended treatment.[29]

American Academy of Neurology criteria for the diagnosis of neuroborreliosis[39]:

- Possible exposure to Ixodes ticks in a Lyme-endemic area.
- One or more of the following:
  - EM.
  - Histopathologic, microbiologic, or PCR proof of *B. burgdorferi* infection.
  - Immunologic evidence of exposure to *B. burgdorferi*.
- Occurrence of a clinical disorder within the realm of those associated with LD, without other apparent cause.

Treatment

The treatment of LD with antimicrobial therapy is usually successful when treated early in patients with EM. The treatment may be less effective after disease progression which may require an extended treatment regimen. Successful treatment is directed toward the eradication of infection causing clinical manifestations and to prevent the occurrence of new complications or relapse due to LD.[4] The details of the treatment regimen recommended by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR) for the treatment of LD are given in Table 1. As per recent guidelines, no treatment is required for PLDS.[39]

Lyme Carditis

The treatment of Lyme carditis has evolved in the last few years. In some patients, the use of a pacemaker may be indicated in addition to antibiotics. Besant et al. proposed a risk stratification tool, the Suspicious Index in Lyme Carditis (SILC) Score, with the acronym COSTAR (constitutional symptoms, outdoor activities, male sex, tick bite, age <50, and EM rash), with high (93–100%) sensitivity, to evaluate the likelihood of Lyme carditis in patients with high degree AV blocks.[40] The use of doxycycline, amoxicillin, or cefuroxime axetil is recommended in mild cases of heart block, that is, first-degree AV block with a PR interval <300 ms; however, injection ceftriaxone is indicated for severe heart block, that is, first-degree symptomatic AV block with a PR interval ≥300 ms, or second- or third-degree AV block.[41] In a review, Yeung and Baranchuk reported that the symptoms of Lyme carditis usually resolve spontaneously, the

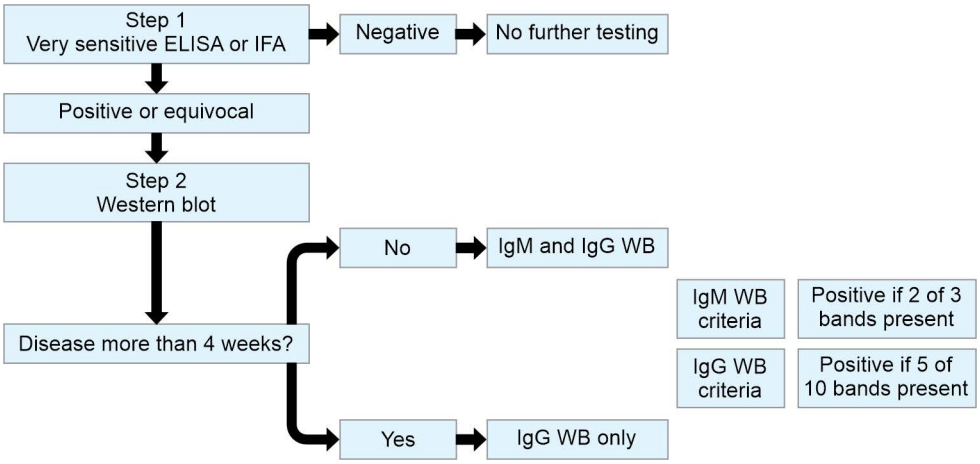

Fig. 3: Current CDC recommendations on serologic diagnosis of LD (*source*: https://www.cdc.gov/lyme/index.html)

Table 1: Treatment of specific manifestations of LD[37]

Disease manifestation	*Route*	*Medication*	*Duration days*
Erythema migrans	Oral	Doxycycline	10
		Amoxicillin or cefuroxime axetil	14
		Azithromycin	5–10
Meningitis or radiculopathy	Oral	Doxycycline	14–21
	IV	Ceftriaxone	14–21
Cranial nerve palsy	Oral	Doxycycline	14–21
Carditis	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	14–21
Arthritis	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	28
Initial treatment	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	28
Recurrent or refractory arthritis	IV	Ceftriaxone	14
ACA	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	21–28
Borrelial lymphocytoma	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	14

use of antibiotics shortens the duration of illness, prevents further progression of the disease, and they further recommended a systemic approach for the diagnosis and management of Lyme carditis and high-degree AV block (Fig. 4).[42]

Lyme Arthritis

The use of an oral antibiotic for 28 days has been recommended for the treatment of Lyme arthritis. For patients with Lyme arthritis with mild residual joint swelling after oral antibiotic use, there are no recommendations for or against a second course of antibiotics. However, patients who do not respond or still have moderate to severe joint swelling with minimal reduction of the joint effusion after a course of oral antibiotics, the use of intravenous ceftriaxone for 2–4 weeks is recommended over a second course of oral antibiotics. The use of antibiotics longer than 8 weeks is not expected to provide additional benefit to patients with persistent arthritis if the treatment regimen included intravenous therapy. For patients with persistent arthritis even after a course of oral antibiotics followed by intravenous antibiotics, the guidelines recommend referral to a rheumatologist for consideration of the use of disease-modifying antirheumatic drugs, biologic agents, intra-articular steroids, or arthroscopic synovectomy.[41]

Neuroborreliosis

Patients suffering from facial palsy due to LD may improve spontaneously, and a course of oral antibiotics will prevent sequelae. However, patients with meningitis, encephalitis, and encephalopathy will require hospitalization and treatment with intravenous ceftriaxone for 28 days. Patients presenting with late neurological LD affecting the central or peripheral nervous system should be treated with intravenous therapy. The response of neurological symptoms to treatment can be slow and often incomplete, and maximum improvement of neurological symptoms may take up to 6 months irrespective of the treatment regimen used.[41]

Prevention

Prevention mainly targets tick and human behavior. Preventative ecological techniques focus on the reduction of hosts responsible for harboring ticks, the reduction of the population of ticks, and reducing the chances of transmission of pathogenic infection in ticks or hosts. IDSA recommends the following measures for the prophylaxis of LD.[39]

Personal Protective Measures

A person who is at risk of exposure to ticks should practice personal protective strategies to decrease the chances of exposure to tick and acquiring infection from pathogens transmitted by tick (good practice statement).

Repellents to Prevent Tick Bites

To prevent tick bites, *N*, *N*-diethyl-meta-toluamide (DEET), picaridin, ethyl-3-(*N*-n-butyl-*N*-acetyl) aminopropionate (IR3535), oil of lemon eucalyptus (OLE), p-Menthane-3,8-diol (PMD), 2-undecanone, or permethrin are recommended by the IDSA (strong recommendation, moderate-quality evidence).

Removal of Attached Ticks

The Infectious Diseases Society of America has recommended prompt removal of attached ticks by mechanical means using a clean fine-tipped tweezer (or a comparable device) inserted between the tick body and the skin (good practice statement).

Antibiotic Prophylaxis to Prevent Lyme Disease

The Infectious Diseases Society of America has recommended the use of antibiotic prophylaxis, within a period of 72 hours only, upon identified high-risk tick bite, but not for equivocal-risk or low-risk bites (strong recommendation, high-quality evidence).

A tick bite is designated as high risk only upon meeting the following three criteria: the tick bite was from (i) an identified *Ixodes* spp. vector species (ii) occurring in an area highly endemic for LD, and (iii) the tick remained attached for ≥36 hours.

A single dose of doxycycline is used for prophylaxis (adult: 200 mg and children: 4.4 mg/kg maximum dose of 200 mg).

Human Vaccine

Currently, no vaccine is commercially available for human use against LD. However, in 1998, the FDA licensed the use of LYMERix for the prevention of LD in the adult population. The vaccine was based upon recombinant outer surface protein A (Osp-A), and three doses of vaccine were required to be given over two tick seasons. An efficacy of up to 76% has been reported for the prevention of LD upon completion of three doses of the vaccine.[4]

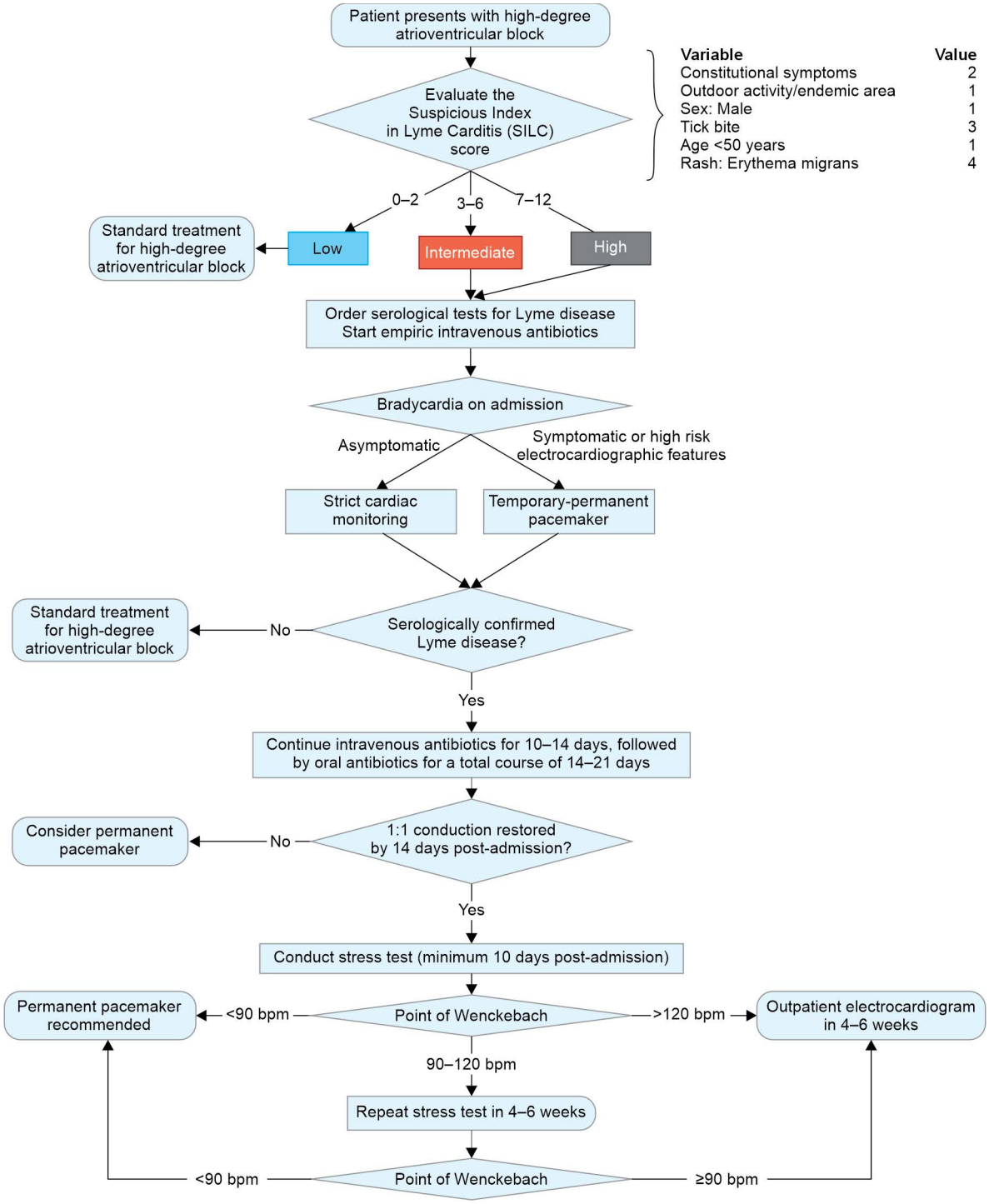

Fig. 4: Systemic approach to the diagnosis and management of Lyme carditis and high-degree AV blocks (Yeung and Baranchuk)[40]

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References

1. Stanek G, Wormser GP, Gray J, et al. Lyme borreliosis. Lancet 2012;379:461–473.
2. Steere AC, Malawista SE, Snydman DR, et al. Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Arthritis Rheum 1977;20(1):7–17.
3. Forrester JD, Vakkalanka JP, Holstege CP, et al. Lyme disease: what the wilderness provider needs to know. Wilderness Environ Med 2015;26(4):555–564.
4. Bobe JR, Jutras BL, Horn EJ, et al. Recent progress in Lyme disease and remaining challenges. Front Med 2021;8:666554.
5. Rudenko N, Golovchenko M, Grubhoffer L, et al. Updates on *Borrelia burgdorferi sensu lato* complex with respect to public health. Ticks Tick Borne Dis 2011;2(3):123–128.
6. Chomel B. Lyme disease. Rev Sci Tech 2015;34(2):569–576.
7. Patial RK, Kashyap S, Bansal SK, et al. Lyme disease in a Shimla boy. J Assoc Physic Ind 1990;38(7):503–504.
8. Sharma RS, Verghese T, Gupta RS, et al. Epidemiology of Lyme disease in the Nilgiri hills—1992—a preliminary report. In: Proceedings of the 3rd Symposium of Vectors and Vector Borne Diseases. Mumbai, India: Haffkine's Institute; 1992.
9. Praharaj AK, Jetley S, Kalghatgi AT. Seroprevalence of *Borrelia burgdorferi* in North Eastern India. Med J Armed Forces India 2008;64(1):26–28.
10. Babu K, Murthy KR, Bhagya M, et al. Seroprevalence of Lymes disease in the Nagarahole and Bandipur forest areas of South India. Indian J Ophthalmol 2020;68(1):100–105.
11. Negi T, Kandari LS, Arunachalam K. Update on prevalence and distribution pattern of tick-borne

diseases among humans in India: a review. Parasitol Res 2021;120(5):1523–1539.
12. ICMR Project: Clinical and Epidemiological Study of Lyme Disease. A Multi-centric Task Force Study in India; 2025.
13. Fingerle V, Schulte-Spechtel UC, Ruzic-Sabljic E, et al. Epidemiological aspects and molecular characterization of *Borrelia burgdorferi s.l.* from southern Germany with special respect to the new species Borrelia spielmanii sp. nov. Int J Med Microbiol 2008;298(3–4):279–290.
14. Strle K, Drouin EE, Shen S, et al. *Borrelia burgdorferi* stimulates macrophages to secrete higher levels of cytokines and chemokines than *Borrelia afzelii* or *Borrelia garinii*. J Infect Dis 2009;200(12):1936–1943.
15. Gray JS. Review. The ecology of ticks transmitting Lyme borreliosis. Exp Appl Acarol 1998;22(5):249–258.
16. Steinbrink A, Brugger K, Margos G, et al. The evolving story of *Borrelia burgdorferi sensu lato* transmission in Europe. Parasitol Res 2022;121(3):781–803.
17. Wormser GP, Brisson D, Liveris D, et al. *Borrelia burgdorferi* genotype predicts the capacity for hematogenous dissemination during early Lyme disease. J Infect Dis 2008;198(9):1358–1364.
18. Zajkowska J, Grygorczuk S, Kondrusik M, et al. New aspects of pathogenesis of Lyme borreliosis. Przegl Epidemiol 2006;60(Suppl 1):167–170.
19. Pal U, Yang X, Chen M, et al. OspC facilitates *Borrelia burgdorferi* invasion of *Ixodes scapularis* salivary glands. J Clin Invest 2004;113(2):220–230.
20. Asbrink E, Hovmark A. Classification, geographic variations and epidemiology of Lyme borreliosis. Clin Dermatol 1993;11(3):353–357.
21. Biesiada G, Czepiel J, Leśniak MR, et al. Lyme disease: review. Arch Med Sci 2012;8(6):978–982.
22. Gerber MA, Shapiro ED, Burke GS, et al. Lyme disease in children in southeastern Connecticut. Pediatric Lyme Disease Study Group. N Engl J Med 1996;335(17):1270–1274.
23. Borchers AT, Keen CL, Huntley AC, et al. Lyme disease: a rigorous review of diagnostic criteria and treatment. J Autoimmun 2015;57:82–115.
24. Murray TS, Shapiro ED. Lyme disease. Clin Lab Med 2010;30(1):311–328.
25. Stanek G, Fingerle V, Hunfeld KP, et al. Lyme borreliosis: clinical case definitions for diagnosis and management in Europe. Clin Microbiol Infect 2011;17(1):69–79.
26. Arvikar SL, Steere AC. Diagnosis and treatment of Lyme arthritis. Infect Dis Clin North Am 2015;29(2):269–280.
27. Gade A, Matin T, Rubenstein R, et al. Acrodermatitis chronica atrophicans. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
28. Halperin JJ, Shapiro ED, Logigian E, et al. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. Neurology 2007;69(1):91–102.
29. Hansen K, Lebech AM. The clinical and epidemiological profile of Lyme neuroborreliosis in Denmark 1985-1990. A prospective study of 187 patients with *Borrelia burgdorferi* specific intrathecal antibody production. Brain 1992;115(Pt 2):399–423.
30. Ścieszka J, Dąbek J, Cieślik P. Post-Lyme disease syndrome. Reumatologia 2015;53(1):46–48.
31. Steere AC, Glickstein L. Elucidation of Lyme arthritis. Nat Rev Immunol 2004;4(2):143–152.
32. Brown SL, Hansen SL, Langone JJ. Role of serology in the diagnosis of Lyme disease. JAMA 1999;282(1):62–66.
33. Tugwell P, Dennis DT, Weinstein A. Laboratory evaluation in the diagnosis of Lyme disease. Ann Intern Med 1997;127(12):1109–1123.
34. Mead P, Petersen J, Hinckley A. Updated CDC recommendation for serologic diagnosis of Lyme disease. MMWR Morb Mortal Wkly Rep 2019;68(32):703.
35. Fallon BA, Pavlicova M, Coffino SW, et al. A comparison of Lyme disease serologic test results from 4 laboratories in patients with persistent symptoms after antibiotic treatment. Clin Infect Dis 2014;59(12):1705–1710.
36. Bunikis J, Barbour AG. Laboratory testing for suspected Lyme disease. Med Clin North Am 2002;86(2):311–340.
37. Ružić-Sabljić E, Maraspin V, Cimperman J, et al. Comparison of isolation rate of *Borrelia burgdorferi* sensu lato in two different culture media, MKP and BSK-H. Clin Microbiol Infect 2014;20(7):636–641.
38. Li X, McHugh GA, Damle N, et al. Burden and viability of *Borrelia burgdorferi* in skin and joints of patients with erythema migrans or Lyme arthritis. Arthritis Rheum 2011;63(8):2238–2247.
39. Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical practice guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN) and American College of Rheumatology (ACR): 2020 guidelines for the prevention, diagnosis, and treatment of Lyme disease. Clin Infect Dis 2021;72(1):e1–e48.
40. Besant G, Wan D, Yeung C, et al. Suspicious index in Lyme carditis: systematic review and proposed new risk score. Clin Cardiol 2018;41(12):1611–1616.
41. Meyerhof JO. Lyme disease; 2023.
42. Yeung C, Baranchuk A. Diagnosis and treatment of Lyme carditis: JACC review topic of the week. J Am Coll Cardiol 2019;73(6):717–726.