Lyme Disease: Etiology, Transmission, Impact and Control

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ABSTRACT

Lyme disease is an infection caused by bacteria known as Borrelia burgdorferi sensu lato, is the most widespread vector-borne disease in the United States, and transmitted to human beings through the bite of Ixodes tick. However, significant portion (10-30%) individuals may experience ancillary non-specific symptoms that last months after the completion of therapy. The group of symptoms known as post-treatment Lyme disease syndrome (PTLDS), a form of the more general term "chronic Lyme disease," includes tiredness, cognitive impairment, and musculoskeletal discomfort. These symptoms are linked to disability and last longer than six months. Patients with nonspecific symptoms assumed to be caused by a supposed persistent Borrelia burgdorferi infection and may or may not exhibit signs of Lyme disease are referred to as having chronic Lyme disease. The diagnosis of PTLDS and chronic Lyme disease has become more and more important in immunologists' practices because it is difficult to diagnose. ELISA and western blot testing are useful in diagnosing Lyme disease. The cornerstone of care is still antibiotic therapy. This chapter reviews the evidence that supports current understanding of the life cycle, historical biogeography, and evolution of Ixodes spp., the ticks that carry the Lyme disease, as well as their methods of dispersal, and disease-transmission mechanisms, and the efficacy of vector control interventions.

Key words: Lyme disease, Borrelia burgdorferi, Tick-borne diseases, PTLDS, Lyme Arthritis

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1. INTRODUCTION

Lyme disease is a vector borne zoonotic disease that is usually caused by bacteria known as *Borrelia burgdorferi* sensu lato. A tick vector of the disease, *Ixodes scapularis*, spreads in different regions of North America and became a major cause of the upsurge of Lyme disease in the above mentioned region of America between 2004 and 2016 (Pitrak et al. 2022). The disease shows the symptoms like arthritis in the beginning of the infection. Later on, different kinds of rashes appear on the body and in some sever cases it associated with the different kinds of disorders involving the nervous and cardiac systems (Coburn et al. 2021). The first clinical manifestation of the Lyme disease was elaborated by Buchwald in 1883 and referred the formation of lesions as diffused idiopathic skin atrophy. Afterwards, the continuous study revealed many interesting facts about the Lyme disease such as the serum analysis of the patient affected with the disease had very high number of antibodies titers which supported the argument that the disease caused by a microorganism (Cardenas-de la Garza et al. 2019).

Lyme disease is a kind of arthritis. In its initial stages it causes skin rash, fever, fatigue, and headache. If it remains untreated for a long time, it penetrates to the joints, heart, and nervous system as well. Lyme disease is a multisystem zoonotic bacterial vector borne disease caused by *Borrelia burgdorferi* sensu lato that is transferred due to the bite of infected *Ixodes pacificus* or *Ixodes scapularis* ticks. *Borrelia Burgdorferi* supported in nature in enzootic cycle containing numerous vertebrate species; humans are accidentally infected when manifested by infected ticks in highly forested areas. Almost 30,000 outlined cases and approximately 300000 cases occurring yearly. *Borrelia burgdorferi* is frequently outlined vector borne disease in the United States of America. It constitutes about 62.6 percent of increasing outlined vector borne disease cases. Most cases of Lyme disease arise in Northeastern and North Central States where number of endemic and highly prevalent countries is continue to inflate (Bisanzio et al. 2020).

Lyme disease was first identified in 1976 when a bunch of juvenile arthritis cases was identified. Many of these patients also have cutaneous skin lesions that are identical to those of outlined in Europe that were formerly related with tick bites. There was a strong impression that infectious agent was fundamental cause of both of the cases in old Lyme, CT and also in Europe. But later in 1982 the spirochete presented in Ixodes ticks was recommended to be the cause. The part of this bacterium as infectious agent named *Borrelia burgdorferi* as the causative agent of Lyme disease was rapidly developed as the bacterium was retrieved from both patients and as well as from reservoir host, such as in white footed mice. While it was first identified because of its relation with arthritis, it became obvious that arthritis was a later stage indication and that acute infection was personified with a distinctive erythema migrans rash, and in some cases with the involvement of cardiac and neurological system (Coburn et al. 2021).

2. HISTORY

The Midwest focus for Lyme disease historically focused on forested areas of Wisconsin and Minnesota, which present habitats that are extremely worthy for *Ixodes scapularis* populations and *B. burgdorferi* hosts in both regions and where first Midwestern cases of Lyme disease were stated (Gardner et al. 2020).

Lyme disease appears in North America, Europe, and Asia. However; the majority of cases occur in certain endemic locations. It is the most prevalent vector-borne illness in Europe and North America. Vector tick species differ substantially according to their geographic location. The most common vector in the United States is *Ixodes scapularis*. *I. pacificus* is without a doubt the most significant vector in the western United States. From 1993 to 2013, the prevalence in the United States nearly tripled. The geographic region has expanded in tandem with the rise in incidence. Inadequately discussed Lyme

disease is a major problem, and it is predicted that the real frequency is eight times higher than that reported (Cardenas-de la Garza et al. 2019).

3. POST-TREATMENT LYME DISEASE SYNDROME

Even after receiving correct therapy, some persons (5% to 15%) may endure persistent weariness, achiness, or headaches. This is referred to as post-treatment Lyme disease syndrome (PTLDS). The symptoms do not indicate that you are still infected. Additional antibiotics are unlikely to help PTLDS. The majority of persons in this category experience symptoms that subside during the next six months after the diagnosis of Lyme disease (Doshi 2022).

4. CHRONIC LYME DISEASE

Chronic Lyme disease is a phrase that is used to describe a situation in which a person has Lyme disease as well as the symptoms of PTLDS. Some individuals believe that chronic Lyme disease and PTLDS is the same thing. However, some persons are diagnosed with chronic Lyme disease without first being diagnosed with Lyme disease. This word has been used to describe symptoms in individual who have neither diagnostic nor clinical evidance of previous infection with *B. burgdorferi* because some individuals believe they get Lyme disease without being bitten by a tick. There is insufficient evidence that mosquitoes may spread Lyme disease. Many specialists disagree with the use of phrase "chronic Lyme disease" due to the ambiguity and lack of well-established clinical description (Lantos et al. 2021).

5. TICK PHYSIOLOGY

From the perspective of the vector, physiological variations across tick species are likely to produce an effect on vector ability. Ixodes species are three-host ticks in common and biotic and abiotic conditions dictate wherever they may thrive. On-host feeding periods are brief in comparison to off-host periods, which include genetically designed diapause or quiescence due to adverse environment (Waldman et al. 2023). Temperature, humidity and day length are all abiotic elements that influence tick physiology, influencing host seeking phenology, egg hatching success, and immature and adult overwintering. Hot circumstances during off-host seasons might cause cold and overheating in chilled temperatures or dryness in dry environments. The circumstances necessitate ticks seeking shelter for cooling or rehydration. The suitable habitats with sufficient plant or leaf trash layer are important in the tick's life cycle (Udobi 2023).

The seasonal synchronization of nymphal and larval feeding patterns was found in Ixodes scapularis populations in the Midwestern United States. Investigations into the infection pattern of Borrelia burgdorferi sensu lato indicated that lineages carrying 16S-23S rRNA intergenic spacer restriction fragment lead to lengthen the polymorphism sequence of type 1 which is more commonly identified in Northeastern Ixodes populations (Paulauskas 2023).

6. TICK IMMUNITY

The idea that tick immunity contributes to varying vector competence seems appealing. The intricacy of the tick's immune system has been better understood in recent years (Margos et al. 2022). The presence of immune effectors and modulators in Ixodes species has been demonstrated. These include recognition molecules, such as thioester-containing proteins (T-TEPS that act as lectins labeling cells for immune assault, defensins, phagocytotic hemocytes, lysozymes, the antimicrobial peptides, a dityrosine

network, and signaling pathways. Toll, Immunodeficiency, and JAK-STAT are three of the signaling pathways that control the immune system. There is also an indirect, cross-species signaling pathway that detects the cytokine interferon gamma in the blood of the vertebrate host (Sri-In et al. 2023). Therefore, it is quite likely that immune effectors are crucial in deciding whether an Ixodes species is capable of attacking a Borrelia species and vice versa.

7. MICROBIOME OF TICKS

Tick's micro biome has received a lot of research in the last 10 years with increased focus. These researches have demonstrated that the gut microbiome, endosymbiontic bacteria, and microorganisms connected to the tick's exterior surface make up the tick microbiome (Wiesinger et al. 2023). In the majority of research, bacterial taxa including Spiroplasma, Coxiella, Lariskella, Midichloria, Francisella, Wolbachia, Francisella, Arsenophonus, and Rickettsia that are recognized tick symbionts were discovered. This demonstrated that Rickettsia and *B. burgdorferi* sensu lato were the dominant bacteria in the gut microbiome of *I. scapularis* in the majority of adult patients. Only a small percentage of tick samples had very diverse microbiomes, with bacteria from the families Enterobacteriaceae and the genera Bacillus and Pseudomonas present in their midguts (Remmal et al. 2023).
In areas where these species coexist in sympatry, the hybrid progeny of numerous tick vector species such as *Ixodes persulcatus and Ixodes ricinus* may present a chance for vector switching. The hybrid ticks inherit genes from both parents, and immune system or mid gut receptor molecules may phenotypically resemble both parents. The hybrid ticks might assist in the survival and adaptation of an invasive Borrelia species to a new vector (Rana et al. 2022).

8. SIGN AND SYMPTOMS

Clinically, Lyme disease frequently presents with a variety of dermatological or viral-like signs and symptoms during the acute phase including intermittent fever, chills, malaise, sweats, fatigue, and achiness which can lead to neurologic, joint, and cardiac involvement in advanced stages of the infection as the causing bacteria disperse homogenously. In addition to these physical indicators persistent and recurring symptoms such as tiredness, arthralgia, myalgia, sleep disturbance, and headache are common throughout the late stages of untreated Lyme disease and are responsible for the majority of the patient complaints. Patients with intermittent attacks of late Lyme arthritis are more likely to experience similar symptoms in the interim. Symptoms without any physical, laboratory, or other objective evidence are sometimes the main or only indication of untreated Lyme disease. The use of direct tests such as polymerase chain reaction (PCR), culture test, or antigen detection for *B. burgdorferi* to assist doctors in diagnosis is fairly restricted because *B. burgdorferi* cannot be cultivated in non-research materials. A two-tier antibody test is available internationally and can be useful despite its severe sensitivity limits, particularly in the early stages of illness and following antibiotic treatment of primary Lyme disease (Rebman and Aucott 2020).

9. LYME DISEASE ETIOLOGY

Borrelia burgdorferi is a member of the phylum spirochetes and the class spirochete. Many families in this class include spirochaetaceae and leptospiraceae. Other human bacteria in this family include Leptospira interrogans, *Treponema pallidum* and *Borrelia recurrentis* are responsible for producing leptospirosis, relapsing fever borreliosis, and syphilis. *B. burgdorferi* is a gram-negative bacterium which is 20 to 30µ in length and 0.2 to 0.3µ in breadth. This can be grown in Barbour-stoenner-kely media however; it is only

rarely retrieved from human samples (Chuma et al. 2020). *B. burgdorferi* is a diverse group of 18 bacterial species, just three of which are primarily related with Lyme disease: *B. burgdorferi sensu stricto, B. garinii,* and *B. afzelli*. In addition to this, six additional species, including *B. spielmanii, B.valasiana,* and *B.bissettii*, are human pathogenic and have been implicated in human illnesses (Barriales San Miguel 2021).

The specific clinical spectrum of many Borrelia species is yet unknown. Different species differ in their vectors and reservoirs, and they also differ in their geographical distribution. *Borellia burgdorferi* sensu stricto is the most common species in North America. The enzootic cycle is quite complex (Bernard et al. 2020).

The ticks of *Ixodes ricinus* are the primary vectors of Lyme disease. In America, *I. scapularis* and *I. pacificus* predominate whereas *I. ricinus* and *I. persulcatus* predominate in Eurasia (Wodecka and Kolomiiets 2023). Many animals play a part as intermediate reservoir, including white footed mouse known as *Peromyscus leucopus* is considered to be dominant. A number of species of small mammals like rats, shrews, squirrels as well as birds are additional reservoirs that could aid in the dissemination of disease. The ticks have a life cycle of three stages that obtained the bacteria by nourishing on infected reservoir. Earlier cases reports tend to suggest that ticks are responsible for transferring the spirochete to humans principally during nymph stage. Despite the fact that deer are inadequate hosts for Borrelia species, but they play an important part in Lyme disease because they are principal feeding hosts for Ixodes ticks (Cardenas-de la Garza et al. 2019).

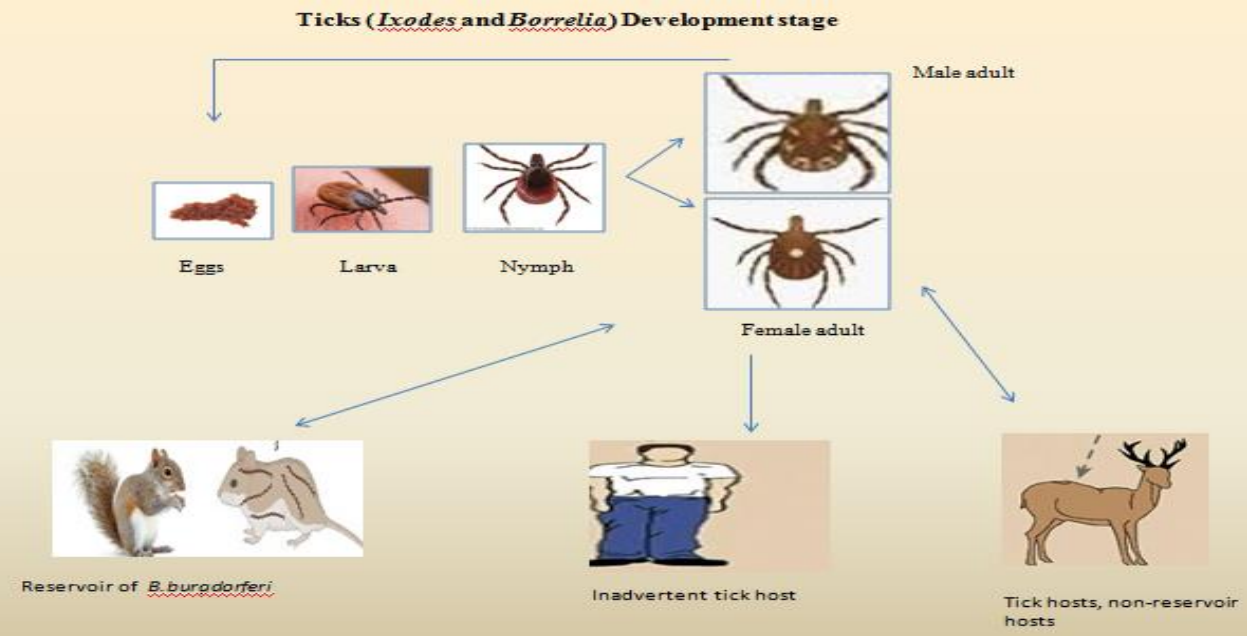

Fig. 1: Transmission of *Borrelia burgdorferi*

10. TRANSMISSION OF LYME DISEASE

Ixodes ticks transmit a broad range of infections, containing Lyme disease to animals as well as human (Fig. 1). Lyme disease is an important tick-borne illness that promotes extensive distribution and caused by group of spirochetes related to *Borrelia burgdorferi* sensu lato complex. Latterly new virulent strains of Borrelia pathogens have been discovered, containing new clinical isolates *Borrelia burgdorferi* sensu lato, *B. bissettii, B. miyamotoi* and *B.mayoni* are related with severe human disorders and are also

transmitted by Ixodes ticks. Globally, the Borrelia species that are frequently related with Lyme disease include *B. burgdorferi* sensu stricto which is wide spread throughout the US and Europe, and *B. garinii* and *B.afzelii* which are dispersed throughout Eurasia (Rollins et al. 2023). In Europe and North America, Lyme disease spirochetes commonly are supported in nature by a complex tick rodent infection cycle. Humans and household animals that acquire Lyme disease are secondary hosts and are not involved in natural transmission cycle (Pal et al. 2021).

11. THE SPIROCHETE

The spirochete host interfaces the outermost membrane like all other spirochetes. *B. burgdorferi* is a diderm comprising an outer membrane surrounding the periplasmic space, the cytoplasmic membrane, the peptidoglycan, and the protoplasmic cylinder. The organs for motility are flagella contained completely in the periplasmic compartment. Additionally to propagating a planer wave that allows spirochete to invade collagen matrices as well as in connective tissues and endothelial junctions, the flagella also provide a cytoskeletal function.
B. burgdorferi containing the host pathogen interface in all milieus by which the spirochete transported or in which spirochete takes up final residence; it is not astonishing because this structure are of great importance from past. Because of its double membrane structure *B. burgdorferi* frequently referred to Gram negative bacteria (Radolf et al. 2021).

12. THE *B. BURGDORFERI* LIFE CYCLE IN TICKS

B. burgdorferi persists throughout the mammalian infection life cycle of ticks. In the absence of vertical transmission, the pathogen needs to be obtained during one of its vector's life stages, namely during a downpour on infected creatures, primarily wild rodents. After attachment of tick to the host, the arthropod tends to prepare itself for its blood meal ingestion during first 12 hours. The transfer of the spirochete to the vector has already started but transmission of *B. burgdorferi* between vertebrate and arthropod host remains unclear. The transfer of spirochete occurs either by active chemotactic dispersion or by passive transfer together with host fluid. During possession, spirochetes enter the tick's stomach from the dermis and fluid of the infected host and are likely to continue migrating until the tick becomes fully engorged, which normally occurs in 72-96 hours. *B. burgdorferi* becomes informally associated with the mid gut tissues during 48 hours of feeding which remains in the gut throughout the whole life of arthropod (Narasimhan et al. 2022). When the tick consumes a successive blood meal, the spirochete tends to increase in the gut and at this time, an unspecified fraction of B. burgdorferi population present in the gut that penetrates the hemocoel and then disperse towards the salivary gland, and it is transferred by the salivary stream to new mammalian host (Pal et al. 2021).

13. RISK FACTORS

Almost all states in the United States have recorded instances, despite the fact that there is a spatial risk within endemic areas. But in 2012, 13 states—Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Vermont, Virginia, and Wisconsin—reported 95% of all instances. The risk of infection is highest in the late spring and summer because *B. burgdorferi*-transmitting ticks are vulnerable to desiccation and require continual high relative humidity.

Ticks can be brought into homes by pets and onto lawns by animals. Ticks typically live in overgrown brush and the border regions between lawns and woodlands (Merryweather 2023).

14. CLINICAL MANIFESTATIONS

The clinical manifestations of Lyme disease are classified into three stages to make easier for the diagnosis.

1. Early localized stage: This is the first stage, which is distinguished by erythema migrans that appear at tick bite site. It happens within the first several weeks following vaccination.
2. Early disseminated stage: This is the second stage, which appears weeks to months after tick contact and is characterized by many erythema migrans lesions, Lyme neuroborreliosis, carditis, borrelial lymphocytoma, and in rare cases Lyme arthritis.
3. Late disseminated stage: This is the third stage, which is distinguished by acordermatitis chronica atrophicans, Lyme arthritis, and Lyme neurological symptoms (Cardenas-de la Garza et al. 2019).

These warning signs and symptoms might be present in different geographic areas and in different animals.

14.1. DERMATOLOGIC MANIFESTATIONS

The most prevalent dermatologic symptom of Lyme disease is erythema migrans, which Azfelius first described as erythema chronicum migrans. During the first three weeks after vaccination, it is prevalent in 70–95 percent of the infected patients. Children experience it more frequently than adults do. It appears as a circular or oval, red to bluish-red area with centrifugal growth and the possibility of center clearing. The head and neck, as well as the extremities or pelvic area, are the most often impacted areas in both adults and children. Sometimes, a burning feeling or pruritus is mentioned. Erythema migrans may be accompanied by broader symptoms such fever, lymphadenopathy, and malaise. The lesions might last for weeks or months if untreated. Rarely, individuals will have many erythema migrans lesions at this stage (Strle and Wormser 2022).

14.2. LYME ARTHRITIS

The second most typical clinical manifestation in patients previously termed antibiotic refractory Lyme arthritis in them. is Lyme arthritis. Untreated EM patients develop arthritis in over 60% of cases within 6 months. Transient or recurring bouts of asymmetrical, monoarticular, or oligoarticular arthritis can occur. The knee joint is most frequently impacted. Periarticular involvement is common, and each episode typically affects fewer than five joints with synovitis. Typically, the pain is low to moderate while the joint swelling is considerable. While inflammatory indicators are often high and serum white blood cell (WBC) count typically falls within the average range (Arvikar and Steere 2022).

White blood cell (WBC) counts in synovial fluids vary from range 10,000 to 25,000 cells/mm3. Treatment is necessary if anti-Borrelia antibodies are present or prior history of erythema migrans. Even though most cases of arthritis respond effectively to antimicrobial treatment and Nonsteroidal anti-inflammatory drugs (NSAIDs). Treatment for these complex instances may be comparable to that given for other forms of chronic inflammatory arthritis, such as methotrexate and hydroxychloroquine (Cardenas-de la Garza et al. 2019).

14.3. LYME CARDITIS

Lyme carditis is an uncommon occurrence with an estimated frequency of 4-10% in United States and 0.3-4% in Europe in individuals who are untreated. However, more recent statistics indicate that the incidence may be as low as 1% in the United States perhaps as a result of earlier diagnosis and rapid treatment of Lyme disease. The existence of *B. burgdorferi* sensu lato genospecies in Europe which are less cardiotropic such as *B. garinii* and *B. afzelii* opposed to *B. burgdorferi* are the most prevalent species in United States. Due to the behavior of the vector, reservoir, and host chances of Lyme carditis to take place are more commonly ranges from June to December. After a tick bite or the development of erythema migrans, symptoms might appear anywhere from a few days and seven months later. However, cutaneous (erythema chronicum migrans), joint (arthritis), or neurologic (neuroborreliosis) signs are more frequently present in addition to cardiac involvement (Radesich et al. 2022).

14.4. LYME NEUROBORRELIOSIS

The early disseminated stage of *B. burgborferi* infection is often when the neurologic symptoms first appear. The three main ways that Lyme borreliosis damages the neurological system are mononuclear cell meningitis, cranial neuropathies, and radiculoneuropathies, the latter of which is a catch-all term for painful radiculopathies and unifocal or multifocal peripheral nerve involvement. Much has been discovered about the interplay between the pathogenic infection and the brain system, and diagnostic methods have been greatly improved, including enhanced peripheral blood and CSF on the basis of diagnosis of serum (Halperin et al. 2022). Clinical manifestations of Lyme disease have been enlisted in Table 1.

15. DIAGNOSIS OF LYME DISEASE

Erythema migrans might be used to make a clinical diagnosis of Lyme disease, as can a combination of clinical symptoms and serologic tests. Patients may also experience non-specific manifestations like pain in muscles, headache, and weakness. Infected persons have clinical findings of Lyme disease like arthritis, erythema migrans, heart block, or cranial nerve paralysis. In the USA, there is a significant prevalence of non-specific subjective symptoms, with up to 40% of persons experiencing chronic pain and 10% to 15% of people expressing exhaustion (Wong et al. 2022). Although patients with Lyme disease frequently have vague symptoms, many patients also simultaneously display objective Lyme disease symptoms. Serologic test results for Lyme disease in people with subordinate pretest likelihood of infection show weak positive predictive value (Kobayashi and Auwaerter 2022).

The Centers for Prevention and Control of Diseases advise using a two-step test. Either an immunofluorescence test (IFA) or an enzyme immunoassay (EIA) should be carried out first.

- If IFA test is positive, Western blot analysis should be performed during which patients with symptoms less than 30 days will be supposed to check for IgG and IgM and those with symptoms more than 30 days will be supposed to test for IgG isotype. Assays for antibodies are often negative in the first few weeks following infection.
- Histopathology is frequently used to rule out other comparable disorders and may aid in the diagnosis.
- Additionally, biopsy analysis by PCR or Borrelia culture may be used to verify the diagnosis although the sensitivity of these tests varies greatly.

Table 1: Clinical manifestations of Lyme disease (Cardenas-de la Garza et al. 2019; Miller and Aucott 2021)

Clinical manifestations	Signs and symptoms
Dermatologic manifestations	• Erythema migrans • Borrelial lymphocytoma • Lymphoma • Lichen sclerosus • Parry–Romberg syndrome • Acrodermatitis chronica atrophicans
Lyme Arthritis in them.	• Asymmetrical, monoarticular, or oligoarticular arthritis in them. • Swelling of joint • Pain in joint • Elevated level of inflammatory markers
Lyme Carditis	• Atrioventricular (AV) block • Angina pectoris • Acute heart failure • Palpitations • Dyspnea • Infrequently pericarditis and myocarditis
Lyme Neuroborreliosis	• Lymphocytic meningitis • Encephalitis • Bannwarth's syndrome • Myelitis • Intracerebral hemorrhage • Sleep disturbances • Headache • Subarachnoid hemorrhage • Fatigue or stroke • Paresthesia

 Serologic testing should only be carried out in accredited labs that adhere to the Centers for Disease Control and Prevention's (CDC) guidelines for immunoblot interpretation in order to prevent the misdiagnosis of Lyme disease.
 The diagnosis may be aided by histopathological examination, PCR, or tissue culture; however high-titer tests are frequently enough (Simon et al. 2022).

16. PREVENTION AND TREATMENT OF LYME DISEASE

Depending on the clinical presentation, there are several approaches to Lyme disease prevention and therapy. The cornerstone of care is still antibiotic therapy, however there are few reliable data indicating the most efficient and economical antibiotic, dosage, route, and duration.
To avoid Lyme disease, it is recommended that tick bites be avoided. The use of protective clothes, inspect skin and cloth frequently. The use of tick and bug repellent, and the timely removal of attached ticks are all recommended. The antibiotics are recommended after tick bite. New and current antibiotics with potential against bacterial cells from diverse bacterial genera including Staphylococcus and E. coli have been identified to either directly kill or reactivate persister cells. Most research involving antibiotics and small molecule medications for LD and PTLD employ innovative synthetic pharmaceuticals or homeopathic extracts that have not yet obtained FDA clearance, or they use pre-approved drugs that have been repurposed alone or in conjunction with existing antibiotics (Adkison and Embers 2023). The recommended dosage of various drugs in different ages has been enlisted in Table 2.

Table 2: Recommended oral dosage of Lyme disease (Nguyen et al. 2022)

Age	Recommended dosage
Pediatric	4 mg/daily in 2 divided doses Doxycycline + 30 mg/kg in 2 divided doses Cefuroxime + 50 mg/kg in 3 divided doses Amoxicillin
8 years children	4 mg/kg Doxycycline
Adults	Single 200 mg Doxycycline

Lyme meningitis is a rare but devastating clinical symptom of Lyme disease. The first-line therapy for Lyme meningitis was intravenous ceftriaxone, but it is linked with a high prevalence of complications. Although studies on oral doxycycline's efficacy and effectiveness (or real-world evidence) are sparse, practice recommendations have recently been modified to prescribe either oral doxycycline or ceftriaxone as first-line therapies for Lyme meningitis (Nigrovic et al. 2023). Borrelial lympochytoma, erythema migrans, and cranial nerve paralysis should be treated with 14-day antibiotic treatment orally whereas ACA should be treated with a 21-day regimen. Lyme arthritis without involvement of the neurological system treated with a 28-day course of oral antibiotics.

17. CONCLUSION

Estimation of persistent or chronic Lyme disease in an immunology may be complex. The tiredness and anxiety are unexplained symptoms which are common in the broad-spectrum population but definite relationship between these symptoms and Lyme disease has not been established. Furthermore, no clear standard for the diagnosis of chronic Lyme disease has been established. The individuals with Lyme disease have arrived with a wide range of symptoms and histories. There is scant evidence that *B. burgdorferi* cause symptoms or result in a down regulated immune response. At this time, no conclusions about the etiology and pathophysiology of these individuals' ongoing symptoms can be evaluated till now. There is also no evidence about the further use of antibiotic treatment in individuals report with chronic Lyme disease symptoms

REFERENCES

Adkison H and Embers ME, 2023. Lyme disease and the pursuit of a clinical cure. Frontiers in Medicine 10: 1183344.

Arvikar SL and Steere AC, 2022. Lyme arthritis. Infectious Disease Clinics 36: 563-577.

Barriales San Miguel D, 2021. Plasticity of macrophage responses to activating factors.

Bernard A et al., 2020. Lyme-associated uveitis: Clinical spectrum and review of literature. European Journal of Ophthalmology 30: 874-885.

Bisanzio D et al., 2020. Current and future spatiotemporal patterns of Lyme disease reporting in the Northeastern United States. Journal of the American Medical Association 3: e200319-e200319.

Cardenas-de la Garza JA et al., 2019. Clinical spectrum of Lyme disease. European Journal of Clinical Microbiology and Infectious Diseases 38: 201-208.

Chuma IS et al., 2020. Pathogenic spirochetes in monkeys: stealthy pathogens of global importance. Neglected Diseases in Monkeys: From the Monkey-Human Interface to One Health 2020: 95-119.

Coburn J et al., 2021. Lyme disease pathogenesis. Current issues in molecular biology 42: 473-518.

Doshi S, 2022. Long-Term Cognitive Effects of Post-Treatment Lyme Disease. PhD Dissertation, Fairleigh Dickinson University.

Gardner AM et al., 2020. Landscape features predict the current and forecast the future geographic spread of Lyme disease. Proceedings of the Royal Society B 287: 20202278.

Halperin JJ et al., 2022. Lyme neuroborreliosis: known knowns, known unknowns. Brain 145: 2635-2647.

Kobayashi T and Auwaerter PG, 2022. Diagnostic Testing for Lyme Disease. Infectious Disease Clinics 36: 605-620.

Lantos PM et al., 2021. 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. Clinical Infectious Diseases 72: e1-e48.

Margos G et al., 2022. Characteristics of Borrelia burgdorferi sensu lato. In: Hunfeld K, Gray J, editors. Lyme Borreliosis: Cham, Springer International Publishing; pp: 1-29.

Merryweather JA, 2023. The Geographic Pattern and Socioecological Factors of Helicobacter pylori Infections in the United States.

Miller JB and Aucott JN, 2021. Stages of Lyme arthritis. Journal of Clinical Rheumatology 27: e540-e546.

Narasimhan S et al., 2022. Tick transmission of Borrelia burgdorferi to the murine host is not influenced by environmentally acquired midgut microbiota. Microbiome 10: 1-17.

Nguyen CT et al., 2022. Prevention and Treatment of Lyme Disease. Journal of the American Medical Association 327: 772–773.

Nigrovic LE et al., 2023. Protocol: Comparative effectiveness and complications of intravenous ceftriaxone compared with oral doxycycline in Lyme meningitis in children: a multicentre prospective cohort study. Journal of Biomedicine 13.

Pal U et al., 2021. Interactions between ticks and lyme disease spirochetes. Current Issues in Molecular Biology 42: 113-144.

Paulauskas A, 2023. Abstracts of the 8th Baltic Genetics Congress. Biologija 69.

Pitrak D et al., 2022. Diagnosis of Lyme disease. JAMA 327: 676-677.

Radesich C et al., 2022. Lyme carditis: from pathophysiology to clinical management. Pathogens 11: 582.

Radolf JD et al., 2021. Lyme disease in humans. Current Issues in Molecular Biology 42: 333-384.

Rana VS et al., 2022. Immune evasion strategies of major tick-transmitted bacterial pathogens. Trends in Microbiology.

Rebman AW and Aucott JN, 2020. Post-treatment Lyme disease as a model for persistent symptoms in Lyme disease. Frontiers in Medicine 57.

Remmal I et al., 2023. Characterization of the Bacterial Microbiome in Natural Populations of Barley Stem Gall Midge, Mayetiola hordei, in Morocco. Microorganisms 11: 797.

Rollins RE et al., 2023. Out of Asia? Expansion of Eurasian Lyme borreliosis causing genospecies display unique evolutionary trajectories. Molecular Ecology 32: 786-799.

Simon TL et al., 2022. Rossi's principles of transfusion medicine. John Wiley and Sons, Incorporated.

Sri-In C et al., 2023. 34-kDa salivary protein enhances duck Tembusu virus infectivity in the salivary glands of Aedes albopictus by modulating the innate immune response. Scientific Reports 13: 9098.

Strle F and Wormser GP, 2022. Early Lyme disease (erythema migrans) and its mimics (southern tick-associated rash illness and tick-associated rash illness). Infectious Disease Clinics 36: 523-539.

Udobi MI, 2023. Time Since Blood-feeding (hunger) in Ixodes Ricinus Ticks: Measurement and Consequences.

Waldman J et al., 2023. Putative target sites in synganglion for novel ixodid tick control strategies. Ticks and Tick-borne Diseases 102123.

Wiesinger A et al., 2023. Revealing the tick microbiome: insights into midgut and salivary gland microbiota of female Ixodes ricinus Ticks. International Journal of Molecular Sciences 24: 1100.

Wodecka B and V Kolomiiets, 2023. Genetic Diversity of Borreliaceae Species Detected in Natural Populations of Ixodes ricinus Ticks in Northern Poland. Life 13: 972.

Wong KH et al., 2022. A review of post-treatment Lyme disease syndrome and chronic Lyme disease for the practicing immunologist. Clinical Reviews in Allergy and Immunology 2022: 1-8