International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	LYME DISEASE – AN UPDATED REVIEW OF CLINICAL FEATURES, DIAGNOSTIC METHODS, AND THERAPEUTIC OPTIONS
DOI	https://doi.org/10.31435/ijitss.2(50).2026.5399
RECEIVED	01 March 2026
ACCEPTED	10 June 2026
PUBLISHED	18 June 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

LYME DISEASE – AN UPDATED REVIEW OF CLINICAL FEATURES, DIAGNOSTIC METHODS, AND THERAPEUTIC OPTIONS

Ewa Maraszewska *(Corresponding Author, Email: e.maraszewska@gmail.com)*
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0003-0992-7144

Jędrzej Sztajura
Students' Scientific Club, Department of Neurosurgery, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0009-8975-731X

Maksymilian Szklarski
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0001-6977-0666

Karol Józef Szkarłat
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0004-2889-8382

Szymon Targosz
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0005-2251-5229

Michał Stachel
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0008-3264-4747

Weronika Szymacha
Faculty of Medical Sciences in Katowice, Medical University of Silesia in Katowice, Poland
ORCID ID: 0009-0000-1592-5602

Aleksandra Płecka
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0007-0075-5234

Karol Zimnicki
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0001-9687-2641

Alicja Stępień
Voivodship Dental Clinic, Consulting Dental Prosthetics Department, 31-135 Cracow, Poland
ORCID ID: 0009-0003-2717-6030

ABSTRACT

Introduction and purpose: Lyme borreliosis represents the most common vector-borne disease in temperate regions, with its incidence steadily increasing as a result of climate change and the progressive expansion of tick habitats. This review synthesizes current epidemiological data, explores the complex clinical landscape across different geographic regions, and critically evaluates both the persistent obstacles and recent innovations in clinical and laboratory diagnostics.
Description of the state of knowledge: The pathogenesis of Borrelia burgdorferi relies heavily on the immunomodulatory properties of tick saliva and extensive antigenic variation to evade host innate defenses and disseminate systemically. Clinical progression is traditionally categorized into early localized, early disseminated, and late disseminated stages, which can involve the skin, central nervous system, joints, and heart. While the pathognomonic erythema migrans rash allows for a definitive clinical diagnosis, other manifestations depend on a standard two-tiered serological testing algorithm. This indirect testing approach frequently lacks sensitivity during the early stages of infection, complicating accurate diagnosis. Standard management relies on targeted antibiotic therapy, such as doxycycline or ceftriaxone, which successfully resolves active infection. However, for patients presenting with Post-Treatment Lyme Disease Syndrome (PTLDS), prolonged antibiotic regimens offer no sustained clinical benefit and significantly increase the risk of severe adverse events.
Conclusions: While early recognition and prompt antibiotic administration consistently yield an excellent clinical prognosis, the inherent limitations of standard serological testing remain a critical diagnostic barrier. Addressing these challenges requires the urgent development and implementation of advanced diagnostic technologies, including host-based biomarkers and rapid point-of-care biosensors. Furthermore, optimal patient management mandates multidisciplinary symptomatic support for post-treatment syndromes, alongside continued research into next-generation vaccines to prevent transmission.

KEYWORDS

Lyme Borreliosis, *Borrelia Burgdorferi*, Erythema Migrans, Post-Treatment Lyme Disease Syndrome

CITATION

Ewa Maraszewska, Jędrzej Sztajura, Maksymilian Szklarski, Karol Józef Szkarłat, Szymon Targosz, Michał Stachel, Weronika Szymacha, Aleksandra Płecka, Karol Zimnicki, Alicja Stępień. (2026) Lyme Disease – An Updated Review of Clinical Features, Diagnostic Methods, and Therapeutic Options. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.5399

Introduction

Lyme borreliosis (LB) has established itself as the most prevalent vector-borne pathology across the Northern Hemisphere, with its incidence continuing to climb due to a variety of environmental and anthropogenic factors [21]. In Europe specifically, the disease has transformed into a significant public health challenge, as shifting ecological conditions expand the geographical range of *Ixodes* ticks and, consequently, the risk of human exposure [31]. While the United States and Europe share the burden of this infection, the clinical landscape in Europe is notably more complex due to the broader genetic diversity of the *Borrelia burgdorferi sensu lato* complex, which includes species like *B. afzelii* and *B. garinii* that are not typically found in North America [2].

Despite its increasing frequency, Lyme disease remains a diagnostic dilemma for many clinicians. In primary care settings, the initial presentation can be subtle or entirely non-specific, leading to significant under-reporting or, conversely, diagnostic uncertainty [9]. The current standard recommended diagnostic algorithm, which relies on a two-tiered serological approach, is frequently criticized for its lack of sensitivity during the early stages of infection. This limitation often results in "therapeutic wandering," where patients remain undiagnosed or receive inappropriate treatments while the infection potentially progresses to more severe, disseminated forms [4]. The reliance on indirect testing methods means that clinical judgment must remain the primary tool for diagnosis, yet the variability of symptoms often complicates this process in everyday medical practice [4,9].

The primary objective of this study is to synthesize current evidence regarding the evolving epidemiology of Lyme borreliosis and to critically evaluate the persistent hurdles in its laboratory and clinical

diagnosis. Through a comparative analysis of clinical manifestations observed in European and American cohorts, this review underscores the limitations of a uniform diagnostic approach and examines emerging strategies aimed at overcoming the shortcomings of conventional serological methods [2]. Furthermore, this paper explores recent innovations in diagnostic techniques that seek to bridge the gap left by traditional serology, ultimately aiming to provide a clearer framework for early intervention and improved patient outcomes [4,31].

Methodology

This literature review on Lyme borreliosis utilized articles that were published between 2019 and 2024 to ensure the inclusion of the most recent epidemiological data, diagnostic innovations, and clinical guidelines. All the studies were sourced from the PubMed database. This review focuses on the pathogenesis, epidemiology, clinical presentation, diagnosis, prevention, treatment and prognosis of Lyme disease. From the initial pool of identified literature, 32 publications were selected based on their clinical relevance and methodological rigor. The search used the following keywords: “Lyme disease,” “Borrelia burgdorferi,” and “Post-Treatment Lyme Disease Syndrome.”

Pathogenesis

The establishment of *Borrelia burgdorferi* infection is fundamentally dependent on the exceptional bioactive qualities of tick saliva, which neutralizes host hemostasis and local inflammatory responses [29]. These salivary components create a localized immunomodulatory environment that is essential for the spirochetes to survive the initial encounter with the host's innate defenses [22,29]. Thanks to these special properties, they are able, among other things, to adapt to higher temperatures, changes in pH, or variations in nutrient availability-that is, to the conditions prevailing in the host organism [22].

During the transition from the vector to the mammal, the pathogen undergoes a rapid proteomic remodeling known as the "Osp switch," characterized by the downregulation of midgut-binding OspA, whose expression is active in unfed ticks, and the induction of OspC [25]. The expression of OspC is indispensable for early mammalian infection, as it protects the spirochetes from macrophage-mediated phagocytosis and complement-induced lysis [22,25].

Systemic dissemination is achieved through the hematogenous and lymphatic routes, requiring the bacteria to adhere to vascular endothelium and tissue barriers [21]. This process is mediated by specialized lipoproteins, such as decorin-binding proteins A and B (DbpA/B), which facilitate the anchoring of spirochetes to the extracellular matrix in target organs like heart and synovial spaces [21,22]. To ensure long-term persistence in an immunocompetent host, *Borrelia* utilizes the VlsE recombination system to generate extensive antigenic variation, thereby evading detection by the adaptive immune system [22]. Furthermore, the pathogen can sequester itself in specialized niches or adopt dormant states, which complicates the host's ability to achieve complete bacterial clearance [15].

The clinical manifestations of the disease are primarily driven by the host's immunopathological reaction rather than direct bacterial toxicity [13]. Erythema migrans is a form of early localized infection. It is a skin lesion characterized by a circular rash that develops at the site of the bite [21]. A characteristic feature is the formation of interstitial and perivascular infiltrates composed of various types of immune system cells-primarily T cells, dendritic cells, and macrophages, as well as the less common plasma cells, mast cells, and neutrophils. If left untreated, the infection may disseminate hematogenously to distant sites, including the heart, joints, and central nervous system [13]. For instance, the characteristic recruitment of B-cells to the central nervous system during neuroborreliosis is orchestrated by the significant elevation of the chemokine CXCL13 [13,21].

Epidemiology

Lyme borreliosis represents the most prevalent vector-borne illness across the Northern Hemisphere, specifically in the United States and Europe [2]. The disease is widely distributed geographically, with *Borrelia burgdorferi sensu stricto* serving as the primary causative agent in North America, while European cases are also frequently attributed to *B. garinii* and *B. afzelii* [1]. Surveillance data from the United States indicates between 30,000 and 42,000 annual cases reported to the Centers for Disease Control and Prevention (CDC) [3,10]. However, these figures likely represent significant underreporting; actual annual incidence is estimated to reach approximately 476,000 cases in the U.S. and over 200,000 in Western Europe [2,9].

Incidence rates vary considerably across the European continent, ranging from high endemicity in Lithuania, Slovenia, and Austria, where rates can exceed 100 cases per 100,000 population, to significantly lower frequencies in Iceland and Southern Italy [19]. In the United States, the disease follows a bimodal age distribution, with peak occurrences in children aged 5 to 15 years and adults over 50, alongside a slight male predominance [21]. In contrast, several European countries report higher infection rates among women, particularly those in their 50s and 60s, a trend potentially influenced by gender-specific health-seeking behaviors regarding skin manifestations [19].

Occupational exposure presents a major risk factor, particularly for outdoor workers such as forest rangers, whose seroprevalence rates have been recorded as high as 22% in Poland and 28% in the Netherlands [1,12]. General risk is closely tied to time spent in tick-infested habitats, including forests dominated by deciduous trees characterized by adequate moisture levels due to a thick layer of decomposing plant matter and even residential backyards [3,12]. The transmission of the pathogen is highly seasonal, with new cases peaking during the summer months of June through August [21]. This seasonality is directly linked to the period of greatest activity for nymphal ticks, which serve as the primary stage for transmission to humans [11,21].

The geographic range of Lyme borreliosis has seen an expansion over the last three decades, emerging in northern regions like Southern Canada and encroaching into major urban centers such as New York City and Chicago [21]. This epidemiological shift is driven by a complex interplay of environmental factors, most notably climate change and milder winters that extend the active periods for tick vectors [21,19]. Additional drivers include increased densities vertebrate reservoirs, bird-mediated dispersal of infected ticks, and ecological changes that decrease biodiversity in endemic areas [21]. Consequently, as public awareness and diagnostic understanding improve, the number of new cases is expected to remain high or continue to increase globally [21].

Clinical symptoms

The clinical progression of Lyme disease is categorized into three sequential stages: early localized, early disseminated, and late disseminated phases [32]. Following the initial appearance of erythema migrans, the infection may progress over several weeks as spirochetes propagate through the circulatory and lymphatic systems, leading to multisystemic involvement characterized by constitutional symptoms as well as potential neurological and cardiac complications [18,32]. While late-stage disease is primarily defined by large-joint arthritis, timely pharmacological intervention has been shown to reduce the incidence of such musculoskeletal sequelae to approximately 10% [32].

CUTANEOUS MANIFESTATIONS

Dermatological signs constitute the most prevalent clinical features of Lyme borreliosis, serving as critical diagnostic markers across different stages of the infection. These manifestations are primarily categorized into erythema migrans, borrelial lymphocytoma, and acrodermatitis chronica atrophicans, each associated with specific chronopathological phases of the disease [1,2].

Erythema migrans represents the highly characteristic sign of early localized Lyme disease, appearing in approximately 70% to 80% of infected individuals [32,18]. Typically emerging at the site of the tick bite within a 3- to 32-day incubation period, the lesion manifests as an expanding erythematous macule that frequently surpasses 5 cm in diameter and can, if left untreated, reach dimensions as large as 61 cm [1,32]. Often described central clearing is an inconsistent feature; it is significantly more common in European patients than in North American cohorts, where clearing may occur in as few as 9% of cases [2,21]. While multiple EM lesions indicate early hematogenous or lymphatic dissemination, the diagnosis of both localized and disseminated EM remains clinical, as serological testing is frequently non-reactive during this initial phase [1].

Borrelial lymphocytoma is an early disseminated manifestation occurring almost exclusively in Europe [2,18]. It presents as a painless, slow-growing, bluish-red nodule or plaque, typically localized to the earlobes in children or the nipple and scrotum areas in adults [1,18].

Acrodermatitis chronica atrophicans is the hallmark of late-stage cutaneous Lyme disease [1]. The condition initiates as a chronic inflammatory phase characterized by edematous, reddish-blue discoloration on the extensor surfaces of the extremities [2]. Over months or years, the lesion transitions into a definitive atrophic stage, where the skin becomes abnormally thin, wrinkled, and translucent, often revealing underlying vascular structures [1, 2].

NEUROLOGICAL MANIFESTATIONS

Neurological involvement, referred to as neuroborreliosis, constitutes the second most prevalent clinical manifestation of Lyme borreliosis, affecting even 15% of patients [1, 16]. Over 90% of these cases emerge during the early disseminated phase of the infection, typically appearing within six months of the initial exposure [1]. In Europe, where *Borrelia garinii* and *Borrelia afzelii* are the primary etiological agents, the disease most frequently presents as Garin-Bujadoux-Bannwarth syndrome, which is characterized by lymphocytic meningitis, painful radiculitis, and cranial nerve palsies [1,16,20]. The associated radicular pain is often intense, tends to worsen at night, and frequently originates in the anatomical region where the tick bite or erythema migrans was first observed [16]. Facial nerve palsy is a hallmark of this stage, occurring in a significant portion of cases; in children, it often presents as an isolated symptom and may manifest bilaterally or asynchronously [1,16,32].

While less common, late-stage neuroborreliosis develops more than six months post-infection in about 1% to 9% of patients, potentially manifesting as chronic encephalomyelitis characterized by spasticity, ataxia, and progressive cognitive impairment [1,20].

A profound clinical and psychosocial challenge involves the management of persistent, subjective symptoms-such as fatigue, memory deficits, and impaired concentration-which often lack objective clinical markers [28,30]. This "illness without disease" phenomenon frequently leads to diagnostic uncertainty, complicating the therapeutic relationship and significantly altering the patient's life trajectory and daily functioning [28,30].

ARTICULAR MANIFESTATIONS

Joint involvement in Lyme borreliosis typically manifests as episodic or chronic monoarthritis, predominantly affecting the knee in approximately 85% of cases. Other affected joints are elbow, ankle or temporomandibular joint [1,26,18]. Arthralgia is a symptom that appears anywhere from a few weeks to two years after the bite [1]. Distinctively, the presentation is characterized by significant joint effusions with relatively preserved range of motion and an absence of systemic fever, which helps differentiate the condition from septic bacterial arthritis [26].

CARDIAC MANIFESTATIONS

Cardiac involvement, commonly referred to as Lyme carditis, is a relatively infrequent but potentially severe complication, occurring in 0.3% to 4% of cases globally, with a higher prevalence of up to 10% documented in the United States [1]. Clinical manifestations typically emerge within a median of 21 days following the onset of erythema migrans, though cardiac symptoms may also present as the initial sign of infection or occur after a subclinical period [1]. The hallmark of this condition is the disruption of the cardiac conduction system, primarily manifesting as atrioventricular (AV) blocks of varying severity [1,18,21]. These conduction disturbances, particularly third-degree blocks, are characterized by their extreme instability and potential for rapid progression-sometimes within minutes-from minor delays to complete heart block [21].

In addition to nodal blocks, patients may present with other rhythm disturbances such as atrial fibrillation, sick sinus syndrome, and both supraventricular and ventricular tachycardias, but they are not reported very often [1,20]. Myocardial and pericardial involvements are also less frequent; myocarditis is reported in up to 4% of European cases, while pericarditis may be present in approximately 23% of Lyme carditis patients [1]. Such involvement often results in mild to moderate left ventricular dysfunction and can be identified by elevated cardiac biomarkers, including troponin and natriuretic peptides [1].

OCULAR MANIFESTATIONS

Ophthalmic symptoms of Lyme borreliosis remain a relatively poorly characterized aspect of the disease, primarily because many clinical reports are based on serological associations rather than definitive evidence of ocular tissue infection [1]. Confirmed instances of direct ocular tropism-documented through positive polymerase chain reaction (PCR) in eye tissue or uveitis occurring alongside laboratory-confirmed neuroborreliosis are exceptionally rare in the literature [1].

During the initial stages of the infection, patients most frequently present with conjunctivitis, episcleritis, or subtle forms of keratitis [32]. As the disease advances into later phases, more complex inflammatory conditions may emerge, such as uveitis, orbital myositis, or chronic intraocular inflammation, which typically manifests with photophobia and vitreous floaters [32]. These late-stage manifestations often present a diagnostic challenge as they can closely mimic other serious pathologies, including orbital pseudotumor, lymphoma, or thyroid-associated orbitopathy [32].

Prevention

Primary prevention of Lyme disease relies heavily on avoiding tick bites, as Ixodes ticks, which are the primary vectors, remain active from spring to autumn in continental climates and throughout the entire year in oceanic regions. The most effective protective strategy involves wearing appropriate clothing, such as long-sleeved shirts and trousers tucked into socks, preferably in light colors to make wandering ticks more visible [1]. Children are particularly vulnerable to bites from questing ticks due to their short stature, making head coverings a highly recommended precaution during outdoor activities [1]. As an adjunctive measure, chemical repellents containing active ingredients like DEET or IR35/35 can be applied to exposed skin, though they merely disrupt the tick's olfactory sensors rather than killing the arachnid [1]. These chemical agents must be used with caution, adhering strictly to age restrictions, avoiding simultaneous application with sunscreen, and recognizing that natural essential oils offer inadequate protection due to their rapid evaporation [1]. Following potential exposure in wooded or endemic areas, individuals must conduct meticulous body inspections, paying special attention to warm, moist anatomical regions like the groin, armpits, and scalp [1]. If an attached tick is discovered, it must be extracted immediately using mechanical tools such as fine-tipped tweezers, avoiding bare hands or folk remedies like ether, which do not prevent the rapid transmission of pathogens. Following extraction, the bite site should be disinfected and monitored for four weeks for the appearance of erythema migrans. Testing the removed tick for pathogens is broadly discouraged due to the low overall risk of infection [1,16]. Research shows that the likelihood of developing Lyme borreliosis after a tick bite remains below 5%, even in regions with high endemicity and in cases where the tick has been attached for an extended period [1].

Although international guidelines have historically differed regarding antibiotic prophylaxis after a tick bite, current U.S. recommendations support a single 200 mg dose of doxycycline administered within 72 hours following a clearly defined high-risk Ixodes tick exposure. In contrast, European guidelines remain more conservative, largely due to differences in Borrelia species distribution and limited evidence supporting the effectiveness of this strategy in European settings [1,5].

Currently, there is no approved vaccine available for human use against Lyme disease, as the only previously licensed OspA-based vaccine was withdrawn from the market due to economic reasons and unsubstantiated public concerns [1,16,25]. However, researchers are actively developing new preventive strategies, including a multivalent OspA chimeric vaccine (VLA15) that is currently in clinical trials to provide broad protection against multiple bacterial strains [16]. In addition to targeting the bacteria directly, novel approaches like mRNA vaccines are being tested to target tick salivary proteins, aiming to induce tick immunity and prevent the transmission of the pathogen altogether [16].

Diagnostic approach

While the appearance of erythema migrans is considered highly characteristic and allows for a definitive clinical diagnosis without the need for laboratory confirmation, most other clinical presentations require supportive serological evidence [11,7,1].

Laboratory diagnosis of Lyme borreliosis primarily relies on indirect serological methods to detect the host’s immune response, as the direct isolation or culture of *Borrelia burgdorferi sensu lato* from clinical specimens remains technically challenging and time-consuming [11, 4]. The recommended reference method for this purpose is the standard two-tiered testing (STTT) algorithm, which initiates with a highly sensitive screening tool-typically an enzyme-linked immunosorbent assay (ELISA) or an indirect immunofluorescence assay (IFA) followed by a highly specific Western blot to confirm any positive or equivocal results [11,4,16]. To improve diagnostic accuracy and simplify laboratory workflows, a modified two-tiered testing (MTTT) approach has been validated, which replaces the second-tier Western blot with a second, more specific ELISA, often utilizing recombinant antigens such as the VlsE C6 peptide [11,4,16].

Despite the high specificity of these methods in late-stage disease, they suffer from significant sensitivity limitations during the early localized phase, as the adaptive immune response may take several weeks to reach detectable levels [11,8]. This diagnostic window often leads to false-negative results in the early stages, whereas the persistence of IgG antibodies for years after successful treatment may lead to misinterpretation as indicating active infection [4,11]. For neurological manifestations, diagnosis necessitates the analysis of cerebrospinal fluid (CSF) to demonstrate inflammatory markers such as pleocytosis and to calculate a specific antibody index, which confirms the intrathecal synthesis of anti-*Borrelia* antibodies [11,16]. Direct detection methods, such as polymerase chain reaction (PCR), have limited utility in blood or CSF but remain a valuable adjunctive tool for identifying *Borrelia* DNA in synovial fluid in cases of suspected Lyme arthritis [11,4,3].

Recent advancements in the field are focusing on the identification of novel host-based biomarkers, including specific acute-phase proteins and cytokines, which may allow for earlier detection by measuring the body's immediate systemic response to the infection [23, 4]. Furthermore, the development of portable biosensors and microfluidic point-of-care devices aims to provide rapid, inexpensive testing that could eventually replace or supplement traditional laboratory-bound assays [8,4]. These innovations are particularly relevant given the clinical and social complexities associated with conditions where patients report persistent subjective symptoms that do not align with current objective diagnostic criteria [28,24].

Treatment

The treatment of Lyme borreliosis is fundamentally based on the administration of appropriate antibiotics to eradicate the *Borrelia burgdorferi* spirochete and resolve inflammatory manifestations. As it was mentioned above, early recognition and prompt therapy are critical, as they can accelerate symptom regression and prevent the progression to late-stage manifestations like arthritis or chronic neurological disorders [16]. Early localized Lyme disease (erythema migrans) is typically treated with a 2-4 week course of oral antibiotics, most commonly doxycycline, amoxicillin, or cefuroxime [15,16,9].

In the management of Lyme neuroborreliosis, several antibiotics have proven effective, including doxycycline, ceftriaxone, cefotaxime, and penicillin G [16,32]. Orally administered doxycycline and intravenous beta-lactam antibiotics demonstrate similar efficacy in the resolution of neurological symptoms such as meningitis, cranial neuritis, and radiculitis [16, 20]. European guidelines frequently support the use of oral doxycycline for these conditions, reserving parenteral (intravenous) regimens for more severe central nervous system (CNS) involvement or cases that fail to respond to oral therapy [20]. The recommended duration for treating early neuroborreliosis is typically 14 days, while late manifestations such as myelitis or encephalitis may require 14 to 21 days [20,16]. There is currently no scientific evidence to support extending antibiotic treatment beyond 21 to 28 days, even in late-stage neurological disease. Specific recommended dosages include intravenous ceftriaxone (2–4g daily), intravenous cefotaxime (2g every 8 hours), and oral doxycycline (200mg daily) [20,16].

Lyme arthritis, a late-stage manifestation, is initially treated with a 28-day (or 30-day) course of oral doxycycline (100 mg twice daily) or amoxicillin (500 mg three times daily) [26]. If mild joint swelling persists after the initial 28 days, the oral antibiotic regimen may be repeated for an additional month. However, for patients who show a minimal response or continue to have moderate-to-severe swelling after the first month, switching to intravenous ceftriaxone (2g daily) for 4 weeks is the recommended protocol [26]. Physical therapy is often required following antibiotic treatment to restore function and address muscle atrophy. In a small subset of patients where synovial inflammation persists despite multiple rounds of antibiotics-a condition known as post-infectious or post-antibiotic arthritis-clinicians may employ disease-modifying anti-rheumatic drugs (DMARDs) like methotrexate or hydroxychloroquine [26].

Pregnant women with acute Lyme disease are generally treated with a two- to four-week course of oral amoxicillin or cefuroxime [27]. Doxycycline must be avoided during pregnancy due to its potentially harmful effects on the developing fetus [27,23]. Additionally, while US guidelines rely on these safe oral alternatives, some European authorities recommend utilizing intravenous ceftriaxone to treat pregnant women, even for early manifestations like erythema migrans [2].

A significant area of clinical concern is Post-Treatment Lyme Disease Syndrome (PTLDS), defined by the persistence of subjective symptoms such as fatigue, musculoskeletal pain, and cognitive impairment for more than six months following standard antibiotic therapy [6,14,17]. Systematic reviews of randomized controlled trials have consistently shown that extended or repeated antibiotic treatment does not provide a sustained benefit for quality of life, cognition, or fatigue in these patients. Furthermore, prolonged antibiotic therapy is associated with a statistically significantly higher risk of adverse events, including serious complications like catheter-associated sepsis or thrombosis [14,2]. Current medical consensus, therefore, strongly discourages the use of antibiotics for PTLDS, recommending instead a multidisciplinary approach focused on symptom-based differential diagnosis and targeted symptomatic support [16,14].

Prognosis

The overall prognosis for early Lyme disease is highly favorable, as prompt and appropriate antibiotic treatment leads to an excellent recovery with a low rate of residual symptoms [14,21]. Positive long-term outcomes are also generally expected for specific manifestations such as neuroborreliosis, Lyme arthritis, and gestational infections, provided that targeted therapy is administered without significant delay [20, 26,27]. For the small subset of patients who develop persistent, non-specific symptoms after treatment, these issues typically represent a natural, self-resolving response to the infection that will gradually improve over time [24].

Conclusions

Lyme borreliosis is a growing public health challenge with diverse clinical manifestations and regional pathogenic variations that complicate its diagnosis. While early recognition and prompt antibiotic therapy consistently yield an excellent prognosis, the low sensitivity of standard two-tiered serological testing during the early stages often delays care and contributes to "therapeutic wandering." Consequently, there is an urgent need for advanced diagnostic technologies, such as host-based biomarkers and rapid biosensors. Furthermore, for patients experiencing persistent post-treatment symptoms (PTLDS), prolonged antibiotic regimens are ineffective and carry high risks; management should instead focus on multidisciplinary symptom support. Ultimately, combating Lyme disease requires heightened clinical vigilance, improved early diagnostics, and the development of next-generation vaccines.

Authors Contribution:

Conceptualization: Ewa Maraszewska
Methodology: Aleksandra Płecka, Karol Szkarłat
Software: Jędrzej Sztajura, Maksymilian Szklarski
Check: Alicja Stępień, Karol Zimnicki
Formal analysis: Weronika Szymacha, Michał Stachel
Investigation: Karol Szkarłat, Szymon Targosz
Resources: Szymon Targosz, Aleksandra Płecka
Data curration: Maksymilian Szklarski, Karol Zimnicki
Writing – rough preparation: Weronika Szymacha, Alicja Stępień
Writing – review and editing: Jędrzej Sztajura
Visualization: Michał Stachel, Ewa Maraszewska
Supervision: Ewa Maraszewska, Karol Szkarłat
Project administration: Ewa Maraszewska

All authors have read and agreed with the published version of the manuscript

Funding Statement: The study did not receive any special funding

Conflict of Interests Statement: The authors declare no conflict of interest.

Declaration of the use of generative ai and ai-assisted technologies in the writing process: During the preparation of this work, the authors used Google Gemini to improve language and readability. The authors subsequently reviewed and edited the content; they take full responsibility of the published work.

REFERENCES

1. Figoni, J., Chirouze, C., Hansmann, Y., Lemogne, C., Hentgen, V., Saunier, A., Bouiller, K., Gehanno, J. F., Rabaud, C., Perrot, S., Caumes, E., Eldin, C., de Broucker, T., Jaulhac, B., Roblot, F., Toubiana, J., Sellal, F., Vuillemet, F., Sordet, C., . . . Tattevin, P. (2019). Lyme borreliosis and other tick-borne diseases. Guidelines from the French Scientific Societies (I): Prevention, epidemiology, diagnosis. *Médecine et Maladies Infectieuses, 49*(5), 318–334. https://doi.org/10.1016/j.medmal.2019.04.381
2. Marques, A. R., Strle, F., & Wormser, G. P. (2021). Comparison of Lyme disease in the United States and Europe. *Emerging Infectious Diseases, 27*(8), 2017–2024. https://doi.org/10.3201/eid2708.204763
3. John, T. M., & Taege, A. J. (2019). Appropriate laboratory testing in Lyme disease. *Cleveland Clinic Journal of Medicine, 86*(11), 751–759. https://doi.org/10.3949/ccjm.86a.19029
4. Guérin, M., Shawky, M., Zedan, A., Octave, S., Avalle, B., Maffucci, I., & Padiolleau-Lefèvre, S. (2023). Lyme borreliosis diagnosis: State of the art of improvements and innovations. *BMC Microbiology, 23*(1), Article 204. https://doi.org/10.1186/s12866-023-02935-5
5. Zhou, G., Xu, X., Zhang, Y., Yue, P., Luo, S., Fan, Y., Chen, J., Liu, M., Dong, Y., Li, B., Kong, J., Wen, S., Liu, A., & Bao, F. (2021). Antibiotic prophylaxis for prevention against Lyme disease following tick bite: An updated systematic review and meta-analysis. *BMC Infectious Diseases, 21*(1), Article 1141. https://doi.org/10.1186/s12879-021-06837-7
6. Geebelen, L., Lernout, T., Devleesschauwer, B., Kabamba-Mukadi, B., Saegeman, V., Belkhir, L., De Munter, P., Dubois, B., Westhovens, R., Humtick Hospital Group, Van Oyen, H., Speybroeck, N., & Tersago, K. (2022). Non-specific symptoms and post-treatment Lyme disease syndrome in patients with Lyme borreliosis: A prospective cohort study in Belgium (2016–2020). *BMC Infectious Diseases, 22*(1), Article 756. https://doi.org/10.1186/s12879-022-07686-8
7. Tokarska-Rodak, M., Pańczuk, A., Fota-Markowska, H., & Matuska, K. (2021). Analysis of selected serological parameters in patients with diagnosed Lyme borreliosis and in seropositive patients with no clinical symptoms. *Annals of Agricultural and Environmental Medicine, 28*(3), 397–403. https://doi.org/10.26444/aaem/124088
8. Flynn, C., & Ignaszak, A. (2020). Lyme disease biosensors: A potential solution to a diagnostic dilemma. *Biosensors, 10*(10), Article 137. https://doi.org/10.3390/bios10100137
9. Cairns, V. (2020). Lyme disease: Implications for general practice. *British Journal of General Practice, 70*(692), 106–107. https://doi.org/10.3399/bjgp20X708341
10. Forrest, I. S., O'Neal, A. J., Pedra, J. H. F., & Do, R. (2023). Cholesterol contributes to risk, severity, and machine learning-driven diagnosis of Lyme disease. *Clinical Infectious Diseases, 77*(6), 839–847. https://doi.org/10.1093/cid/ciad307
11. Branda, J. A., & Steere, A. C. (2021). Laboratory diagnosis of Lyme borreliosis. *Clinical Microbiology Reviews, 34*(2), Article e00018-19. https://doi.org/10.1128/CMR.00018-19
12. Magnavita, N., Capitanelli, I., Ilesanmi, O., & Chirico, F. (2022). Occupational Lyme disease: A systematic review and meta-analysis. *Diagnostics, 12*(2), Article 296. https://doi.org/10.3390/diagnostics12020296
13. Snik, M. E., Stouthamer, N. E. I. M., Hovius, J. W., & van Gool, M. M. J. (2024). Bridging the gap: Insights in the immunopathology of Lyme borreliosis. *European Journal of Immunology, 54*(12), Article e2451063. https://doi.org/10.1002/eji.202451063
14. Dersch, R., Torbahn, G., & Rauer, S. (2024). Treatment of post-treatment Lyme disease symptoms—A systematic review. *European Journal of Neurology, 31*(7), Article e16293. https://doi.org/10.1111/ene.16293
15. Donta, S. T. (2022). What we know and don't know about Lyme disease. *Frontiers in Public Health, 9*, Article 819541. https://doi.org/10.3389/fpubh.2021.819541
16. Rauer, S., Kastenbauer, S., Hofmann, H., Fingerle, V., Huppertz, H. I., Hunfeld, K. P., Krause, A., Ruf, B., Dersch, R., & Consensus Group. (2020). Guidelines for diagnosis and treatment in neurology—Lyme neuroborreliosis. *German Medical Science, 18*, Article Doc03. https://doi.org/10.3205/000279
17. Steere, A. C. (2020). Posttreatment Lyme disease syndromes: Distinct pathogenesis caused by maladaptive host responses. *Journal of Clinical Investigation, 130*(5), 2148–2151. https://doi.org/10.1172/JCI138062
18. Myszkowska-Torz, A., Frydrychowicz, M., Tomaszewski, M., Figlerowicz, M., Mania, A., & Mazur-Melewska, K. (2023). Neuroborreliosis and post-treatment Lyme disease syndrome: Focus on children. *Life, 13*(4), Article 900. https://doi.org/10.3390/life13040900
19. Petrulionienė, A., Radzišauskienė, D., Ambrozaitis, A., Čaplinskas, S., Paulauskas, A., & Venalis, A. (2020). Epidemiology of Lyme disease in a highly endemic European zone. *Medicina, 56*(3), Article 115. https://doi.org/10.3390/medicina56030115
20. Garcia-Monco, J. C., & Benach, J. L. (2019). Lyme neuroborreliosis: Clinical outcomes, controversy, pathogenesis, and polymicrobial infections. *Annals of Neurology, 85*(1), 21–31. https://doi.org/10.1002/ana.25389
21. Radolf, J. D., Strle, K., Lemieux, J. E., & Strle, F. (2021). Lyme disease in humans. *Current Issues in Molecular Biology, 42*, 333–384. https://doi.org/10.21775/cimb.042.333

22. Coburn, J., Garcia, B., Hu, L. T., Jewett, M. W., Kraiczy, P., Norris, S. J., & Skare, J. (2021). Lyme disease pathogenesis. *Current Issues in Molecular Biology, 42*, 473–518. https://doi.org/10.21775/cimb.042.473
23. Zhou, Y., Qin, S., Sun, M., Tang, L., Yan, X., Kim, T. K., Caballero, J., Glusman, G., Brunkow, M. E., Soloski, M. J., Rebman, A. W., Scavarda, C., Cooper, D., Omenn, G. S., Moritz, R. L., Wormser, G. P., Price, N. D., Aucott, J. N., & Hood, L. (2020). Measurement of organ-specific and acute-phase blood protein levels in early Lyme disease. *Journal of Proteome Research, 19*(1), 346–359. https://doi.org/10.1021/acs.jproteome.9b00569
24. Marques, A. (2022). Persistent symptoms after treatment of Lyme disease. *Infectious Disease Clinics of North America, 36*(3), 621–638. https://doi.org/10.1016/j.idc.2022.04.004
25. Chen, W. H., Strych, U., Bottazzi, M. E., & Lin, Y. P. (2022). Past, present, and future of Lyme disease vaccines: Antigen engineering approaches and mechanistic insights. *Expert Review of Vaccines, 21*(10), 1405–1417. https://doi.org/10.1080/14760584.2022.2102484
26. Arvikar, S. L., & Steere, A. C. (2022). Lyme arthritis. *Infectious Disease Clinics of North America, 36*(3), 563–577. https://doi.org/10.1016/j.idc.2022.03.006
27. Williams, M. E., Schwartz, D. A., DeBiasi, R. L., & Mulkey, S. B. (2024). Examining infant and child neurodevelopmental outcomes after Lyme disease during pregnancy. *Pathogens, 13*(12), Article 1029. https://doi.org/10.3390/pathogens13121029
28. Puppo, C., Hansmann, Y., Moinot, L., Duval, X., Chirouze, C., & Préau, M. (2023). The social representations of diagnosing Lyme disease. *PLOS ONE, 18*(2), Article e0276800. https://doi.org/10.1371/journal.pone.0276800
29. Perner, J., Kucera, M., Frantova, H., Urbanova, V., Kopacek, P., & Sima, R. (2022). Lyme disease transmission by severely impaired ticks. *Open Biology, 12*(2), Article 210244. https://doi.org/10.1098/rsob.210244
30. Nymark, A., Huniche, L., Skarphedinsson, S., & Christensen, H. M. (2024). Initial symptoms and late complication in Lyme neuroborreliosis from the perspective of patients and relatives: A qualitative study. *BMC Primary Care, 25*, Article 379. https://doi.org/10.1186/s12875-024-02624-w
31. Stark, J. H., Pilz, A., Jodar, L., & Moïsi, J. C. (2023). The epidemiology of Lyme borreliosis in Europe: An updated review on a growing public health issue. *Vector-Borne and Zoonotic Diseases, 23*(4), 139–141. https://doi.org/10.1089/vbz.2022.0068
32. Valand, H. A., Goyal, A., Melendez, D. A., Matharu, S. S., Mangat, H. S., & Tu, R. K. (2019). Lyme disease: What the neuroradiologist needs to know. *American Journal of Neuroradiology, 40*(12), 1998–2000. https://doi.org/10.3174/ajnr.A6301