



Interdisciplinary Clinical Management of Lyme Disease: Implications for Nursing Practice, Pharmacotherapy, Diagnostic Laboratory Services, Radiological Assessment, and Public Health Surveillance

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Abstract

Background: Lyme disease is the most common tick-borne illness in the United States and a major global public health concern, progressing through early localized, early disseminated, and late stages, each with distinct clinical features. Its epidemiology is closely linked to Ixodes tick ecology, with high incidence in Northeastern and Midwestern U.S. regions.

Aim: This study aims to provide a comprehensive interdisciplinary review of Lyme disease, summarizing its etiology, epidemiology, clinical manifestations, diagnostic evaluation, and management to guide healthcare professionals in effective diagnosis and treatment.

Methods: A structured review of clinical, epidemiologic, diagnostic, and therapeutic evidence was conducted, synthesizing details on pathophysiology, histopathology, serologic testing, complications, and management approaches described in the source material.

Results: Lyme disease presents with dermatologic, neurologic, musculoskeletal, and cardiac manifestations across stages, with erythema migrans affecting ~70% of patients. Two-tier serologic testing remains the diagnostic standard for non-EM presentations. Stage-specific antibiotic therapy is effective in most cases, though 10–20% of patients may develop post-treatment Lyme disease syndrome (PTLDS).

Conclusion: Early recognition and timely treatment significantly reduce progression and complications, while interdisciplinary coordination enhances patient outcomes across diverse clinical presentations.

Keywords: Lyme disease, *Borrelia burgdorferi*, erythema migrans, tick-borne infections, serologic testing, PTLDS, antibiotic therapy.

Introduction

Lyme disease, also known as Lyme borreliosis, represents the most prevalent tick-borne infectious disease in the United States and ranks among the most frequently reported vector-borne infections globally. Its public health significance continues to increase due to expanding tick habitats and improved diagnostic awareness. The disease follows a well-recognized clinical progression that is

classically categorized into three sequential stages: early localized, early disseminated, and late-stage disease. Each stage reflects distinct pathological processes and clinical manifestations, although overlap between stages may occur in some patients. The early localized stage typically develops shortly after transmission through an infected tick bite and is most characteristically identified by erythema migrans. This lesion presents as an expanding

erythematous rash, often with central clearing, at the site of inoculation. Alongside this hallmark dermatologic finding, affected individuals may experience nonspecific systemic symptoms such as fatigue, headache, low-grade fever, muscle pain, and joint discomfort. In the majority of cases, the disease remains confined to this initial stage, and symptoms may resolve either spontaneously or with appropriate antimicrobial therapy. Approximately one fifth of patients progress to the early disseminated stage, during which hematogenous spread of the pathogen leads to multisystem involvement. This phase is commonly associated with the appearance of multiple erythema migrans lesions, reflecting secondary cutaneous dissemination. Patients may also report generalized flu-like symptoms, enlarged lymph nodes, worsening musculoskeletal pain, and neurological complications. Cranial neuropathies, particularly facial nerve palsy involving cranial nerve VII, are frequently observed. Ocular manifestations and lymphocytic meningitis further underscore central nervous system involvement. Cardiac complications may also emerge at this stage, including conduction disturbances, myocarditis, and pericarditis, which can pose significant clinical risk if unrecognized. Late-stage Lyme disease is most often characterized by inflammatory arthritis, typically presenting as intermittent or persistent pauciarticular joint involvement. Large joints, especially the knees, are most commonly affected, leading to pain, swelling, and functional limitation [1][2]. Despite its potentially progressive nature, Lyme disease remains a treatable and curable condition when diagnosed promptly and managed with appropriate therapeutic interventions [1][2].

Etiology

Lyme disease is caused by infection with spirochete bacteria of the genus *Borrelia*, with the specific species varying by geographic region. In the United States, the primary pathogen responsible for Lyme disease is *Borrelia burgdorferi*, although *Borrelia mayonii* has been identified in rare cases. Transmission occurs through the bite of infected black-legged ticks of the genus *Ixodes*. In Europe and Asia, the causative agents differ, with *Borrelia burgdorferi*, *Borrelia afzelii*, and *Borrelia garinii* representing the most common pathogens [3][4]. Geographic variation in pathogenic species contributes to differences in clinical manifestations. For instance, *B. burgdorferi* demonstrates a strong tropism for joint tissue, frequently leading to arthritic complications, whereas *B. garinii* predominantly affects the nervous system, resulting in neurologic symptoms. *B. afzelii* exhibits a preference for cutaneous tissue, often manifesting as dermatologic lesions. The epidemiology of Lyme disease is closely tied to the ecology of its vector ticks. In the United States, *Ixodes scapularis* serves as the main vector in the Northeastern and upper Midwestern regions, while *Ixodes pacificus* predominates in the Western region.

In Europe, *Ixodes ricinus* is the principal vector, whereas *Ixodes persulcatus* is responsible for transmission in Asia. Understanding the tick lifecycle is crucial to identifying periods of highest risk for human infection. *Ixodes* ticks undergo a 2- to 3-year life cycle that includes four stages: egg, larva, nymph, and adult. Advancement from larva to nymph and from nymph to adult requires a blood meal, and female ticks rely on blood consumption for reproduction. During these feeding events, ticks acquire *Borrelia* bacteria from animal host reservoirs, typically small mammals such as mice and voles or birds. Ticks attach to their hosts for periods ranging from three to seven days, allowing efficient transmission of the pathogen. Although ticks may feed on larger mammals, such as deer, these animals are not competent reservoirs for *Borrelia*. Infected nymphs and adult ticks subsequently transmit the bacteria during each feeding, sustaining the cycle of infection.

Epidemiology

Lyme disease is predominantly reported in the Northeastern and upper Midwestern regions of the United States, reflecting the distribution of the primary vector, *Ixodes scapularis*. States with the highest endemicity include Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, and Wisconsin. Cases have also been documented sporadically in northern California, Oregon, and Washington, highlighting the potential for geographic expansion beyond traditional endemic areas [5][6]. The incidence of Lyme disease exhibits strong seasonality, with most infections occurring during late spring, summer, and early fall. This pattern corresponds to the peak activity of nymph-stage ticks, which are more likely to feed on humans due to their small size and less noticeable bites. Human behavior during these months, including increased outdoor activity in wooded and grassy areas, further elevates the risk of exposure. In 2022, the US Centers for Disease Control and Prevention (CDC) received reports of 62,551 confirmed and probable Lyme disease cases. However, surveillance data are widely recognized as underestimating the true burden of disease, with some models suggesting the actual number of infections may be tenfold higher. Epidemiological trends indicate a higher incidence among males compared with females. Age distribution demonstrates a bimodal pattern, with children under 15 years and adults aged 45 years and older representing the largest affected groups. While Lyme disease can occur across all ethnicities, most reported cases are among White individuals, reflecting demographic patterns in endemic areas. These epidemiologic characteristics are essential for guiding public health interventions, informing risk communication, and targeting prevention strategies in populations at highest risk of infection.

Pathophysiology

Lyme disease is initiated when *Borrelia* spirochetes, residing in the midgut of infected Ixodes ticks, are transmitted to a human host during a blood meal. The feeding process stimulates the proliferation of spirochetes and induces the expression of outer surface protein C (OspC), a critical factor that facilitates the migration of the bacteria from the tick midgut to the salivary glands. This migration is necessary for effective transmission and explains why prolonged attachment of the tick—generally exceeding 15 hours—is required for the spirochete to infect humans. Once inoculated into the skin, *Borrelia* spirochetes disseminate locally and systemically, spreading through the bloodstream and connective tissues to target organs, including the joints, nervous system, and heart. The dissemination pattern and timing vary according to both the species of *Borrelia* and the developmental stage of the tick vector, influencing the clinical presentation of the disease [7]. Following infection, the host immune system responds through both innate and adaptive mechanisms. Macrophages recognize and attempt to phagocytize the spirochetes, while humoral immunity generates antibodies directed against *Borrelia* antigens. In some individuals, these immune responses are sufficient to eradicate the infection before clinical disease develops. However, *Borrelia* species possess sophisticated immune evasion strategies, including antigenic variation, inhibition of complement activation, and intracellular localization, which allow them to persist within host tissues despite an active immune response. Tissue damage observed in affected organs, such as the myocardium, synovial membranes, and neural tissues, is largely a result of host inflammatory processes rather than direct cytotoxic effects of the spirochete itself. The inflammatory response is responsible for the clinical manifestations observed in early disseminated and late-stage disease, including arthritis, carditis, and neurological complications [7].

The pathophysiology of posttreatment Lyme disease syndrome (PTLDS) remains incompletely understood. Evidence does not support ongoing active infection by *Borrelia* following standard antibiotic therapy. Proposed mechanisms include residual inflammatory activity, persistent immune dysregulation, or sustained responses to bacterial debris that remain after microbial clearance. Some patients exhibit chronic fatigue, musculoskeletal pain, and cognitive disturbances, suggesting that persistent inflammation or aberrant immune activation may contribute to ongoing symptoms. However, no single explanatory model has been universally validated, and further research is required to elucidate the underlying mechanisms [8]. Postinfectious Lyme arthritis provides a model for understanding host–pathogen interactions in the absence of active infection. In these cases, bacterial components or antigens may persist within the joint tissues, continuing to stimulate local immune responses. The immune system may also

react excessively to specific *Borrelia* proteins, generating prolonged synovial inflammation even in the absence of live organisms. This interplay between residual bacterial antigens and host immune overactivation illustrates the complexity of disease pathophysiology and highlights the need for targeted therapeutic strategies aimed at modulating immune responses rather than eliminating persistent infection [9]. This understanding of *Borrelia* pathophysiology underscores the importance of early diagnosis and treatment to prevent dissemination, reduce tissue inflammation, and limit the risk of chronic sequelae.

Histopathology

Erythema migrans, the hallmark cutaneous manifestation of early Lyme disease, typically does not require biopsy for clinical diagnosis. Histologic findings in erythema migrans are generally nonspecific and reflect a local immune response to the tick-borne *Borrelia* infection rather than a pathognomonic pattern. Examination of affected skin often demonstrates a perivascular cellular infiltrate composed primarily of histiocytes, lymphocytes, and plasma cells. In some cases, mast cells and neutrophils may be present, though they are less commonly observed. Eosinophilic infiltrates can occasionally be detected, likely representing a localized reaction to the tick bite itself. While spirochetes can sometimes be visualized using antibody-labeled or silver-based staining techniques, their detection in skin biopsy specimens is uncommon. Consequently, histologic identification of *Borrelia* organisms is not considered a reliable diagnostic criterion and should not replace clinical assessment [10]. Acrodermatitis chronica atrophicans (ACA), a late-stage dermatologic manifestation of Lyme disease, requires histopathological evaluation to confirm diagnosis and distinguish it from clinically similar conditions such as morphea, mycosis fungoides, or lichen sclerosis. Histopathology of ACA characteristically demonstrates interstitial granulomatous infiltrates with a predominance of CD68-positive histiocytes and CD3-positive lymphocytes. Plasma cells may be detected infrequently and are visualized with CD138 staining. Thickened collagen bundles are a common feature, accompanied by band-like infiltrates of CD4-positive T cells. Interstitial fibroblasts are typically reduced in number and can be highlighted through CD34 staining. The combination of these features provides essential diagnostic information, allowing differentiation from other chronic inflammatory or fibrosing dermatoses [10].

Borrelial lymphocytoma represents another cutaneous manifestation of Lyme disease that can pose diagnostic challenges, particularly in cases where clinical history is insufficient for definitive diagnosis. Histopathologic examination serves to exclude neoplastic or other nodular etiologies. Biopsy specimens commonly reveal a dense dermal polyclonal lymphocytic infiltrate, often organized into lymphoid follicles with pseudoterminal centers,

resembling a pseudolymphoma. This pattern reflects the host immune response to *Borrelia* antigens rather than direct bacterial toxicity. Despite the presence of these histologic features, findings remain nonspecific, underscoring the importance of integrating clinical, epidemiologic, and serologic data when establishing a diagnosis of *Borrelia* lymphocytoma [11]. Overall, histopathologic evaluation in Lyme disease provides important supportive evidence, particularly in atypical or late-stage dermatologic manifestations. While tissue analysis can reveal characteristic inflammatory patterns, the absence of detectable spirochetes in skin biopsies highlights the limitations of relying solely on histology for diagnosis. Integrating histopathologic findings with clinical presentation and laboratory confirmation ensures accurate identification and appropriate management of Lyme disease across its varied cutaneous manifestations.

History and Physical

Lyme disease is a multisystem infection caused by *Borrelia* species, and its clinical course is classically divided into three stages: early localized, early disseminated, and late disease. Although a small proportion of patients—estimated between 1.6% and 7%—may remain asymptomatic following infection [7], most individuals develop clinical manifestations at some stage. The initial presentation is most frequently erythema migrans, a cutaneous lesion that serves as a hallmark of early localized disease. This characteristic rash typically appears one to two weeks following a tick bite and represents the earliest recognizable sign of infection. When untreated, the infection may progress to early disseminated or late-stage disease, affecting multiple organ systems. In the early localized stage, patients often present with the erythema migrans rash accompanied by nonspecific systemic symptoms. The rash usually appears at the site of the tick bite and can expand over several days, sometimes developing concentric rings that create the classic “bull’s-eye” appearance. Erythema migrans occurs in approximately 70% of patients and may be associated with mild pruritus, burning, or may be asymptomatic. Concurrent systemic manifestations can include low-grade fever, myalgia, neck stiffness, and headache. Ophthalmologic findings such as eye redness and tearing have also been reported. Without treatment, the lesion may persist for two to three weeks and expand up to 20 cm in diameter. Recurrent or multiple lesions occur in roughly 20% of patients, reflecting secondary dissemination of the spirochete. Flu-like symptoms often accompany the rash during this stage, indicating systemic immune activation.



Fig. 1: Lyme disease.

The early disseminated phase generally occurs three to twelve weeks after the initial infection and reflects hematogenous and tissue dissemination of *Borrelia*. Patients may present with general malaise, fever, dizziness, headache, myalgia, and cardiac symptoms including chest pain, palpitations, or dyspnea. Neurological involvement is seen in approximately 20% of cases, manifesting as lymphocytic meningitis, cranial neuropathies, radiculopathy, peripheral neuropathy, or, less commonly, encephalomyelitis. Facial nerve palsy (Bell palsy) occurs in about 5% of patients and may present unilaterally or bilaterally. The classic neurologic triad of meningitis, cranial neuropathy, and radiculoneuropathy may be seen, although individual components can occur independently. Cardiac manifestations during this stage include transient conduction abnormalities, arrhythmias, and rarely fulminant carditis. Most conduction disturbances are self-limiting, and permanent pacemaker placement is seldom required. Ocular involvement is uncommon but can include conjunctivitis, keratitis, uveitis, retinal vasculitis, or optic neuropathy. Borrelial lymphocytoma, a slow-growing, painless, red-blue plaque or nodule, is another rare manifestation, more frequently reported in European populations, often affecting the earlobe in children or the breast in adults. These lesions may resolve spontaneously without intervention [11]. Late-stage Lyme disease develops months after the initial infection and frequently involves neurological and musculoskeletal systems. Notably, many patients may lack a history of erythema migrans. Neurological sequelae may include sensory axonal polyneuropathy, mononeuropathy, or encephalomyelitis. Cognitive deficits are common, with patients reporting difficulties in concentration, memory, and executive function. Mood disturbances, including irritability and depression, are also frequently observed. Severe neurological involvement may present with ataxia, seizures, hemiparesis, autonomic dysfunction, or hearing loss.

Musculoskeletal manifestations primarily involve large joints, particularly the knee, presenting as arthritis with swelling, stiffness, and pain. Less commonly, smaller joints such as the elbow may be affected, and inflammatory episodes may involve bursitis or tendinitis. Most cases of Lyme arthritis resolve over time; however, a subset of patients develops chronic inflammatory arthritis, referred to as postinfectious Lyme arthritis, which resembles rheumatoid arthritis in its presentation.

Acrodermatitis chronica atrophicans (ACA) represents a late dermatologic manifestation of Lyme disease, predominantly observed in older women. This condition typically affects the dorsum of the hands and feet and initially presents as bluish-red discoloration with mild swelling. Over time, the lesions expand and result in atrophic skin changes. ACA may manifest years after the primary infection and is often misdiagnosed due to its clinical similarity to morphea. Histopathologic evaluation and a careful patient history are essential for accurate diagnosis, particularly in European cohorts where the condition is more commonly reported. Overall, the history and physical examination of Lyme disease require careful attention to the stage-specific manifestations. Recognizing erythema migrans, neurological deficits, musculoskeletal involvement, and late dermatologic changes is crucial for timely diagnosis and effective management, especially in endemic regions and in patients with potential exposure to tick habitats. Coinfections with other tick-borne pathogens, including *Babesia microti* and *Ehrlichia* species, should also be considered, as they may complicate the clinical picture and affect treatment strategies. Approximately 10% of patients with Lyme disease experience such coinfections, emphasizing the need for comprehensive clinical assessment [12].

Evaluation

The evaluation of Lyme disease poses significant challenges due to the nonspecific nature of its clinical presentation and the fact that many patients do not recall a tick bite or the presence of erythema migrans. Early manifestations such as fatigue, headache, myalgia, and low-grade fever are common but overlap with a wide range of other conditions. Consequently, clinical suspicion often guides initial assessment, especially in individuals residing in or traveling to endemic areas. The Centers for Disease Control and Prevention (CDC) recommends a two-step serologic testing approach using FDA-cleared assays for suspected cases where the diagnosis is uncertain [13]. Serologic testing is limited in the early stages of infection, as the immune system requires time to mount a detectable antibody response. For patients presenting with the characteristic erythema migrans rash and a compatible exposure history, clinical diagnosis may suffice, and treatment can be initiated without laboratory confirmation. In later stages, serologic testing is essential for establishing the diagnosis. The first step involves a quantitative

screening test for serum antibodies to *Borrelia burgdorferi* using a sensitive enzyme immunoassay (EIA) or immunofluorescent antibody assay. If the initial test is negative, further testing is not recommended. Positive or equivocal results are confirmed using Western blot analysis, following the standard two-tier approach. According to CDC criteria, a positive IgM immunoblot requires at least two of three specific bands within 30 days of symptom onset, whereas a positive IgG immunoblot requires five to ten bands at any time [13]. This approach achieves greater than 80% sensitivity in patients with neurologic or cardiac involvement [14][15][16]. Sequential serologic testing is not recommended during acute infection, as antibody titers may remain elevated for months or years, making interpretation difficult. Testing of the tick itself is also discouraged due to the lack of predictive value. False positives can occur in conditions such as syphilis, rheumatoid arthritis, relapsing fever, and Epstein-Barr virus infection.

In patients with suspected cardiac involvement, serologic testing is indicated for acute myocarditis or pericarditis of unknown origin in epidemiologically relevant settings. Screening electrocardiograms are recommended for individuals presenting with palpitations, dyspnea, chest pain, syncope, or other cardiac symptoms in endemic regions. Severe manifestations, including PR interval prolongation exceeding 300 milliseconds, pericardial effusion, elevated cardiac biomarkers, or exercise intolerance, warrant hospital admission for continuous ECG monitoring. This approach ensures early identification of potentially life-threatening cardiac complications. Neurologic evaluation is warranted for patients presenting with meningitis, radiculoneuritis, mononeuropathy multiplex, cranial neuropathies, or evidence of central nervous system inflammation. Testing is particularly important in patients with plausible exposure to *Borrelia*-infected ticks [17]. Timely identification allows prompt initiation of therapy to prevent irreversible neurologic damage. For suspected Lyme arthritis, joint aspiration is indicated only when inflammatory arthritis is suspected. Serum antibody testing remains the preferred method for diagnosing Lyme-related joint involvement, while polymerase chain reaction (PCR) testing of synovial fluid or tissue is reserved for cases with diagnostic uncertainty despite positive serologies. Culture of blood or tissue is rarely necessary and is not recommended for routine evaluation. Overall, the evaluation of Lyme disease requires a nuanced integration of clinical findings, epidemiologic risk factors, and appropriate laboratory testing. Early recognition and accurate diagnostic methods are essential to guide therapy, prevent disease progression, and manage complications across diverse organ systems.

Treatment / Management

The management of Lyme disease depends on the stage of infection, clinical manifestations, and patient-specific factors, with treatment primarily aimed at eradicating *Borrelia* species and preventing progression to more severe disease. In asymptomatic patients who have experienced a known tick bite, prophylactic therapy may be indicated under specific conditions. The CDC recommends a single oral dose of doxycycline at 200 mg for adults or 4.4 mg/kg (maximum 200 mg) for children when the bite involves an identified *Ixodes* species, occurred in a highly endemic area, and the tick was attached for 36 hours or longer [17]. This approach aims to prevent the establishment of infection before the onset of clinical symptoms. For patients presenting with erythema migrans, the initial manifestation of early localized Lyme disease, immediate antibiotic therapy is recommended without awaiting confirmatory testing, particularly in endemic regions. First-line oral treatments include doxycycline for ten days, or amoxicillin or cefuroxime axetil for 14 days. Patients with allergies or intolerance to these antibiotics may receive azithromycin for five to ten days. In cases where the rash is atypical but suggestive of Lyme disease, serologic testing may be used to support the clinical diagnosis prior to initiating therapy [17]. Prompt treatment at this stage is critical to prevent progression to early disseminated or late disease, which may involve neurologic, cardiac, or musculoskeletal complications. Neurologic manifestations, such as meningitis, radiculopathy, or cranial neuropathies, require a more aggressive approach. Intravenous antibiotics, including ceftriaxone, cefotaxime, or penicillin G, are recommended for 14 to 21 days, though oral doxycycline may be considered in selected cases. The choice between oral and intravenous therapy depends on patient factors including tolerability, access to care, and risk of adverse effects [17]. Cardiac involvement, such as Lyme carditis with heart block, generally resolves with appropriate antibiotic therapy. Mild cases may be managed with outpatient oral doxycycline, while severe presentations requiring hospitalization benefit from intravenous ceftriaxone, with a transition to oral therapy as clinical improvement occurs. Temporary pacing may be used in symptomatic heart block, but permanent pacemakers are rarely necessary, reflecting the reversible nature of antibiotic-responsive cardiac involvement [17].

Lyme arthritis is typically treated with a 28-day course of oral doxycycline. Partial responders may receive a second course of oral therapy, while refractory cases are treated with intravenous ceftriaxone for two to four weeks. For patients who develop persistent postantibiotic Lyme arthritis without evidence of active infection, referral to a rheumatologist is recommended for consideration of intra-articular corticosteroids, disease-modifying antirheumatic drugs, or other advanced therapeutic

strategies [17]. Borrelial lymphocytoma and acrodermatitis chronica atrophicans, rare cutaneous manifestations, are treated with oral antibiotics for 14 days and 21 to 28 days, respectively [17]. A subset of patients, approximately 10% to 20%, may experience persistent symptoms following standard therapy, termed posttreatment Lyme disease syndrome (PTLDS) [18]. PTLDS is characterized by nonspecific symptoms such as fatigue, pain, and cognitive difficulties in the absence of objective disease findings. Additional antibiotic therapy has not demonstrated clinical benefit. Management is focused on symptom control, with analgesics, nonsteroidal anti-inflammatory drugs, heat therapy, physical rehabilitation, and medication review to minimize neurocognitive contributors. Multidisciplinary referral to rheumatology, neurology, physical therapy, and psychiatry may be appropriate to optimize quality of life. Special populations require careful selection of antibiotics. Doxycycline is contraindicated in children under eight and during pregnancy due to the risk of tooth staining and bone growth interference. In these cases, amoxicillin or cefuroxime is preferred. Dosing duration is tailored to age and disease stage, with ten days for early localized disease in patients over eight treated with doxycycline and 14 days for younger children receiving alternative agents [19][20][21].

Clinicians should also monitor for the Jarisch-Herxheimer reaction, a transient inflammatory response occurring in 5% to 15% of patients during the first 24 hours of antibiotic therapy. This cytokine-mediated reaction results from rapid spirochete lysis and may temporarily exacerbate symptoms, including fever, myalgia, and malaise. Supportive care with acetaminophen or oral nonsteroidal anti-inflammatory drugs is usually sufficient, and treatment should continue without interruption. In summary, Lyme disease management is stage-specific, symptom-directed, and evidence-based. Early recognition and timely initiation of appropriate antibiotics are essential to prevent dissemination and chronic complications. Multidisciplinary care is critical for patients with persistent symptoms or refractory disease, ensuring comprehensive management of both physical and neurocognitive sequelae. Effective therapy, adherence to treatment protocols, and close monitoring can substantially improve patient outcomes and reduce the risk of long-term disability.

Differential Diagnosis

The diagnosis of Lyme disease relies heavily on clinical evaluation, particularly in patients presenting with erythema migrans, where careful history taking and physical examination are often sufficient. However, a significant proportion of patients do not recall a tick bite or never develop the characteristic rash, complicating the diagnostic process. In such cases, clinicians must consider a broad differential diagnosis that aligns with the observed clinical manifestations. For patients with erythema migrans, conditions that may mimic the rash

include arthropod hypersensitivity reactions, Southern tick-associated rash illness (STARI), cellulitis, erysipelas, erythema multiforme, tinea infections, nummular eczema, granuloma annulare, contact dermatitis, urticaria, fixed drug eruptions, pityriasis rosea, parvovirus B19 infection, dermatomyositis, and systemic lupus erythematosus. Neuroborreliosis, characterized by neurologic manifestations such as facial palsy, radiculopathy, or meningitis, requires differentiation from viral meningitis, other causes of cranial neuropathies, multiple sclerosis, and autoimmune-mediated encephalomyelitis. Cardiac involvement in Lyme disease, including conduction abnormalities or myopericarditis, must be distinguished from other infectious and noninfectious cardiac disorders that can present similarly. Lyme arthritis shares clinical overlap with conditions such as gout, calcium pyrophosphate deposition disease, septic arthritis, viral arthritis, psoriatic arthritis, reactive arthritis, early rheumatoid arthritis, seronegative spondyloarthritis, and sarcoid arthritis. Rare dermatologic presentations, such as acrodermatitis chronica atrophicans, require consideration of aging-related skin changes, chilblains, venous insufficiency, superficial thrombophlebitis, eczema, morphea, and scleroderma, while borrelial lymphocytoma must be differentiated from centrollicular or follicular B-cell lymphoma, Paget disease, inflammatory breast cancer, sarcoidosis, chronic infections, and insect bite reactions. Posttreatment Lyme disease syndrome, presenting with nonspecific symptoms, overlaps with conditions including long COVID, depression, hypothyroidism, fibromyalgia, myalgic encephalomyelitis, and micronutrient deficiencies such as vitamin B12 deficiency. Accurate differentiation among these conditions is crucial to avoid misdiagnosis, unnecessary treatments, or delayed intervention, highlighting the need for clinicians to integrate epidemiologic risk, clinical presentation, and serologic testing in the evaluation process [21].

Prognosis

The prognosis of Lyme disease is generally favorable when treatment is initiated early. For patients diagnosed and managed during the initial stages of infection, clinical resolution occurs in more than 80% of cases following standard antibiotic regimens [7]. Early recognition and timely intervention substantially reduce the risk of progression to disseminated or late-stage disease and limit complications affecting the nervous system, heart, or joints. Despite effective therapy, approximately 10% to 20% of patients experience lingering symptoms, collectively referred to as posttreatment Lyme disease syndrome (PTLDS), which may persist for six months or longer. These symptoms often include fatigue, musculoskeletal discomfort, and cognitive difficulties, and while they are not typically associated with active infection, they

may significantly impact quality of life. The development of PTLDS underscores the importance of ongoing patient monitoring and supportive management strategies. Advances in preventive measures include a novel vaccine targeting *Borrelia* outer surface protein A, currently under evaluation in a three-year clinical trial initiated in 2022. If successful, this vaccine has the potential to significantly reduce the incidence of Lyme disease, particularly in high-risk populations, providing a proactive tool for prevention and complementing existing strategies such as personal protective measures, environmental interventions, and early therapeutic management.

Complications

Lyme disease can result in a range of systemic complications if left untreated or inadequately managed. Musculoskeletal involvement often manifests as Lyme arthritis, predominantly affecting large joints such as the knees, and in some cases leading to chronic postinfectious inflammatory arthritis. Cardiac complications, collectively referred to as Lyme carditis, may include conduction abnormalities, myopericarditis, and, rarely, fulminant cardiac events requiring hospitalization. Neurologic deficits encompass cranial neuropathies, radiculopathies, meningitis, and, in severe cases, encephalomyelitis or polyneuropathy. Ocular manifestations, although uncommon, may include conjunctivitis, keratitis, iridocyclitis, optic neuropathy, or retinal vasculitis. Dermatologic sequelae such as acrodermatitis chronica atrophicans and borrelial lymphocytoma may result in chronic skin lesions that persist over months to years. These complications underscore the importance of early diagnosis, accurate staging, and timely initiation of appropriate antimicrobial therapy to prevent long-term morbidity and facilitate recovery [7][8][9].

Consultations

Management of Lyme disease frequently requires interdisciplinary collaboration, particularly when patients present with complex or multisystem involvement. Consultations from infectious disease specialists are essential for diagnostic confirmation and selection of appropriate antimicrobial regimens. Dermatology input is valuable in cases with atypical rashes, chronic skin lesions, or conditions such as acrodermatitis chronica atrophicans. Neurology consultations are indicated for patients with cranial neuropathies, radiculopathies, meningitis, or cognitive deficits. Rheumatology may be required for persistent or postantibiotic Lyme arthritis, while cardiology evaluation is critical in cases of symptomatic heart block or myopericarditis. Effective coordination among these specialties ensures comprehensive evaluation, prompt intervention, and optimal patient outcomes [21].

Patient Education

Prevention of Lyme disease relies on personal protective measures, environmental

awareness, and early recognition of exposure risk. Individuals in endemic regions are advised to utilize chemical repellents containing DEET, picaridin, IR3535, oil of lemon eucalyptus, PMD, 2-undecanone, or permethrin to reduce the likelihood of tick attachment [17]. Additional protective strategies include wearing long-sleeved clothing, long pants, and closed footwear, showering immediately after outdoor activities, and conducting thorough inspections for ticks on the body and scalp. For children, particular attention should be given to the scalp, ears, groin, and buttocks. Mechanical removal of attached ticks using fine-tipped tweezers is recommended, with careful observation of the tick's features to aid in reporting and potential evaluation by healthcare professionals. Patients who develop signs of Lyme disease, such as erythema migrans, fever, fatigue, neurologic symptoms, or joint and cardiac complaints, should seek immediate medical attention. Prophylactic antibiotics may be considered for high-risk tick exposures, but routine post-bite antibiotic therapy is not indicated for asymptomatic individuals unless specific criteria are met [17].

Other Issues

Clinicians should remain vigilant for potential coinfections with other tick-borne pathogens, including *Babesia microti* and *Anaplasma phagocytophilum*, particularly in regions where *Ixodes scapularis* is prevalent. Coinfected patients may present with more severe symptoms, prolonged fever, and laboratory abnormalities such as anemia, leukopenia, and thrombocytopenia. Management requires tailored antimicrobial therapy for each pathogen to achieve complete resolution. Awareness of coinfections is critical to prevent treatment failure and ensure comprehensive patient care.

Enhancing Healthcare Team Outcomes

Optimal management of Lyme disease depends on an interprofessional approach spanning prevention, early recognition, and timely intervention. Primary care clinicians play a pivotal role in educating patients on preventive strategies, recognizing early disease manifestations, and initiating appropriate diagnostic testing. Urgent care and emergency medicine providers are essential in identifying both early and late-stage disease, ordering appropriate serologic tests, and facilitating specialist referrals. Collaboration with infectious disease specialists ensures diagnostic accuracy, while input from dermatology, cardiology, neurology, and rheumatology supports evaluation of complex presentations. Pharmacists contribute to safe and effective antimicrobial therapy, and nursing staff provide patient education, monitoring, and support throughout treatment. Effective communication and coordinated care among these team members are critical to achieving favorable patient outcomes, minimizing complications, and promoting comprehensive management of Lyme disease across the continuum of care [21].

Conclusion:

Lyme disease remains a complex multisystem illness requiring timely recognition, accurate staging, and prompt treatment to prevent long-term morbidity. Early localized infection—often marked by erythema migrans—is highly responsive to short-course antibiotic therapy, preventing progression to neurologic, cardiac, or rheumatologic involvement. As the disease advances, manifestations become more diverse, necessitating careful diagnostic integration of clinical findings, epidemiologic risk, and serologic confirmation. Effective management is stage-specific, with oral or intravenous antibiotics selected based on organ involvement, and interdisciplinary care improving outcomes for complex cases. Despite appropriate treatment, a subset of patients may experience persistent symptoms consistent with PTLDS, emphasizing the need for supportive, multidisciplinary follow-up rather than prolonged antibiotic use. Overall, improving public awareness, enhancing preventive measures, and ensuring coordinated healthcare delivery are essential to reducing disease burden and optimizing long-term outcomes for affected individuals.

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