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Epidemiology of Lyme Disease 495
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Lyme disease is the most common vector-borne illness in North America and Europe. The etiologic agent, Borrelia burgdorferi sensu lato, is transmitted to humans by certain species of Ixodes ticks, which are found widely in temperate regions of the Northern hemisphere. Clinical features are diverse but death is rare. The risk of human infection is determined by the distribution and abundance of vector ticks, ecologic factors influencing tick infection rates, and human behaviors that promote tick bite. Rates of infection are highest among children aged 5 to 15 years and adults aged more than 50 years. In the northeastern United States where disease is most common, exposure occurs primarily in areas immediately around the home. Knowledge of disease epidemiology is important for patient management and proper diagnosis.

Early Lyme Disease (Erythema Migrans) and Its Mimics (Southern Tick-Associated Rash Illness and Tick-Associated Rash Illness) 523
Franc Strle and Gary P. Wormser

Erythema migrans, an expanding erythematous skin lesion that develops days to weeks following an Ixodes species tick bite, is the most common clinical manifestation of Lyme disease. Presentations in the United States differ somewhat from that in Europe, presumably because of the different etiologic agents. Diagnosis is based on the appearance of the skin lesion, rather than on laboratory testing. After treatment with an appropriate oral antibiotic for 10 to 14 days, the prognosis is excellent. Two conditions that cause a similar skin lesion following a tick bite, but are of unknown cause, are Southern tick-associated rash illness in the United States and tick-associated rash illness in Japan.

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Early disseminated Lyme disease can involve the peripheral or central nervous system, but with early diagnosis and treatment, prognosis for full recovery is excellent. The typical clinical presentations of neuroborreliosis are highlighted, and an approach to diagnosis and treatment is described.
Cardiac Manifestations of Lyme Disease 553
Richard V. Shen and Carol A. McCarthy

Lyme carditis is an uncommon manifestation of Lyme disease. Most cases present with heart block of varying degrees, but the spectrum of disease includes other transient arrhythmias and structural manifestations, such as myopericarditis or cardiomyopathy. Antibiotics hasten the resolution of Lyme carditis, and cardiac pacing can be an adjunctive therapy. Outcomes are generally good, but there are rare fatalities associated with Lyme carditis. The latter underscores the continued need for improved modes of prevention of Lyme disease and the importance of its early recognition and treatment.

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Sheila L. Arvikar and Allen C. Steere

Arthritis is the most common late manifestation of Borrelia burgdorferi infection in the United States, usually beginning months after the tick bite. In most patients with Lyme arthritis (LA) today, arthritis is the presenting manifestation of the disease. Patients have swelling and pain in one or a few large joints, especially the knee. Serologic testing is the mainstay of diagnosis. Responses to antibiotic treatment are generally excellent, although a small percentage of patients have persistent, postinfectious synovitis after 2 to 3 months of oral and IV antibiotics, which respond to anti-inflammatory therapies. Herein we review the clinical presentation, diagnosis, and management of LA.

Nervous System Lyme Disease–Facts and Fallacies 579
John J. Halperin

The central or peripheral nervous systems may be involved in up to 15% of patients with untreated infection with B burgdorferi sensu lato, characteristic involvement including meningitis, cranial neuritis, and radiculoneuritis. Diagnosis, based on a logical combination of clinical context and antibody-based testing, is usually straightforward, as is treatment. Misconceptions about what does and does not constitute neurologic disease, and about laboratory testing in this infection, have resulted in widespread anxiety that a broad range of other disorders may be attributable to nervous system Lyme disease. This article will review the reasons for these misunderstandings and the arguments against them.

Lyme Disease in Children 593
Carol A. McCarthy, Jason A. Helis, and Brian E. Daikh

Lyme disease is now the most frequently reported vector-borne disease in the United States. The highest incidence is in children aged 5 to 9 years with a male predominance. The most common manifestation, erythema migrans, is sometimes not recognized, leading to risk of complications. Testing for Lyme disease should only be done if there is a consistent clinical syndrome with exposure in a Lyme-endemic area. Most forms of Lyme disease are successfully treated with short courses of oral therapy. Prevention and management of tick bites is important.
Diagnostic Testing for Lyme Disease

Takaaki Kobayashi and Paul G. Auwaerter

Standard 2-tier testing (STTT), incorporating a screening enzyme immunoassay (EIA) or an immunofluorescence assay (IFA) that reflexes to IgM and IgG immunoblots, has been the primary diagnostic test for Lyme disease since 1995. In 2019, the Food and Drug Administration approved a modified 2-tier test strategy using 2 EIAs: offering a faster, less expensive, and more sensitive assay compared with STTT. New technologies examine early immune responses to Borrelia burgdorferi have the potential to diagnose Lyme disease in the first weeks of infection when existing serologic testing is not recommended due to low sensitivity.

Persistent Symptoms After Treatment of Lyme Disease

Adriana Marques

Most patients with Lyme disease will fully recover with recommended antibiotic therapy. However, some patients report persisting nonspecific symptoms after treatment, referred to as posttreatment Lyme disease symptoms (PTLDS) or syndrome (PTLDs), depending on the degree to which the individual’s symptoms impact their quality of life. PTLDS occur in a portion of patients diagnosed with chronic Lyme disease (CLD), a controversial term describing different patient populations, diagnosed based on unvalidated tests and criteria. Practitioners should review the evidence for the Lyme disease diagnosis and not overlook unrelated conditions. Current evidence shows that prolonged antibiotic therapy provides little benefit and carries significant risk. Further research to elucidate the mechanisms underlying persistent symptoms after Lyme disease and to understand CLD is needed.

Human Granulocytic Anaplasmosis

Douglas MacQueen and Felipe Centellas

Human granulocytic anaplasmosis (HGA) is a bacterial infection caused by Anaplasma phagocytophilum and transmitted by the bite of the black-legged (deer tick) in North America. Its incidence is increasing. HGA can be transmitted after 24 to 48 hours of tick attachment. The incubation period is 5 to 14 days after a tick bite. Symptoms include fever, chills, headache, and myalgia. Complications include shock, organ dysfunction, and death. Mortality is less than 1% with appropriate treatment. Doxycycline is first line treatment for all ages. Start it empirically if symptoms and risk factors suggest HGA. PCR is the confirmatory test of choice.

Human Babesiosis

Rami Waked and Peter J. Krause

Babesiosis is caused by intraerythrocytic parasites that are transmitted primarily by ticks, infrequently through blood transfusion, and rarely through transplacental transmission or organ transplantation. Human babesiosis is found throughout the world, but the incidence is highest in the Northeast and upper Midwestern United States. Babesiosis has clinical features that resemble malaria and can be fatal in immunocompromised and older patients. Diagnosis is confirmed by identification of
Babesia parasites on blood smear or Babesia DNA with polymerase chain reaction. Standard treatment consists of atovaquone and azithromycin or clindamycin and quinine for 7 to 10 days.

**Powassan Virus Encephalitis**

Anne Piantadosi and Isaac H. Solomon

Powassan virus is an increasingly recognized cause of severe encephalitis that is transmitted by Ixodes ticks. Given the nonspecific clinical, laboratory, and imaging features of Powassan virus disease, providers should consider it in patients with compatible exposures and request appropriate testing.

**When to Think About Other Borreliae: Hard Tick Relapsing Fever (Borrelia miyamotoi), Borrelia mayonii, and Beyond**

Kyle G. Rodino and Bobbi S. Pritt

In North America, several hard tick-transmitted Borrelia species other than Borrelia burgdorferi cause human disease, including Borrelia miyamotoi, Borrelia mayonii, and possibly Borrelia bissettii. Due to overlapping clinical syndromes, nonspecific tickborne disease (TBD) testing strategies, and shared treatment approaches, infections with these lesser known Borrelia are likely under-reported. In this article, we describe the epidemiology, clinical manifestations, diagnosis, and treatment of these less common Borrelia pathogens.

**The Role of the Infectious Disease Consultation in Lyme Disease**

Jean Dejace

A consultation regarding Lyme disease can be challenging for the infectious disease physician when the referral question centers on the use of prolonged or empirical antibiotic treatment of Lyme disease and associated tick-borne infections. Patients who have been infected with Borrelia burgdorferi, and many who have been misdiagnosed, are confronted with a seemingly endless array of misinformation that is not in keeping with the current understanding of the clinical spectrum of Lyme disease and its response to evidence-based treatment. Preparing for these conversations with a good grasp of the public beliefs regarding Lyme disease and its treatment can be beneficial.