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| <p>Lyme borreliosis is a zoonotic, tick-borne disease that infects humans worldwide. The disease is currently recognized as the most common vector-borne disease in Europe and North America. Disease is caused by several genospecies of the <i>Borrelia burgdorferi</i> sensu lato complex. Humans are at high risk of infection in regions where highly competent reservoirs are the primary hosts for the subadult stages of the tick, in contrast to regions where less competent or refractory animals feed ticks. Human infections are also most frequently associated with spring and summer months when the nymph stage of the tick is active.</p> | |
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| <p><i>Borrelia burgdorferi</i> is the tick-borne etiologic agent of Lyme disease. The spirochete must negotiate numerous barriers in order to establish a disseminated infection in a mammalian host. These barriers include migration from the feeding tick midgut to the salivary glands, deposition in skin, manipulation or evasion of the localized host immune response, adhesion to and extravasation through an endothelial barrier, hematogenous dissemination, and establishment of infection in distal tissue sites. <i>Borrelia burgdorferi</i> proteins that mediate many of these processes and the nature of the host response to infection are described.</p> | |
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| <p>Lyme disease is the most common tick-borne illness in the United States and is also seen in areas of Europe and Asia. The growing deer and <i>Ixodes</i> species tick populations in many areas underscore the importance of clinicians to properly recognize and treat the different stages of Lyme disease. Controversy regarding the cause and management of persistent symptoms following treatment of Lyme disease persists and is highlighted in this review.</p> | |
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| <p>Nervous system involvement occurs in 10% to 15% of patients infected with the tick-borne spirochetes <i>Borrelia burgdorferi</i>, <i>B. afzelii</i>, and <i>B. garinii</i>. Peripheral nervous system involvement is common. Central nervous system (CNS) involvement, most commonly presenting with lymphocytic</p> | |

meningitis, causes modest cerebrospinal fluid (CSF) pleocytosis. Parenchymal CNS infection is rare. If the CNS is invaded, however, measuring local production of anti-*B burgdorferi* antibodies in the CSF provides a useful marker of infection. Most cases of neuroborreliosis can be cured with oral doxycycline; parenteral regimens should be reserved for patients with particularly severe disease.

Lyme Disease Diagnosis: Serology

797

Martin E. Schriefer

Serology is the mainstay of confirmation of Lyme borreliosis; direct detection has limited application. Because standardized 2-tier testing (STTT) has been commonly used since the mid 1990s, standardization and performance have improved. STTT detection of early, localized infection is poor; that of late disease is good. The best indicator of stage 1 infection, erythema migrans, is presented in the majority of US cases and should prompt treatment without testing. Clinical and epidemiologic correlates should be carefully assessed before ordering STTT. STTT has great value in confirming extracutaneous infection. Recent developments promise to improve performance, particularly in early disease detection.

Alternatives to Serologic Testing for Diagnosis of Lyme Disease

815

Kevin Alby and Gerald A. Capraro

Although serologic testing remains the gold standard for laboratory diagnosis of Lyme disease, the antibody response may take several weeks to increase greater than the limit of detection. Because of this extended time frame, it is necessary to identify new diagnostic methods for earlier diagnosis and appropriate treatment of Lyme disease. Alternative diagnostic modalities, such as *Borrelia* culture or nucleic acid amplification testing, may be beneficial in specific clinical scenarios. In early phases of acute infection, before the development of an immune response, detection of *Borrelia* DNA from clinical specimens may help establish the diagnosis sooner than serologic methods.

Lyme Disease Coinfections in the United States

827

Adam J. Caulfield and Bobbi S. Pritt

Lyme disease in North America is caused by infection with the spirochetal bacterium *Borrelia burgdorferi* and transmitted by *Ixodes scapularis* and *Ixodes pacificus* ticks. These ticks also have the potential to transmit a rapidly expanding list of other pathogenic bacteria, viruses, and parasites, including *Anaplasma phagocytophilum*, *Babesia microti*, deer tick (Powassan) virus, *Borrelia miyamotoi*, and the *Ehrlichia muris*-like organism. Coinfections with *B burgdorferi* and these other agents are often difficult to diagnose and may go untreated, and thus contribute significantly to patient morbidity and mortality from tick-borne infections.

Relapsing Fever Borreliae: A Global Review 847

Sally J. Cutler

Relapsing fever borreliae were notorious and feared infectious agents that earned their place in history through their devastating impact as causes of both epidemic and endemic infection. They are now considered more as an oddity, and their burden of infection is largely overshadowed by other infections such as malaria, which presents in a similar clinical way. Despite this, they remain the most common bacterial infection in some developing countries. Transmitted by soft ticks or lice, these fascinating spirochetes have evolved a myriad of mechanisms to survive within their diverse environments.

***Borrelia miyamotoi* Disease: Neither Lyme Disease Nor Relapsing Fever** 867

Sam R. Telford III, Heidi K. Goethert, Philip J. Molloy, Victor P. Berardi, Hanumara Ram Chowdri, Joseph L. Gugliotta, and Timothy J. Lepore

Borrelia miyamotoi disease (BMD) is a newly recognized borreliosis globally transmitted by ticks of the *Ixodes persulcatus* species complex. Once considered to be a tick symbiont with no public health implications, *B. miyamotoi* is increasingly recognized as the agent of a nonspecific febrile illness often misdiagnosed as acute Lyme disease without rash, or as ehrlichiosis. The frequency of its diagnosis in the northeastern United States is similar to that of human granulocytic ehrlichiosis. A diagnosis of BMD is confirmed by polymerase chain reaction analysis of acute blood samples, or by seroconversion using a recombinant glycerophosphodiester phosphodiesterase enzyme immunoassay. BMD is successfully treated with oral doxycycline or amoxicillin.

Methods to Prevent Tick Bites and Lyme Disease 883

Nick H. Ogden, L. Robbin Lindsay, and Steven W. Schofield

Current approaches for prevention of tick bites, Lyme disease, and other tick-borne diseases are described. Particular attention is paid to 4 risk-reduction strategies: (i) avoiding risk areas; (ii) personal protective measures that reduce the risk of tick bites or transmission of the agent of Lyme disease, *Borrelia burgdorferi*; (iii) reducing the number of infected ticks in the environment; and (iv) use of prophylactic antibiotic treatments following a bite to prevent clinical Lyme disease.