VIEWPOINT

Lyme Disease in 2018
What Is New (and What Is Not)

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With warmer weather come the annual warnings about tick-borne infections and, in particular, about Lyme disease. There has been considerable publicity about substantial increases in the incidence of Lyme disease; however, even though the incidence of Lyme disease has increased from 2007 to 2016, there has not been a statistically significant increase in the number of reported cases of Lyme disease in the United States during the most recent 4 years (2013-2016) for which data are available.[1] In 2016, a total of 26 203 confirmed cases of Lyme disease were reported in the United States (incidence = 8.1 cases/100 000 population),[1] although an estimate suggests that approximately 300 000 cases occur annually.[2] The geographic distribution of Lyme disease (although still limited primarily to New England, the Middle Atlantic states, and Wisconsin and neighboring states) has increased, with evidence of spread to new areas, generally in locations that are adjacent to recognized endemic areas.

Lyme disease is caused by infection with Lyme *Borrelia*, which include *Borrelia burgdorferi*, *Borrelia garinii*, and others, and are transmitted to humans through the bite of infected *Ixodes* ticks; in the United States, primarily by *Ixodes scapularis*—the deer tick. The vast majority of patients with Lyme disease (≥90%) develop the characteristic skin lesion, erythema migrans. Extracutaneous manifestations may include facial nerve palsy, lymphocytic meningitis, radiculopathy, heart block from myopericarditis, and pauciarticular large joint arthritis.

Lyme Disease vs *Borrelia Miyamotoi* Infection

Borrelia miyamotoi, a member of the relapsing fever group of *Borrelia* first reported to cause human disease in the United States in 2013, is transmitted by the same tick species that transmit Lyme disease. Patients infected with *B miyamotoi* may be misdiagnosed as having Lyme disease because this infection may cause positive results with enzyme-linked immunosorbent assays (ELISAs) used to diagnose Lyme disease. *B miyamotoi* is geographically widespread, and in a survey of nymphal *Ixodes scapularis* ticks in 11 Lyme disease–endemic US states, 2% and 20% were infected with *B miyamotoi* or with *B burgdorferi*, respectively. No diagnostic tests for *B miyamotoi* infection have been approved by the US Food and Drug Administration.

Active infection is most appropriately diagnosed by a polymerase chain reaction assay on a blood sample. Unlike with Lyme disease, patients infected with *B miyamotoi* in the United States typically do not have a rash, but instead present with fever in conjunction with headache (96%), myalgia (84%), arthralgia (76%), and malaise/fatigue (82%).[3] Laboratory abnormalities include leukopenia (51%) and thrombocytopenia (60%), which are rarely seen in patients with Lyme disease, as well as elevated liver enzymes (75%).[3] Fever may be relapsing in untreated patients. Severely immunocompromised patients may develop chronic meningitis. Full assessment of the clinical epidemiology of this infection, including the frequency of clinically inapparent infections, awaits development of better diagnostic tools. Both doxycycline and amoxicillin appear to be effective for treatment of immunocompetent patients with this infection.

Recent Proposals Involving Lyme Disease

There is a proposal to change the official name of the genus of the bacteria that cause Lyme disease from *Borrelia* to *Borreliella*, primarily to distinguish these strains from strains of *Borrelia* in the relapsing fever group (such as *B miyamotoi*). However, this change would be controversial, is unnecessary, and is likely to cause even more confusion about an already confusing topic.

There also have been recent proposals to change the recommended 2-tier algorithm for serologic testing for Lyme disease from the current standard (an ELISA usually is the first-tier assay, followed by a Western immunoblot as the second-tier assay) to one in which a Western blot is not used. Instead, the second-tier assay would also be an ELISA, but a different one from that used as the first-tier assay.[4] This approach would make the tests easier to perform, results would be available sooner, costs would be reduced, and it would eliminate the subjective element inherent in interpretation of Western blots. Studies using this algorithm have found that its specificity is comparable with that of standard 2-tier testing (generally >95% for either),[4] although patients infected with *B miyamotoi* may have false-positive results with this algorithm even if the otherwise highly specific C6 ELISA is used as the second-tier assay. However, even if such a change in 2-tier testing were to occur, it is not likely to have a major influence on the problems commonly encountered with use of antibody tests for diagnosis of Lyme disease, which primarily are testing of patients with a low probability of having Lyme disease and misinterpretation of the test results.

Tests to Identify Lyme Disease

There is a common misconception that poor sensitivity of antibody tests for Lyme disease is a major limitation. However, this is a problem only if clinicians erroneously depend on serologic tests to make a diagnosis of Lyme disease in patients with erythema migrans, which typically precedes the development of detectable antibodies. But because the skin lesion usually is clinically identifiable based on its appearance, serology is neither recommended nor needed to make the diagnosis of erythema migrans in Lyme disease–endemic areas. It is important

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to emphasize the need for a complete examination of the skin in any patient with possible early Lyme disease; erythema migrans lesions often are not noticed by patients when lesions occur on areas not easily seen, such as the popliteal fossa or the back. For extracutaneous manifestations of Lyme disease, the sensitivity of antibody tests is excellent (87%-100%),[4] although some patients with early neurologic manifestations will need a repeat test in 1 to 2 weeks for a result to become positive. Virtually all patients with Lyme arthritis (a late manifestation of Lyme disease) will have a positive immunoglobulin G (IgG) antibody test result at the time of presentation.

The use of serologic tests for Lyme disease for screening patients with a low probability of having Lyme disease results in a large number of false-positive results. Among a nationally representative sample of approximately 77 000 noninstitutionalized adults interviewed in the United States in 2010, 10% of men and 15% of women were either exhausted or very tired either every day or most days in the previous 3 months.[5] Likewise, 17% of the men and 21% of the women often had pain in the previous 3 months.[6] Clearly, Lyme disease is responsible for, at most, a tiny fraction of the many millions of individuals with chronic fatigue, chronic pain, or both. However, although precise data are not available, it is possible that 4 to 5 million antibody tests for Lyme disease are performed annually in the United States.[2] Even with highly accurate tests, if patients with a low probability of having Lyme disease are tested (eg, people who live in nonendemic areas or who have only nonspecific symptoms, such as pain or fatigue, without objective signs consistent with Lyme disease), the vast majority of positive results will be falsely positive, because the predictive value of a positive result is low in this setting. In addition, a recent report by Conant et al[7] found that clinicians may interpret results of serologic tests incorrectly. For example, in a survey about patients with longstanding symptoms (in whom the IgG antibody test result should be positive if the symptoms were due to Lyme disease), 42% of 144 clinicians in a high incidence area for Lyme disease incorrectly interpreted a positive IgM result alone as an overall positive result.[7]

Treatment of Lyme Disease

New information is available about treatment of Lyme disease. In 2018, the American Academy of Pediatrics endorsed short-term (<21 days) use of doxycycline for Lyme disease in children younger than 8 years based on the low risk of dental staining in reports of treatment of a relatively small number of young children with Rocky Mountain spotted fever.[8] Use of doxycycline for young children with Lyme disease is reasonable for some clinical indications (eg, single-dose prophylaxis for a high-risk tick bite or treatment of either Lyme meningitis or of certain co-infections such as anaplasmosis). However, amoxicillin and cefuroxime axetil are as effective as doxycycline to treat erythema migrans, and data do not support that use of doxycycline should be preferred over other antibiotics to reduce the likelihood that patients with erythema migrans will develop a neurologic manifestation of Lyme disease, which occurs infrequently in treated patients, whichever antibiotic is used. Additional controlled data have reconfirmed that among 182 patients with long-term residual symptoms attributed to Lyme disease despite prior treatment, retreating with additional antibiotics was of no benefit.[9] Other studies have reconfirmed the potential for serious adverse events (including death) from unnecessary long-term intravenous antibiotic therapy for such patients.[10]

Conclusion

Lyme disease and other tick-borne infections are a significant health problem in the United States. It is important to continue to conduct well-designed studies so that new approaches to diagnosis and treatment of tick-borne infections are based on scientific studies and not on fear or anecdote.

ARTICLE INFORMATION

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