The Controversy Over Lyme Disease

The diagnosis and treatment of Lyme disease remains controversial because the scientific understanding of this illness continues to evolve and basic questions remain unanswered. The roots of the controversy are the lack of reliable diagnostic tests and biological markers for the disease and the relatively low therapeutic efficacy of commonly prescribed antibiotic regimens. Until we can separate the infected from the uninfected and the cured from the uncured, arguments over diagnostic and therapeutic approaches will continue.

Two schools of thought have emerged with regard to the diagnosis and treatment of Lyme disease. One takes a narrow view, restricting both the disease definition and treatment options.[1] It highlights the risks associated with the over-diagnosis of Lyme disease and longer durations of antibiotic therapy. Subsequently, it requires patients satisfy a strict surveillance case definition of the disease (originally developed for epidemiologic, not clinical purposes) before providing access to treatment.

The other takes a broader view, encouraging clinicians to exercise clinical judgment and perform individualized risk-benefit analyses to determine who should be treated and in what manner. It emphasizes the risks associated with under-diagnosis and inadequate antibiotic regimens; noting that while all medical treatments carry risks, the risks associated with carefully managed antibiotic treatments are generally low.[2]

Today's Patients Can't Wait for Tomorrow's Insights

The scientific understanding of Lyme disease and highly successful treatment strategies may be well-established in the future but until that time, clinicians must manage patients to the best of their ability, basing clinical decisions on the available evidence and their clinical experiences.

Practice guidelines represent a reasonable starting point but recommendations made on a generalized basis should never be substituted for the clinical judgment of the clinician treating an individual patient. Only within the context of a strong patient-physician relationship can the benefits and risks of specific treatments be appropriately weighed and a truly patient-centered care plan developed.

The pursuit of evidence-based medical care requires clinicians to act based on the available evidence but it does not require them to adhere to ineffective diagnostic and treatment modalities pending further research.

Persistent Lyme Disease

Many patients experience ongoing manifestations of Lyme disease following antibiotic therapy. The underlying etiology(s) are poorly understood. Several, including immune dysfunction and persistent infection, have been proposed. Evidence in support of one should not be construed as disproving the other.

Persistent (or chronic) infection is supported by post-treatment Bb-positive cultures and PCR results in humans and multiple animal species. [2,9,12] In a NIH funded xenodiagnostic study, uninfected ticks acquired Bb DNA from a patient who was persistently symptomatic for more than a year post-treatment.[13]

Bb has multiple survival mechanisms. It can evade the immune response via: 1) physical seclusion within immunologically protected tissue sites, collagen-rich tissues, and individual host cells;[14,] and 2) alterations in its appearance (changes in outer surface proteins, cloaking in host proteins and transformation to a cell wall-deficient form).[14,15] Bb can also modulate the immune response by 1) altering neutrophil, macrophage, and dendritic cell functioning; 2) inhibiting complement-mediated killing and 3) altering cytokine and chemokine levels.[14,16,17] In vitro, Bb "persisters" are tolerant to commonly used antibiotics; thus, combination antibiotic therapy may be necessary for eradication.[18]

Given that persistent infection is possible, antibiotic retreatment is a reasonable therapeutic option. Trial evidence is quite limited. Two well-designed studies found that antibiotic retreatment was beneficial in a subset of patients with severe fatigue.[19,20] Two other US retreatment trials[21] and a recent European retreatment trial[22] were poorly designed and thus, uninformative. [23,24]

References

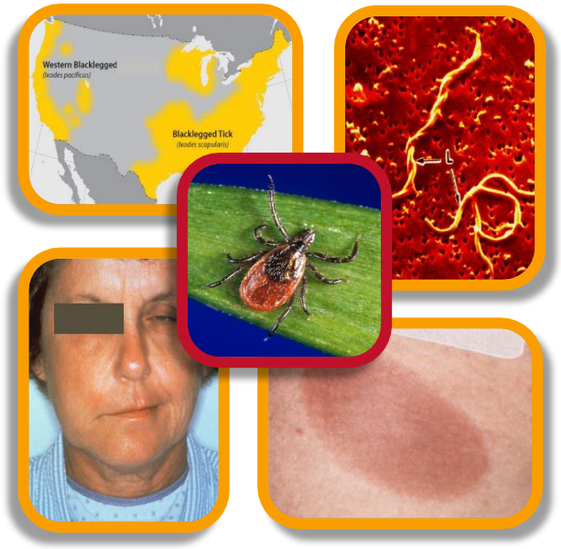
1. Wormser GP Clin Infect Dis. 2006; 43:1089–134.
2. Cameron DJ. Expert Rev Anti Infect Ther. 2014; 12(9):1103-35.
3. CDC estimate of annual incidence. Website last accessed on November 17, 2014. http://www.cdc.gov/media/releases/2013/p0819-lyme-disease.html.
4. Smith R. Ann Intern Med. 2002; 136:421-428.
5. Schwartz AM MMWR Surveill Summ. 2017 Nov 10;66(22):1-12.
6. Caliendo MV. Psychosomatics 1995; 36:69-74.
7. Krause P. JAMA. 1996; 275:1657-1660.
8. Maloney EL. JPANDS. 2009; 14(3): 82-89.
9. Embers ME PLoS One 2012;7(1):e29914
10. Ang CW. Eur J Clin Microbiol Infect Dis. 2011; 30(8):1027-1032.
11. Maloney EL. J Infus Nurs. 2016 Nov; 39(6): 369–375.
12. Strle F. Infection 1993; 21(2):83-88.
13. Marques A. Clin Infect Dis. 2014; 58(7):937-945.
14. Embers ME. Microbes Infect. 2004; 6(3):312-318.
15. Alban PS. Microbiology 2000; 146(Pt 1):119-127.
16. Kraiczy P. Int J Med Microbiol 2002; 291(Suppl 33):141-146
17. Lazarus JJ. Infection Immunity. 2008; 76(3):1153-62.
18. Feng J. Front Microbiol. 2016 May 23;7:743doi: 10.3389/fmicb.2016.00743.
19. Krupp LB. Neurology 2003; 60(12):1923–1930.
20. Fallon BA. Neurology 2008; 70:992-1003.
21. Klempner MS. N Engl J Med 2001; 345:85-92.
22. Berende A. N Engl J Med 2016; 374:1209-1220.
23. Fallon BA. Open Neurol J 2012; 6:79-87.
24. Delong AK. Contemp Clin Trials 2012; 33(6):1132-1142.

Cover credits (center, clockwise from upper left): Jim Gathany; Maloney EL, composite of individual CDC maps of blacklegged tick ranges; Wadsworth Center, New York State Department of Health; CDC; CDC. Content updated on June 10, 2018

What Every Primary Care Clinician Should Know About the Diagnosis of Lyme Disease

Elizabeth Maloney, MD

Content updated August 19, 2018



This brochure is provided by

Partnership for Tick-borne Diseases Education

PTDE provides evidence-based resources, including accredited CME programs, on tick-borne diseases.
Email us at:

ptde.emaloney@gmail.com

Lyme Disease Basics

♦ *Lyme disease is a clinical diagnosis, based primarily on the history.*

♦ *Serology can confirm the diagnosis but cannot rule it out*

Lyme disease is the most common vector-borne illness in the US. The CDC estimates 300,000 new cases occur each year.[3]
Surveillance case reports suggest that people living in the northeast or upper Midwest are at higher risk for Lyme disease but documented cases have been reported from every state. In endemic areas, school-aged children and people who spend time in tick-habitat are at highest risk for the illness.

Lyme disease is a bacterial infection. While several pathogenic *Borrelia* species can cause a Lyme-like illness, *Borrelia burgdorferi sensu stricto* (Bb) is the chief cause of Lyme in the US. European species are rarely seen here. *B. miyamotoi* and *B. mayonii* were recently added to the list of pathogens in the US known to cause a Lyme-like illness.

Lyme disease is transmitted via bites of infected nymphal and adult female blacklegged ticks (adult males do not feed). Nymphal bites appear to cause more disease than adult bites. Female and male adults, nymphal and larval ticks are shown here. While all are small, the size differential between the adult female and nymph is striking.

MN Department of Health
www.health.state.mn.us/divs/idepc/dtopics/tickborne/ticks

Given their small size and painless bites, it is not surprising that few patients were aware of the bite that infected them.

Lyme disease is a multi-staged, multi-systemic Illness. Disease presentations vary by stage. In acute, or early, disease, the bacteria is localized to the skin. Bacterial dissemination to other body sites defines late Lyme. In this stage the infection often involves several body systems, giving rise to a multi-systemic disease. Although the symptoms and signs of late disease may not be apparent for weeks, months or years, dissemination can occur shortly after a bite. It is not unusual for patients to present with late disease. Many will have long-standing manifestations that were not recognized as Lyme disease or were mistakenly attributed to other illnesses. Both stages require antibiotic therapy yet clinical trial evidence is limited. Although complete recovery is more likely for patients with early disease, common antibiotic regimens for either stage are not highly efficacious.[1]

Some patients exhibit a third, persistent, stage of Lyme disease. This stage is marked by the persistence and/or recurrence of Lyme disease manifestations despite prior antibiotic therapy using standard regimens for early or late disease. The clinical course of persistent manifestations is quite variable; some may remain unchanged while others may resolve or progress.

Not all patients exhibit all disease stages.

Early Lyme disease usually begins 3-30 days after a tick bite and is most easily recognized when its hallmark sign, an expanding erythema migrans (EM) rash, is present. EMs vary in appearance, most commonly appearing as homogeneously-colored oval lesions. The classic "bull's-eye" rash is seen in less than 20% of all EM cases.[4] EM rashes will resolve without antibiotic therapy; this should not be construed as evidence that the infection has been cleared. According to CDC surveillance case data, **30% of patients never develop a rash**.[5]

Flu-like symptoms – fever, chills, fatigue, malaise, headache, myalgias, arthralgias and neck stiffness, are common. They may accompany an EM or, in its absence, be the only evidence of an early Lyme infection.

Late Lyme disease produces a wide array of manifestations and can cause marked morbidity. Days to weeks after the bite, patients may exhibit multiple EM rashes, facial nerve palsy or other cranial neuropathies, meningitis, meningoradiculitis, carditis, lymphadenopathy and arthralgia. Constitutional symptoms are frequently present.

Later, arthritis and nervous system disorders may occur. In untreated patients, 60% will develop arthritis. While typically involving the knees, any joint can be affected. Neurologic manifestations such as peripheral and cranial neuropathies, autonomic dysfunction, neuro-psychiatric illnesses, movement disorders, and encephalopathy occur in 15 – 40% of patients.[6]

Symptoms are widespread and variable; relapsing/ remitting patterns are common. Frequently reported symptoms include:

* Extreme fatigue, often interfering with activities
* Headaches, all types
* Recurrent fevers, chills, night sweats
* Myalgias and arthralgias; either may be migratory
* Sleep disturbances
* Cranial nerve dysfunction
* Paresthesias and neuropathic pain syndromes
* Muscle fasciculations and weakness
* Cognitive impairments involving memory, concentration, multi-tasking abilities, information processing, speech and language skills
* Neuropsychiatric problems – irritability, depressed mood, anxiety, panic attacks, mood swings, new onset ADHD, OCD behaviors
* Children may note headaches, fatigue, forgetfulness and depressed mood. They may exhibit behavioral changes and declining school performance. Some may be misdiagnosed with primary ADHD

Although Lyme disease symptoms overlap with those of other diseases such as fibromyalgia, chronic fatigue syndrome, MS, RA, and psychiatric disorders, the overall symptom patterns are often atypical for these other illnesses. It is important to recognize that seemingly unrelated symptoms and symptom clusters may be linked by a Lyme infection, especially so when the autonomic nervous system is involved.

Lyme disease may be complicated by other tick-borne illnesses. Blacklegged ticks transmit a variety of pathogens and simultaneous transmission with Bb is known to occur. *Anaplasma phagocytophilum*, *Borrelia miyamotoi*, *Borrelia mayonii*, Powassan virus, as well as some *Babesia* and *Ehrlichia* species are known co-pathogens. It is likely that *Bartonella* species are also tick-borne pathogens but definitive proof is lacking. Other tick-borne pathogens may be identified in the future.

Co-infections often produce symptoms that overlap with those of Lyme disease, complicating the diagnosis of each. Co-infections may have a synergistic effect. Investigators documented that co-infected humans had increased morbidity and delayed recovery.[7]

Lyme disease is a clinical diagnosis with history playing the key role. Pertinent positives include 1) Lyme symptoms, 2) known exposure to tick habitat (e.g. the transition zone from woods to grass, long grass, brush, leaf litter, and fallen logs), 3) a known tick bite (this is seldom positive), 4) current or past diagnosis of a co-infection, 5) positive family history of a tick-borne illness. Importantly, a positive history of any other diagnosis in the differential or symptoms suggestive of one should trigger an appropriate work-up in order to reach the correct diagnosis.

Lyme disease is symptom rich but exam poor. Findings are often absent or subtle. In addition to the EM rash and arthritic joints, neurologic findings such as decreased sensation; muscle tenderness, weakness, or fasciculations; cognitive impairments and orthostatic changes in BP and P may be present. Clinicians should bear in mind that **a lack of physical findings does not invalidate the diagnosis.**

Lyme disease lacks sensitive diagnostic biomarkers. Serologic testing, ELISA and Western blots (WB), are more specific than sensitive, raising concern over the potential for falsely negative results. Many clinicians follow the two-tier testing strategy adopted by the CDC for use in its surveillance case definition without recognizing that the strategy increases diagnostic specificity but reduces sensitivity. Although heightened specificity may be useful for disease surveillance (because it prevents non-Lyme cases from being wrongly labeled and tracked as Lyme), it is counter-productive in clinical care because it increases the risk that true cases will be dismissed.[8] Adopting a more sensitive test strategy would limit the number of false negatives and rely on ongoing clinical assessments to identify false positives.

Serology poses other problems. Elevated antibody levels are indicative of Bb exposure but not necessarily infection and antibody levels, over time, can fall to normal in the untreated.[9] WB results are often unreproducible.[10] Serologic tests cannot be used as tests of cure because elevated antibody levels are not necessarily indicative of ongoing infection and normal levels are not always indicative of cure.[11]