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

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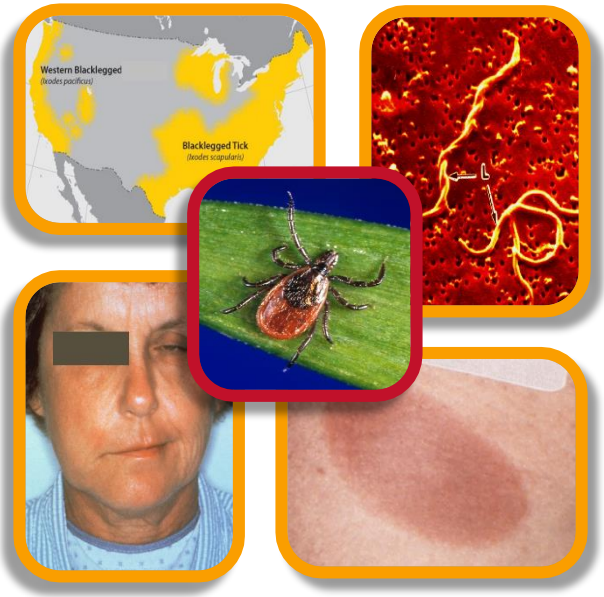

Lyme Disease Basics

♦ *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.

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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]