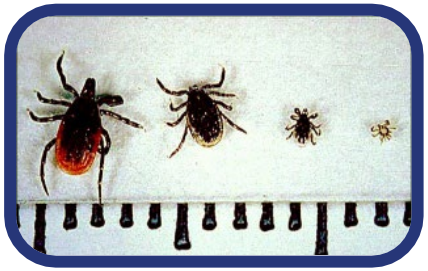
Lyme disease is the most common vector-borne illness in the US

The CDC estimates that 476,000 cases occur annually[1]

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, in the US, *Borrelia burgdorferi sensu stricto* (Bb) is the chief cause of Lyme disease. European species are rarely seen here. *B. mayonii* was recently added to the list of pathogens in the US known to cause a Lyme-like illness.

Lyme disease is transmitted via bites from infected nymphal and adult blacklegged ticks. Nymphal bites appear to cause more disease than adult bites. Female and male adults, nymphal, and larval ticks positioned alongside a metric ruler are shown below. Given their small size and painless bites, it is not surprising that few patients were aware of the bite that infected them. Transplacental transmission has also been documented.[2]



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Concurrent Tick-borne Infections

Lyme disease may be complicated by other tick-borne diseases (TBD). 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 TBDs and can cause illness in the absence of Bb. It is unclear whether *Bartonella* species are also tick-borne pathogens. Other tick-borne pathogens may be identified in the future.

These other infections produce symptoms that overlap with those of Lyme disease, complicating the diagnosis of each. They may have a synergistic effect with Lyme disease; investigators documented that humans with concurrent infections had increased morbidity and delayed recovery.[19]

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VectorWise CME

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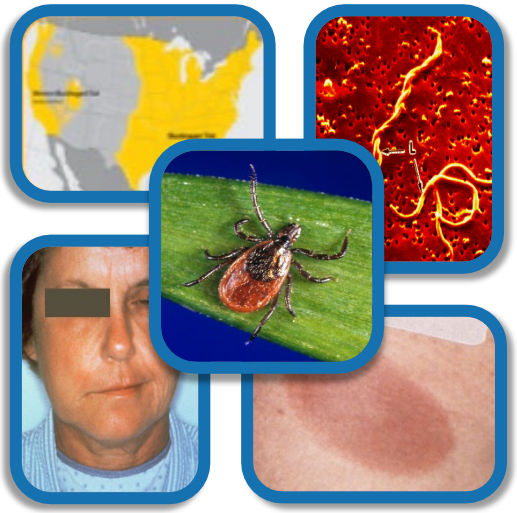
What Every Primary Care Clinician Should Know About the Diagnosis of Lyme Disease

Elizabeth Maloney, MD

Education Director, VectorWise CME

vectorwisecme.org



Lyme Disease is a Clinical Diagnosis

Establishing a Lyme disease diagnosis remains challenging because the scientific understanding of this illness continues to evolve and basic questions remain unanswered.

The root of the problem is the lack of reliable diagnostic tests and biological markers for the disease. Until we can separate the infected from the uninfected and the cured from the uncured, arguments over diagnostic approaches will continue.

♦ *Lyme disease is a clinical diagnosis, based primarily on the history* ♦ *Serology can support the diagnosis but cannot rule it out*

Lyme disease is a multi-staged, multi-systemic illness. Disease presentations vary by stage. In early disease, the bacteria are localized to the skin. Bacterial dissemination to other body sites defines disseminated Lyme. In this stage the infection often involves several body systems, giving rise to a multi-systemic illness.[3] Although the symptoms and signs of disseminated 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 disseminated Lyme. 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; clinical trial evidence to guide therapeutic choices is limited. Although complete recovery is more likely for patients with early disease, common antibiotic regimens for either stage are not highly efficacious.[4]

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.[4,5]The clinical course of persistent manifestations is quite variable; some may remain unchanged while others may resolve or progress.[4]

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.[6] 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**.[7]

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.

Serologic testing is discouraged when evaluating patients who may have early Lyme disease, especially so for patients with EM lesions, because false negative results are common.[8]

Disseminated 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, 50% will develop arthritis.[9] Neurologic manifestations such as peripheral and cranial neuropathies, autonomic dysfunction, neuro-psychiatric illnesses, movement disorders, and encephalopathy occur in 15 – 40% of patients.[10]

Symptoms are widespread and variable; relapsing/ remitting patterns are common.[11] 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.

Serologic testing is highly sensitive for identifying cases of Lyme arthritis but IgG Western blot interpretation criteria are insensitive for neurologic presentations.[12]

Lyme disease is a clinical diagnosis with history playing the key role. Pertinent positives include: 1) Lyme symptoms, 2) exposure to tick habitat – 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 another tick-borne infection, and 5) a 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, cognitive impairments, weakness, fasciculations, and orthostatic changes in BP and P may be present.[11] Clinicians should bear in mind that **a lack of physical findings does not invalidate the diagnosis.**[11]

Lyme disease lacks highly sensitive diagnostic biomarkers. The standard two-tier testing strategy (STTT), a positive EIA followed by immunoblotting, adopted by the CDC for use in its surveillance case definition increases diagnostic specificity but reduces sensitivity.[13] 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.[11] The modified two-tier approach using sequential EIAs, has greater sensitivity for early disease than standard two-tier testing.[13] Newer FDA-cleared MTTT tests incorporate first tier EIA and an IgM or IgG immunoblot in a single test. These tests use different immunoblot interpretation criteria than the CDC's.[14,15] It's unclear whether these will prove to be more sensitive.

Serology poses other problems. Elevated antibody levels are indicative of Bb exposure but not necessarily infection. Animal models suggest that with time, once elevated antibody levels in the untreated can fall into the normal range.[16] WB results are often unreproducible.[17] 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.[18]

Evidence-based medicine requires clinicians to act based on the available evidence but it does not require them to adhere to ineffective diagnostics pending further research.