The scientific understanding of Lyme disease 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 uncurable, 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. 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.

**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.

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. 1-3,12-13 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. 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 protein features, cloaking in host proteins and transformation to a cell wall-deficient form). 14,15 Bb can also modulate the inflammatory response by 1) altering neutrophil, macrophage, and dendritic cell functioning; 2) inhibiting complement-mediated killing and 3) altering cytokine and chemokine levels. 14,16 In vitro, Bb “persisters” are tolerant to commonly used antibiotics; thus, combination antibiotic therapy may be necessary for eradication. 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. 17,20 Two other US retreatment trials 18 and a recent European retreatment trial 19 were poorly designed and thus, uninformative. 23,24

**References**

3. CDC estimate of annual incidence. Website last accessed on November 17, 2014.

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.

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Partnership for Tick-borne Diseases Education

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

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Lyme disease is the most common vector-borne illness in the US. The CDC estimates 300,000 new cases occur each year. Surveillance case reports suggest 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 (deer) ticks (unfed, nymphal, male or female adults). Nymphal ticks 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.

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 disease.

**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. 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.\(^3\)

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, meningoencephalitis, carditis, lymphadenopathy and arthralgia. Constitutional symptoms are frequently present.

Late, 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 illness, movement disorders, and encephalopathy occur in 15 – 40% of patients.\(^4\)

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.

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.

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