

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 root of the controversy is the lack of reliable biological markers and diagnostic tests for the disease. Until we can separate the infected from the non-infected and the cured from the uncured, arguments over diagnosis and treatment approaches will continue.

Two schools of thought, exemplified by ILADS and the Infectious Diseases Society of America (IDSA), have developed with regards to the diagnosis and treatment of Lyme disease. IDSA takes a narrow view, defining the illness in strict terms with limited treatment options. ILADS takes a broad view, believing that clinical judgment can best determine who should be treated and in what manner. Both groups have published evidence based guidelines which can be accessed via the National Guidelines Clearinghouse. While IDSA has expressed concerns about over-treatment, ILADS points out that treatment decisions should be based on an individual's risk-benefit analyses reflecting the health, financial and quality of life costs associated with ongoing, untreated Lyme disease. All medical treatments carry risks; the risks associated with carefully managed antibiotic treatment are generally low.

Today's patients can't wait for tomorrow's research.

In the future our scientific understanding of Lyme disease may be complete. Until that time, clinicians caring for patients must do so to the best of their ability. practice guidelines may present 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. It is within the context of a strong patient-physician relationship that the benefits and risks of specific treatment plans can be appropriately weighed and patient autonomy encouraged and respected.

The pursuit of evidence-based medical therapies requires physicians to act based on the evidence at hand. It does not imply that physicians should adhere to ineffective treatments pending further research.

Borrelia burgdorferi and Persistent Infection

Persistent infection has been demonstrated. Using a mouse model, Hodzic et al demonstrated that in late stage disease, Bb could survive exposure to 30 days of ceftriaxone therapy and that the persisting bacteria remained infectious. [Hodzic E, Antimicrob Agents Chemother 2008; 52:1728-1736.] An earlier study by Yrjanainen et al revealed similar survival after 5 days of ceftriaxone exposure. [Yrjanainen H. J Infect Dis. 2007; 195(10):1489-96]

The unique microbiology of Bb must be considered when discussing the organism's survival potential.

* Bb has long periods between replication cycles. Cell-wall antibiotics work during active replication; unless treatment continues through the longest "rest" phase, bacteria not dividing while these antibiotics are present will survive therapy and the infection may persist.

* Bb can reside in intracellular locations, including endothelial cells, neurons and glial cells.[Ma Y, Infect Immun 1991; 59:671-8. Livengood JA, Microbes Infect 2006; 8: (14-15):2832-40] Here it is unaffected by penicillins and cephalosporins; higher doses of intracellular antibiotics may be needed to obtain adequate levels.

* Bb can evade the immune system by several mechanisms: intracellular locations and protected body sites (brain, eye), antigenic variation, immune suppression and "cloaking" in host derived proteins. [Singh SK, Lancet Infect Dis 2004; 4(9):575-83]

Co-infections

Ticks also carry Babesia, Anaplasma, Ehrlichia, Bartonella, Mycoplasma and other pathogens. The presence of these organisms complicates the diagnosis, testing and treatment of Lyme disease patients. In animal models, co-infections alter the immune response, pathogen load and disease severity.[Thomas V. Infect. Immun. 2001;69:3359-3371.] In humans, co-infections increase morbidity and delay recovery. [Krause P, JAMA 1996; 275:1657-60.]



What Every Primary Care Physician Should Know About Lyme Disease

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Lyme Disease Basics

Lyme disease, a multisystemic illness caused by the spirochete *Borrelia burgdorferi* (Bb), is the most common vector-borne illness in the US.

Approximately 20,000 new cases are reported to the CDC each year and the CDC acknowledges that 90% of cases go unreported. [Adler, J. (2004). Lyme: battles with illness, emotions, insurance. (NJ) Herald News.] Infected black-legged ticks transmit Bb to humans via a bite. These ticks are quite small and easily overlooked; most patients do not recall being bitten prior to becoming ill.

Lyme disease has both early and late disease manifestations. Patients may exhibit one or both of these stages; many patients initially present with late Lyme disease. Any organ system can be involved, but Bb commonly strikes skin, joint, heart and nervous tissue, including the brain.

Early Lyme disease begins 3-30 days after a tick bite and is readily identified by an erythema migrans (EM) rash. EMs vary in appearance. The most common rash is a homogeneously colored oval lesion. The classic “bull’s eye” accounts for less than 20% of all EM cases; [Smith R et al, Ann Intern Med. 2002;136:421-428, Tibbles C, JAMA 2007; 297:2617-27.] **30% of patients never have a rash.** [MMWR 56(23); 573-576] Flu-like symptoms such as fever, fatigue, headache, myalgias, arthralgias and neck stiffness may accompany an EM or be the only evidence of early Lyme disease. [Steere A et al, Am J Med. 2003; 114(1):58-62]

Late Lyme disease develops weeks - years later and is the result of disseminated infection. Early disseminated Lyme disease may cause multiple EM rashes, Bell’s palsy or other cranial neuropathies, meningitis, meningoradiculitis, carditis, lymphadenopathy and arthralgia; constitutional symptoms may be present. In endemic areas, Lyme disease is implicated in 50% of all cases of Bell’s palsy in children. [Cook SP et al, Am J Otolaryngol 1997; 18(5):320-3]

In the US, arthritis and disorders of the nervous system are seen in late disseminated Lyme disease. Arthritis can affect any joint; knees are the most common site. Up to 60% of untreated patients will experience arthritis.

Neurologic conditions include peripheral sensory neuropathies, motor neuropathies, cranial neuropathies, autonomic dysfunction, movement disorders, neuropsychiatric illnesses and encephalopathy. Neuroborreliosis is the term used when Lyme infects the brain. 15 – 40% of Lyme disease patients have neurologic disorders due to the infection. [Caliendo et al, Psychosomatics 1995; 36:69-74] Late disease can be severe with marked morbidity and poor treatment outcomes.

Symptoms

The symptoms of Lyme disease are widespread and variable; relapsing/remitting patterns are common. The validity of individual symptoms has been documented in numerous reports and studies on Lyme disease. Frequently reported symptoms include:

- * Extreme fatigue, often interfering with activities
- * Headaches of all types
- * Recurrent fevers, chills, night sweats
- * Myalgias and arthralgias; either may be migratory
- * Muscle fasciculations and weakness
- * Paresthesias and neuropathic pain syndromes
- * Sleep disturbances
- * Cranial nerve dysfunction
- * Neuropsychiatric problems – irritability, depression, anxiety, panic attacks, new onset ADHD, mood swings similar to bipolar disease, rage attacks, OCD
- * Cognitive losses: memory impairment, difficulty multi-tasking, slowed mental processing, speech and language problems, poor concentration, loss of math skills, impaired visual/spatial processing
- * Children may have behavioral changes, declining school performance, headache, fatigue, forgetfulness, complex partial seizures, depression and be misdiagnosed with primary ADHD.

Although Lyme disease symptoms overlap with symptoms of other conditions such as fibromyalgia, chronic fatigue syndrome, MS, early ALS, RA, lupus and psychiatric disorders, patients with Lyme disease often have symptom patterns which are atypical for these

other illnesses. Making sense of the multitude of reported symptoms can be challenging; but bear in mind that symptoms which appear unrelated may be linked via an underlying autonomic neuropathy or encephalopathy.

Physical Exam in Lyme Disease

Lyme disease patients may have exam findings when carefully assessed but findings may be few or absent in some cases. In addition to a general exam detailed neurologic, dermatologic and rheumatologic exams should be performed.

Serologic Testing in Lyme Disease

Borrelia burgdorferi is very difficult to culture, thus serologic tests are used to detect the presence of antibodies to Bb. In 1995 the CDC, in an move to standardize testing procedures and Western blot interpretations, published guidelines for laboratory testing in Lyme disease. [MMWR 1995; 44:590-1] The CDC recommended a two-tier testing algorithm. Step 1 is an ELISA or IFA; positive or equivocal results advance to step 2, IgM and IgG Western blotting. Samples negative in step 1 are not tested further. **The purpose of standardization was to establish parameters for laboratory confirmation of Lyme disease surveillance cases, not clinical diagnosis.** [Mead P. CT Dept of Public Health Hearing Jan 29, 2004]

Two-tier testing doesn’t work.

The step 1 tests are insufficiently sensitive to be used as “screening” tests. [Trevejo R, JID 1999; 179:931–8.] Western blots, increase specificity but, following a step 1 test, further decrease overall sensitivity. The bands included in the Western blot interpretation schemes were chosen on a statistical, rather than a clinical, basis. [Dressler F. JID 1993; 167:392-400.] Recently, the C6 peptide ELISA alone was proposed as an alternative to the two-tier approach. Unfortunately, the C6 ELISA also lacks adequate sensitivity for clinical use. [Bacon R. J Infect Dis 2003; 187:1187- 99.]

Given the state of the diagnostic testing, Lyme disease, like many other diseases, is a clinical diagnosis; with testing playing a supportive role.