

Update on Lyme Disease

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Though perhaps the most rapidly growing infectious illness in the United States, Lyme disease is widely misunderstood, and its diagnosis is often missed. Low specificity and sensitivity plague the currently available tests, and neither the confirmed bite of a tick nor the disease's hallmark erythema migrans rash is verified in at least half of patients. Similarly, treatment is hindered by the wide variation in strains, intracellular "hiding," and latent forms of Lyme disease's causative spirochete, *Borrelia burgdorferi*—and potentially complicated by coinfection with other tick-borne agents. Although professional organizations take widely differing approaches to Lyme disease, there are important components of Lyme management for every primary care practitioner to bear in mind.

Your patient presents for his or her sixth office visit in two months, complaining of diverse, seemingly unrelated symptoms that don't quite make sense. You have done a thorough work-up but are unable to determine the culprit responsible for your patient's multisystem complaints. The neurologic, cardiac, rheumatologic, urologic, and gastrointestinal symptoms don't quite fit the diagnostic criteria of any disease in the differential diagnosis. You and the patient are both frustrated. Is this all in the patient's head?

This is the scenario played out every day throughout the United States as patients with Lyme disease go from specialist to specialist, hoping for a diagnosis that will explain their plight and offer hope for their eventual recovery. Why is this diagnosis so often missed? And why is so little understood about Lyme disease, the most rapidly growing infectious illness in the country?

Lyme disease, usually contracted through the bite of a tick, is the most common vector-borne disease in the US. Although cases have been reported in every state and research has validated the virulence and complexity of *Borrelia burgdorferi* (*Bb*), the spirochetal agent that carries Lyme disease, there is still much uncertainty and controversy about the diagnosis and treatment of this bacterial illness. Like its close cousin *Treponema pallidum*, the spirochetal agent that causes syphilis, *Bb* can inflict significant morbidity, including severe neurologic and cardiac sequelae. Thus, making a prompt diagnosis and treating this disease ef-

fectively are of the utmost importance. Yet both involve significant challenges.

DIFFICULTIES WITH DIAGNOSIS

The CDC specifically states that the diagnosis of Lyme disease is not dependent on laboratory results, but rather on the clinical opinion of the health care provider.¹ In spite of this, there are still many practitioners who believe that negative results on Lyme testing reliably "rule out" the disease. Since current testing methods are low in specificity and even lower in sensitivity, it falls upon the provider to thoroughly review the patient's tick exposure history and clinical symptoms, and to be well acquainted with the signs and symptoms of Lyme disease in both its acute and chronic forms.²

Another frequent mistake is to discount the possibility of the disease if the patient does not recall having sustained a tick bite. The tick that transmits Lyme disease can be as small as a poppy seed, making it easy to miss; also, the bite may be on the scalp and hidden by hair, or it may be in another difficult-to-see location. Furthermore, the spirochete may remain dormant in the host for months or years before symptoms appear.³

The erythema migrans (or "bull's-eye") rash is the classic sign of acute Lyme disease. The development of this rash following the bite of an infected tick is considered diagnostic in its own right. However, fewer than 50% of infected patients experience a rash, and when they do, the rash may well be atypical. Even in its classic presentation, the erythema migrans rash is often

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unrecognized or misdiagnosed by clinicians.⁴

Other physical findings are not likely to support or refute a diagnosis of Lyme disease, as they are often nonspecific or mild, especially in early disease.

Symptoms of Lyme Disease

In the acute stage of Lyme disease (soon after the tick bite), symptoms may include headache, stiff neck, recurrent rashes, body aches, joint pain, fever, and tender

lymph nodes. As time passes and the infection disseminates, numerous new symptoms may appear (see Table 1^{5,6} for a fairly comprehensive list by body system).

Children may present differently from adults, with changes in behavior and school performance as the predominant symptoms. Parents often observe mood swings, irritability, obsessive-compulsive behavior, and new-onset attention-deficit/hyperactivity disorder. Physical symptoms in children may include fatigue,

TABLE 1

Lyme Disease Symptoms^{5,6}

<p>Musculoskeletal/rheumatologic Joint pain Muscle pain and cramps Muscle and joint stiffness Reduced mobility Loss of muscle tone Back pain, stiffness Neck pain, stiffness Vertebral disc disease Temporomandibular joint syndrome</p> <p>Neurologic Neuropathies Encephalopathy Paresthesias Dizziness, vertigo Cognitive disturbances Cranial nerve disturbances Attention deficit Hypersensitivity to touch, sound, light, smell Bell's palsy Tinnitus Restless legs syndrome Drooping eyelid Transient blurred vision Clumsiness Depression Insomnia, fatigue Difficulty chewing or swallowing Hallucinations Headaches</p>	<p>Involuntary jerking or muscle twitching Irritability Poor balance Sleep disturbances Speech difficulty Weakness of limbs</p> <p>Cardiac Palpitations Arrhythmias Shortness of breath Tachycardia Hypotension Hypertension New-onset heart murmur New-onset chest pain Abnormal ECG Chest pain, tightness</p> <p>Psychiatric (all new-onset) Anxiety Panic disorder Irritability Depression Bipolar disorder Obsessive-compulsive disorder</p> <p>Endocrinologic Low body temperature Night sweats, chills Symptoms of adrenal insufficiency (fatigue, muscle weakness, loss of appetite, weight loss) Flushing</p>	<p>Irregular menses Loss of libido Worsening premenstrual syndrome Menstrual irregularities Milky nipple discharge Hypertriglyceridemia New-onset hypothyroidism Weight change (usually gain)</p> <p>Gastrointestinal/urogenital Abdominal pain and tenderness Bloating, gas Constipation Food allergies Urinary/bowel control problems Nausea Irritable bladder Excessive thirst Dysuria, polyuria, hematuria Testicular/pelvic pain Dyspareunia</p> <p>Other Easy bruising Hair loss Recurrent sinusitis Sore throat Tender glands Tooth pain Unusual rashes Shooting pains throughout body</p>
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Sources: Burrascano. Advanced topics in Lyme disease. 2005⁵; Rubel. Lyme disease symptoms and characteristics. 2005.⁶

frequent headaches or stomachaches, urinary symptoms, and migratory musculoskeletal pains.^{7,8}

TESTING FOR LYME DISEASE

Borrelia burgdorferi is a bacterium that is fastidious,⁹ making it nearly impossible to grow in culture in the laboratory. Consequently, testing has had to rely upon detection of antibodies to the organism. The Lyme enzyme-linked immunosorbent assay (ELISA), which produces a titer of total immunoglobulin G (IgG) and IgM antibodies, is currently the accepted initial screening for suspected Lyme disease.¹ This approach should be reevaluated, however, because commercial ELISA tests do not meet the requirement for an effective screening test, due to their low sensitivity. By definition, a screening test should have at least 90% sensitivity, whereas commercial Lyme ELISA tests have a sensitivity of 65% or less.⁸

The Western blot test, which is commonly used as a confirmatory test for Lyme disease, is more sensitive than the ELISA. The CDC has published stringent criteria for positivity on this test, as is warranted for epidemiologic surveillance. However, the CDC specifically states that these criteria are not to be used for diagnostic purposes.^{1,10} Unfortunately, the CDC's restrictive epidemiologic criteria omit several of the important bands on the blot that are highly sensitive markers for the presence of *Bb*. Therefore, proper interpretation of the test falls upon the clinician, who should become acquainted with the relative sensitivity and specificity of the various bands. A test with negative results based on epidemiologic criteria may well be a positive test, diagnostically.⁷ In one study of 48 patients who were symptomatic and seropositive for Lyme disease, only two cases (4.2%) were reportable according to CDC criteria.¹¹

Interpreting the Western Blot Test for Lyme Disease

The Western blot test is more sensitive than the ELISA because each of 14 to 16 *Bb* protein antigens is analyzed separately. The antigens are detected on blot paper in parallel lines or bands (see figure). Each band is named by the weight in kilodaltons (kDa) of the protein antigen it contains; for example, 41 kDa is the name of the band containing the *Bb* flagellar protein. When the blot is

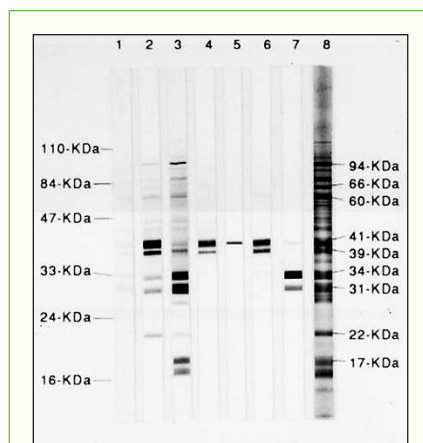
incubated with patient serum, the bands become darker as antibodies attach to the various antigens and antigen-antibody complexes are formed. The interpretation of the test is subjective, as the observer grades the degree of darkness, ie, the intensity of the antibody response to each of the different protein bands.

According to CDC criteria, a Lyme Western blot IgM must have two of the following three bands to be considered positive: 24, 39, and 41 kDa; and a positive IgG must contain five of the following 10 bands: 18, 21, 28, 30, 39, 41, 45, 58, 66, and 93 kDa.¹ Each band has a different degree of specificity; for example, the 39-kDa band is highly specific for *Bb*, whereas the 41-kDa band is not. For epidemiologic purposes, the CDC does not count bands 31 and 34 kDa in its inclusion criteria—even though these bands are so specific for *Bb* that they were chosen for vaccine development.¹²

These degrees of specificity for each band must be kept in mind by the clinician who interprets Western blot results. The bottom line may read “negative,” but if the test reveals at least one highly specific band, the clinician should be suspicious of *Bb* exposure.

Interpretation of Western blot tests for Lyme disease presents other problems. Commercial Western blot tests are based on laboratory strains of *Bb*, and these strains may differ significantly from the “wild-type” strains to which patients may be exposed around the country. As a result, the true sensitivity of commercial Western blot tests for regional strains of the Lyme spirochete is uncertain. Some laboratories have solved this problem by including various strains of *Bb* in more sensitive “home-brewed” blots.

Another confusing aspect of Lyme Western blot test interpretation is the persistence of the IgM reaction. In virtually all infectious disease states, the IgM class of antibody appears first, therefore representing a marker for early infection. In most models of immunity, the IgM antibody gives way to the IgG antibody class, which is usually regarded as the major antibody response in chronic infectious diseases.¹ Positive IgM reactions that do not convert to positive IgG reactions within a few months are generally considered false-positive results. However, a confounding fact in Lyme disease is that the IgM antibody may persist for years—which is very



Significant Lyme disease antibodies detected on Western blot test, including 31- and 34-kilodalton bands. Courtesy of IGeneX, Inc.

unusual in most infectious disease states.

For these reasons, Lyme disease testing remains a controversial area.^{8,10,13,14} It should be noted that polymerase chain reaction (PCR) tests, which can detect *Bb* DNA, are known for false-negative results, and the CDC considers their use (and that of certain other assays) “inadequately validated.”¹⁵ Positive Lyme PCR results are considered reliable, but the test is not widely available.²

TWO STANDARDS OF CARE

Two professional organizations, the Infectious Diseases Society of America (IDSA) and the International Lyme and Associated Diseases Society (ILADS), have published guidelines for the diagnosis and treat-

ment of Lyme disease.^{16,17} As is the case with other illnesses (eg, breast cancer, prostate cancer, heart disease, hyperthyroidism), there are diverse opinions, interpretations of the literature, and approaches to treatment when it comes to Lyme disease. Yet in the case of this illness, the two organizations’ standards of care represent opinions that are adamantly polarized. An emotional “Lyme war” rages on between “rationalists” and “empiricists,” often to the detriment of patients’ best interests.^{8,10,13,14,18}

The basic premise of the IDSA position is that Lyme disease is a rare infection that is difficult to contract and easily treated with a two- to three-week course of oral antibiotics—or, in the case of neurologic disease, with one month’s treatment with IV anti-

biotics. Persistent symptoms after antibiotic treatment are attributed to post-Lyme syndrome or presumed acquired autoimmunity rather than chronic Lyme disease. Long-term antibiotic use for the treatment of persistent Lyme disease symptoms is seen as ineffective and potentially harmful.^{10,19} In the IDSA’s Lyme disease practice guidelines, published in 2000, the authors observe prevention as the best approach but advise close monitoring of patients who have sustained tick bites.¹⁶

The IDSA bases its assumptions on epidemiologic statistics, studies of tick transmission times, a mouse model in which *Bb* infection was putatively eliminated by two weeks of antibiotic treatment, and a study of patients with persistent symptoms that revealed no clear benefit in administering three months of antibiotic treatment.²

By contrast, the stance of ILADS is that Lyme disease is underdiagnosed and underreported.⁴ ILADS proposes that the disease is easily contracted from the bite of an infected tick—and even with immediate treatment will often result in recalcitrant neurologic, cardiac, and rheumatologic symptoms that are responsive only to long-term antibiotic therapy.^{13,17}

ILADS bases its approach on numerous animal and laboratory studies and the vast experience of physicians from many branches of medicine who have elected to specialize in the treatment of tick-borne diseases.²⁰

One Approach to Treatment

According to the ILADS’ 2004 management guidelines for Lyme disease, antibiotics se-

Table 2 Antibiotic Regimens for the Treatment of Lyme Disease ^{7,16,17,21-23}	
For <i>Borrelia burgdorferi</i>	
Oral monotherapy	Imipenem/cilastatin
Tetracycline	Meropenem
Doxycycline, minocycline	Doxycycline
Amoxicillin with or without sulbactam	Intramuscular therapy
	Benzathine penicillin G
Oral combination therapy	For coinfections
A macrolide (clarithromycin, azithromycin) plus a third-generation cephalosporin (cefdinir, cefuroxime, cefibuten, cefixime)	<i>Babesia</i>
A macrolide plus a nitroimidazole (metronidazole, tinidazole)	A macrolide plus atovaquone
A macrolide plus amoxicillin with or without sulbactam	Clindamycin plus quinine
A ketolide (telithromycin) plus a third-generation cephalosporin or a nitroimidazole	A macrolide plus a nitroimidazole
Clarithromycin plus hydroxychloroquine	Doxycycline/minocycline plus mefloquine
	Artemisinin plus trimethoprim-sulfamethoxazole
Intravenous therapy	<i>Anaplasma/Ehrlichia</i>
Ceftriaxone	Doxycycline/minocycline
Cefotaxime	A macrolide
Azithromycin	Rifampin
	<i>Bartonella</i>
	A fluoroquinolone (ciprofloxacin, levofloxacin)
	Macrolides with or without a sulfa drug

Sources: Johnson and Stricker. *Expert Rev Anti Infect Ther.* 2004⁷; Wormser et al. *Clin Infect Dis.* 2000¹⁶; Cameron et al. *Expert Rev Anti Infect Ther.* 2004¹⁷; Burrascano. *Conn's Current Therapy.* 1997²¹; Brorson and Brorson. *Int Microbiol.* 2004²²; Hunfeld et al. *Antimicrob Agents Chemother.* 2004.²³

lected for treatment may be used in combinations and may include agents that are FDA approved but not specifically indicated for Lyme disease (eg, azithromycin, clarithromycin, metronidazole; see Table 2,^{7,16,17,21-23} page 48). Variable response to antibiotics and occasional antibiotic resistance are explained, say proponents, by the existence of more than 100 strains of the Lyme spirochete in the US and 300 strains worldwide.

In addition, a major factor in treatment failure is the presence of coinfection with tick-borne organisms such as *Babesia*, *Anaplasma*, *Ehrlichia*, and *Bartonella*, any or all of which may complicate the course of Lyme disease.^{13,17} Furthermore, ILADS promotes the idea that there are other modes of transmission besides the tick bite, including other insect vectors as well as sexual and in utero exposure analogous to that in transmission of syphilis (the spirochetal cousin of Lyme disease).^{4,20,24}

Additional Complicating Factors

Borrelia burgdorferi, the causative agent of Lyme disease, has the most complex genetic structure of any known bacteria.¹⁸ Experimentally, *Bb* has been shown to “hide” intracellularly in the presence of bactericidal levels of antibiotics. Intracellular bacteria are notoriously difficult to treat and cure.³

Another aspect of *Bb* that makes it resistant to treatment is its ability to change form in response to antibiotics. In addition to the well-known corkscrew-shaped form of the spirochete, at least two other forms are known to exist: the cell wall-deficient, or “L” form, and the dormant, inactive cyst form.⁹ The spirochete may exist latently in the host for years or decades in the cyst form. The three forms require different types of antibiotics for treatment, and *Bb*'s constantly changing morphology often necessitates the use of drug combinations and frequent changes of antibiotic agents to treat chronic Lyme disease.¹⁹

The slow replication rate of *Bb* is another factor in treatment. Many antibiotics do their work when organisms are dividing, and the longer the time between replications, the less opportunity the antibiotic has to kill the bacteria.

Finally, it is difficult to decide when to stop treatment for Lyme disease because there is no test of cure.^{10,18} Between the lack of simple culture techniques and the low sensitivity of antibody tests, a negative test result does not rule out Lyme disease infection. When the decision to discontinue treatment is based solely on the resolution of symptoms, there is always concern that the infection may not have been completely eradicated and that symptoms will reemerge.⁸

IMPORTANT TAKE-HOME POINTS

The Lyme disease controversy aside, primary care providers would do well to take note of the following points:

- The possibility of Lyme disease should not be ruled out in a geographic area that is believed to be nonendemic. Lyme disease has been found in every state. Always consider it in the appropriate differential diagnosis—bearing in mind that people, pets, and ticks all travel.
- Lyme disease requires a clinical diagnosis. Laboratory tests are not dependable, so it falls upon the clinician to take a thorough history and be aware of the protean manifestations of this illness.¹⁸
- Fewer than 50% of patients with Lyme disease recall having had a tick bite.
- The presence of an erythema migrans (“bull’s-eye”) rash is diagnostic, and no further work-up is required. However, fewer than 50% of patients have a rash, and when they do, the rash can present in many different forms.
- The ELISA test has only 65% sensitivity and is therefore unacceptable as the first step in a two-step screening process for Lyme disease. Screening should begin with the Western blot test.
- The CDC surveillance criteria were devised for epidemiologic purposes and were never intended to be used for the clinical diagnosis of Lyme disease. This is important to remember when the Western blot test result is negative according to CDC criteria but the patient’s history and symptoms suggest Lyme disease.
- Only a testing laboratory that reports all of the bands on the Western blot should be used. Remember that antibody reactivity may vary, depending on the antigens used in the blot and the strains to which the patient may have been exposed.

CONCLUSION

One hundred years ago, syphilis was called “the great imitator” because of its confusing presentation. Today’s “great imitator” is another spirochete called *Borrelia burgdorferi*: Lyme disease. This illness should be considered in children with developmental and behavioral problems, unexplained fatigue, learning disabilities, and the sudden onset of unusual constitutional symptoms. In adults, Lyme disease should be considered in the differential diagnosis of neuropsychiatric conditions, rheumatologic diseases, chronic fatigue syndrome, fibromyalgia, and any difficult-to-diagnose multisystem illness.

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In view of the diverse presentations and complexity of Lyme disease, increased education and awareness about this growing health concern are needed both for the practitioner and the general public to enhance accurate diagnosis and effective treatment. ■

For more detailed treatment guidelines and additional information, please visit www.idsociety.org and/or www.ilads.org.

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