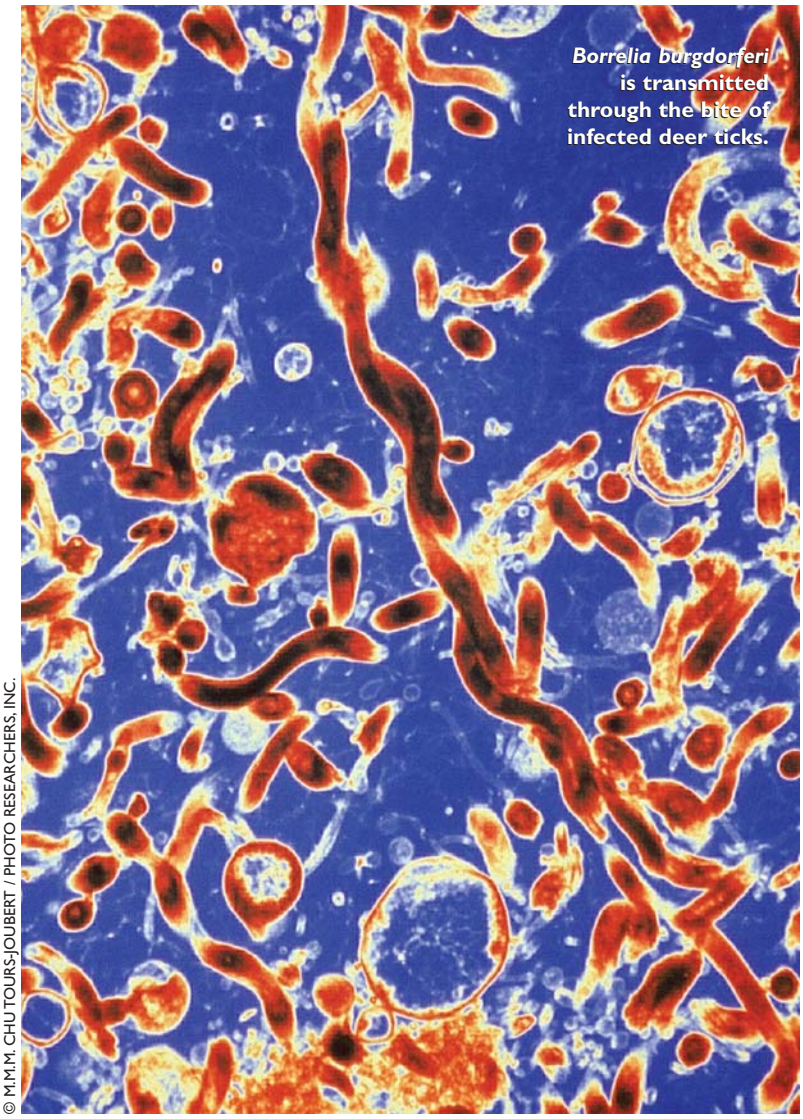
Controversy continues to fuel the "Lyme War"

As two medical societies battle over its diagnosis and treatment, Lyme disease remains a frequently missed illness. Here is how to spot and treat it.



Borrelia burgdorferi is transmitted through the bite of infected deer ticks.

Controversy over the treatment of a particular disease is not uncommon. There are many illnesses for which there are different schools of thought and more than one treatment method—e.g., heart disease, prostate cancer, and breast cancer. When it comes to Lyme disease, a bacterial infection caused by the corkscrew-shaped spirochete *Borrelia burgdorferi*, the battle lines are particularly distinct, and the opposing viewpoints reach vitriolic proportions, to the ultimate detriment of the patients.

Lyme disease, which is most commonly acquired through the bite of an infected tick, has been reported in every state and has become the most common vectorborne disease in the United States. In 2005, the CDC received reports of 23,305 cases, resulting in a national average of 7.9 cases for every 100,000 persons. In the 10 states where the infection is most common, the average was 31.6 cases for every 100,000 persons. The CDC estimates that the disease is grossly underreported, probably by a factor of 10.

Meet the players

The opponents in the battle over the diagnosis and treatment of Lyme disease are the Infectious Diseases Society of America (IDSA), the largest national organization of general infectious disease specialists, and the International Lyme and Associated Diseases Society (ILADS), an organization made up of physicians from many specialties.

IDSA maintains that Lyme disease is relatively rare, overdiagnosed, difficult to contract, easy to diagnose through blood testing, and straightfor-

ward to treat (www.journals.uchicago.edu/CID/journal/issues/v43n9/40897/40897.html. Accessed April 6, 2007). ILADS, by contrast, asserts that the illness is much more common than reported, underdiagnosed, easier to contract than previously believed, difficult to diagnose through commercial blood tests, and difficult to treat, especially when treatment is delayed because of commonly encountered diagnostic difficulties (www.ilads.org/guidelines.html. Accessed April 6, 2007).

Diagnosis: Where it all begins

If all cases were detected and treated in the early stages of Lyme disease, the debate over the diagnosis and treatment of late-stage disease would not be an issue, and devastating rheumatologic, neurologic, and cardiac complications could be avoided. However, Lyme disease is often missed during its early stage when it could be most easily treated (*Table 1*).

Since the deer tick is no larger than the period at the end of this sentence, it is not surprising that people frequently do not realize they've been bitten. In a hairy part of the body, the tick is almost impossible to see, and even when it is noticed, it is often mistaken for a mole or scab. When the tick latches on, it injects salivary components that anesthetize the area and decrease inflammation at the site of the bite, leaving the victim unaware of the tick's presence and allowing it to feast undisturbed.

TABLE 1. Reasons for missed diagnosis of Lyme disease

Patients often don't realize they have been bitten.
Patients often don't have the characteristic and diagnostic Lyme "bull's-eye" rash.
Clinicians are unaware of the widespread prevalence of the disease and do not include it in their differential diagnosis when they think it is not endemic to their area.
The mild flulike symptoms of early Lyme disease are usually attributed to a common virus.
Clinicians are not familiar with the varied signs and symptoms of the organism once it starts to disseminate throughout the body.
Clinicians are unaware of the insensitivity of commercial Lyme tests and therefore are inclined to rule out the disease in the presence of a negative test.
Clinicians do not realize that the CDC has gone on record as saying that commercial Lyme tests are designed for epidemiologic rather than diagnostic purposes, and a diagnosis should be based on clinical presentation rather than serologic results.
The Lyme spirochete can enter a dormant state soon after the tick bite and reappear months to years later, causing symptoms that are not readily associated with the original bite.

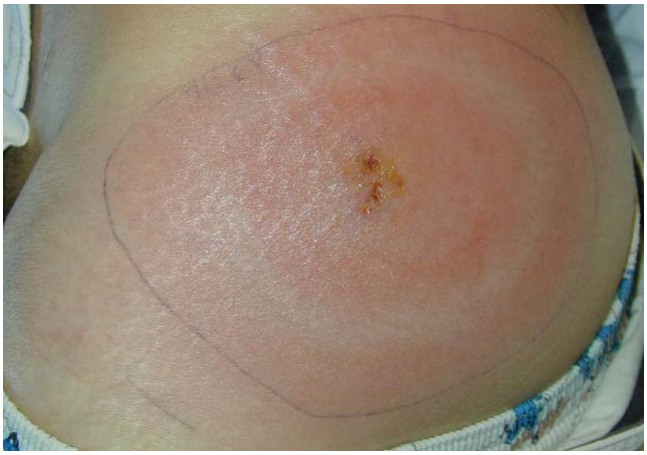


FIGURE 1. The characteristic erythema migrans or "bull's-eye" rash.

The erythema migrans (EM) rash is commonly known as the "bull's-eye" rash for its characteristic shape (*Figure 1*). The CDC maintains that a patient presenting with a bull's-eye rash does not require testing for Lyme disease because the rash is diagnostic in its own right. However, the rash does not always present in the classic pattern of concentric, round, red circles. EMs can be oval in shape and/or solid in color, with shades of pink, purple, and red. The rash may or may not contain pustules, itch, feature a dark spot in the middle, or have a denuded center. The size varies from that of a quarter to 12 in or more. Some victims develop a diffuse rash over the entire body. EMs are commonly misdiagnosed as spider bites, cellulitis, or ringworm. To complicate matters further, as many as half the people who acquire Lyme disease from a tick bite develop no rash at all.

Frequently, a clinician mistakenly assumes that there are no *Borrelia*-carrying ticks in the patient's geographic area and fails to include the disease in the appropriate differential diagnosis. Lyme disease should be considered regardless of where a patient lives. Ticks are carried on numerous animals, including household pets, rodents, deer, and birds, so it is little wonder that Lyme disease-transmitting ticks are not confined to a few distinct geographic areas. A travel history should be obtained to determine whether the patient has recently traveled to a particularly Lyme-endemic area (the northeastern United States, north-central United States, and the Pacific coastal region).

Most clinicians are not familiar with the varied signs and symptoms of Lyme disease (*Table 2*), and this contributes to misdiagnosis (*Table 3*). Children may present differently than adults, with predominant symptoms being changes in behavior and school performance. In affected children, parents typically report mood swings, irritability, obsessive-compulsive behavior, and new-onset attention-deficit/hyperactivity dis-

TABLE 2. Symptoms of Lyme disease by system

MUSCULOSKELETAL	Joint pain, muscle pain and cramps, muscle and joint stiffness, loss of muscle tone, back pain and/or stiffness, neck pain and/or stiffness, heel and foot pain, temporomandibular joint syndrome
NEUROLOGIC	Neuropathies, paresthesias, dizziness, cognitive disturbances, attention deficit, Bell's palsy, tinnitus, restless legs syndrome, drooping eyelid, transient blurred vision, new-onset anxiety or panic attacks, clumsiness, depression, difficulty chewing or swallowing, hallucinations, headaches, involuntary jerking or muscle twitching, irritability, poor balance, sleep disturbances, speech difficulty, weakness of limbs, hypersensitivity to touch, sound, light, and smell
CARDIAC	Exhaustion, palpitations, shortness of breath, tachycardia, hypotension, hypertension, heart murmur, abnormal ECG, chest pain, or tightness
ENDOCRINE	Low body temperature, sweats and/or chills, irregular menses, loss of libido, worsening premenstrual syndrome, pelvic or testicular pain, milky breast discharge, hypertriglyceridemia, Hashimoto's thyroiditis, weight gain
GI AND URINARY	Abdominal pain and tenderness, bloating and/or gas, constipation, loose stools, nausea, urinary frequency, constant thirst, irritable bladder, urine control problems, bowel control problems
OTHER	Easy bruising, hair loss, recurrent sinusitis, sore throats, tender glands, tooth pain, unusual rashes, shooting pains throughout body

TABLE 3. Diagnoses that should be suspect for Lyme disease

IN ADULTS	• Chronic fatigue syndrome • Fibromyalgia • Depression, anxiety, obsessive-compulsive disorder • Somatization disorder • Lupus • Multiple sclerosis • Parkinson's disease • Amyotrophic lateral sclerosis (Lou Gehrig's disease) • Early-onset Alzheimer's disease • Ménière's disease • Viral syndrome
IN CHILDREN	• Failure to thrive • Autism • Attention-deficit/hyperactivity disorder • Learning disabilities

order. Physical symptoms in children may include fatigue, frequent headaches or stomachaches, urinary symptoms, and migratory musculoskeletal pains.

When a patient presents with a collage of seemingly unrelated symptoms, there is a natural tendency to assume that a psychological component is at play. Patients with Lyme disease almost always have negative results on standard blood screening tests and have no remarkable findings on physical exam, so they are frequently referred to mental-health professionals for evaluation.

The testing conundrum

The CDC is aware of the insensitivity of the tests for Lyme disease and encourages clinicians to use judgment rather than a test result to make the diagnosis (www.cdc.gov/ncidod/dvbid/lyme/ld_humandisease_diagnosis.htm. Accessed April 5, 2007). As previously mentioned, however, most clinicians do not feel confident in making this judgment call and continue to look to unreliable test results for confirmation of disease.

The Western blot test

Because *B. burgdorferi* is an extremely difficult bacterium to culture in the lab, testing has relied on detection of antibodies to the organism. The Lyme enzyme-linked immunosorbent assay (ELISA) gives a titer of total immunoglobulin (Ig) G and M antibodies and is currently the accepted initial screen for suspected disease. Since a screening test should have at least 90% sensitivity, the 65% sensitivity of the commercial Lyme ELISA should lead to its reconsideration as an acceptable screening tool.

The Western blot, which is commonly used as a confirmatory test for Lyme disease, is more sensitive than the ELISA. While the CDC has published strict criteria for positivity on the Western blot to make a more exclusive cohort for epidemiologic purposes, it never intended for these criteria to be used for diagnosis. Unfortunately, the restrictive criteria omit several of the important bands on the blot that are highly sensitive markers for the presence of *B. burgdorferi* (see "Interpreting the Western blot," page 59). Clinicians should become acquainted with the relative sensitivity and specificity of each of the bands on the blot to make an appropriate assessment for diagnostic purposes. A negative test based on epidemiologic criteria may be a positive test for diagnostic purposes.

Treatment dilemmas

The Lyme spirochete presents a formidable adversary. With more than 1,500 gene sequences, *B. burgdorferi* is genetically one of the most sophisticated bacteria ever studied. *Treponema*

Interpreting the Western blot

The Western blot is more sensitive than the enzyme-linked immunosorbent assay because each of 14-16 *B. burgdorferi* protein antigens is analyzed separately. The antigens are spread on blot paper in parallel lines or bands. 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 *B. burgdorferi* flagellar protein. When the blot is washed over with patient serum, the bands become darker if antibodies attach to the various antigens, to form antigen-antibody complexes. The interpretation of the test is subjective, as the observer grades this darkness (i.e., the intensity of the antibody response to the different protein bands) (*Figure 1*).

According to CDC criteria, a Lyme Western blot immunoglobulin (Ig) M must have two of the following three bands to be considered positive: 23-25 (a single band), 39, and 41 kDa. A positive IgG must contain five of the following bands: 18, 23-25, 28, 30, 39, 41, 45, 58, 66, and 93 kDa. Each band has a different degree of specificity. The band with the highest specificity for *B. burgdorferi* is band 39 kDa, while the band with the lowest specificity is band 41 kDa. Both of these are included in the CDC criteria. For epidemiologic reasons, the CDC did not count bands 31 and 34 kDa in its inclusion criteria even though these bands were specific enough to *B. burgdorferi* that they were chosen for vaccine development. The degree of specificity of each band needs to be kept in mind when interpreting Western blot results. The bottom line may read "negative," but if the test reveals at least one highly specific band (e.g. 18, 23, 29, 31, 34, 39, 55, or 83 kDa), the clinician should be suspicious of *B. burgdorferi* infection.

Commercial Western blots are based on laboratory strains of *B. burgdorferi*, which may differ significantly from the "wild type" strains that patients are exposed to around the country. The true sensitivity of commercial Western blots for regional strains of the Lyme spirochete is uncertain. A few specialty laboratories have solved this problem by including various strains of *Borrelia* in more sensitive "home brew" blots.

In virtually all Lyme infections, the IgM class of antibody appears first and represents a marker for early infection. In most models of immunity, the IgM antibody gives way to the IgG antibody class, usually regarded as the major antibody response in chronic infectious diseases. Positive IgM reactions that do not convert to positive IgG reactions within a few months are generally considered false positives. However, in Lyme disease, the IgM antibody may persist for years or reappear late in illness, a very unusual situation in most infectious disease states.

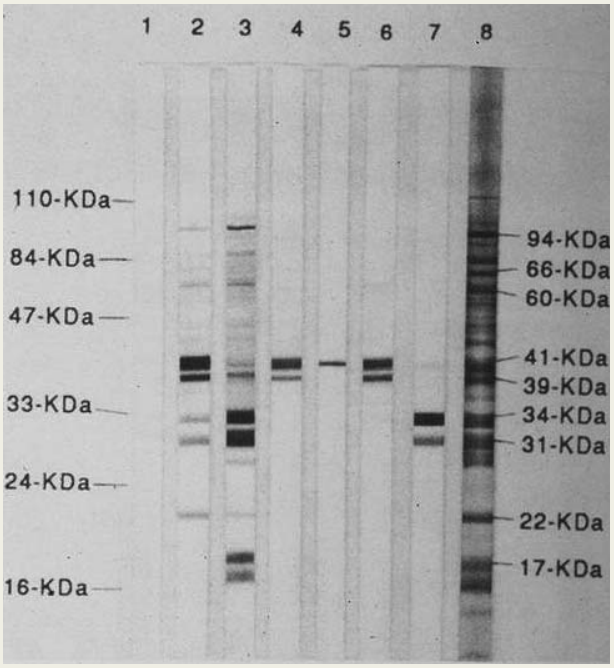


FIGURE 1. Significant antibodies detected by Western blot.

Test results may seem counterintuitive since the sickest patients (or those who have been sick the longest) tend to have fewer positive tests than those who are newly infected or have mild disease. In most laboratory tests that report degrees of positivity, the more positive the test, the greater the predictability of disease and vice versa. It is not surprising that a clinician inexperienced in interpreting the blot of a Lyme patient would assume that a patient with a negative or very weakly positive test could not be suffering from Lyme disease.

A very positive test, in which a large number of antibodies are detected, demonstrates a healthy immune system that is reacting appropriately to an antigenic challenge. The sicker patients have fewer free-floating antibodies and are barely positive (if at all). This paucity of antibodies in the extremely ill Lyme patient may be attributable to several factors: (1) The weakened immune system has become accustomed to the chronic infection and has stopped producing antibodies; (2) antibodies are depleted due to the constant demand; and/or (3) antibodies are tied up in antigen-antibody complexes and are not available to be picked up on the blot.

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Once disseminated, *Borrelia burgdorferi* secludes itself and becomes difficult to detect through lab testing as well as by the host's immune system.

pallidum (the spirochete responsible for syphilis), for example, has 22 functioning genes whereas the Lyme disease spirochete has 132.

Borrelia burgdorferi's stealth pathology makes eradication of the disseminated organism a near impossibility. Before the tick delivers its inoculum of spirochetes into the host, it injects a substance that inhibits the immune response, allowing the spirochete to gain a strong foothold. The spirochete itself secretes enzymes that help it to replicate and infect the host.

Once disseminated throughout the body, *B. burgdorferi* secludes itself and becomes difficult to detect through laboratory testing—and by the host's immune system. The bacterium may hide in its host's WBCs or cloak itself with host proteins. Furthermore, it tends to hide in areas not usually under immune surveillance, such as scar tissue, the central nervous system, the eyes, and deep in joints and other tissues.

TABLE 4. Lyme disease antibiotic treatment options

Doxycycline
Minocycline
Macrolide (clarithromycin, azithromycin) + beta lactam
Macrolide (clarithromycin, azithromycin) + metronidazole or tinidazole
Ketolide + beta lactam or metronidazole

TABLE 5. Treatments for coinfections

Babesia (treat this first and for at least four months) • Atovaquone + azithromycin • Metronidazole + azithromycin • Clindamycin + hydrochloroquine • Lariam + doxycycline *Trends Parasitol.* 2003;19:51-55 and *Emerg Infect Dis.* 2003;9:942-948
Bartonella • Ciprofloxacin or levofloxacin (Levaquin) • Clarithromycin + DS sulfa • Rifampin + doxycycline *J Clin Microbiol.* 2004;42:2799-2801 and *J Spiro Tick Diseases.* 2002;9:23-25
Ehrlichia (many Lyme treatments will cover *Ehrlichia* too) • Doxycycline • More resistant cases, add rifampin *Lancet Infect Dis.* 2001;1:21-28

Phase and antigenic variations allow *B. burgdorferi* to change into pleomorphic forms to evade the immune system and antibiotics. The three known forms are the spiral shape that has a cell wall, the cell-wall-deficient form known as the "L-form" (named not for its shape but for Joseph Lister, the scientist who first identified these types of cells), and the dormant or latent cyst form. Encapsulating itself into the inactive cyst form enables the spirochete to hide undetected in the host for months, years, or decades until some form of immune suppression initiates a signal that it is safe for the cysts to open and the spirochetes to come forth and multiply.

Each of these forms is affected by different types of antibiotics. If an antibiotic targets the bacterium's cell wall, the spirochete will quickly morph into a cell-wall-deficient form or cyst form to evade the chemical enemy.

Borrelia burgdorferi has an in vitro replication cycle of about seven days, one of the longest of any known bacteria. Antibiotics are most effective during bacterial replication, so the more cycles during a treatment, the better. Since the life cycle of *Streptococcus pyogenes* (the bacterium that causes strep throat) is about eight hours, antibiotic treatment for a standard 10 days would cover 30 life cycles. To treat Lyme disease for a comparable number of life cycles, treatment would need to last 30 weeks.

Within the tick gut are hundreds of different types of pathogens. How many infect humans is unknown. Some have been identified and are known to intensify morbidity and complicate treatment of Lyme disease. Awareness of three coinfecting genuses in particular—*Ehrlichia*, *Bartonella*, and *Babesia*—has increased, and persistent infection with these organisms has been described. Testing for and treating these coinfections has become part of the approach for clinicians who specialize in the treatment of Lyme disease.

Treatment methods

IDSA guidelines recommend treating certain high-risk tick bites with a prophylactic single dose of doxycycline. This is recommended only if the tick is clearly a deer tick that was attached for 36 hours or more, the patient was in an endemic area, and if treatment can be started within 72 hours of the time the tick was removed. Most ILADS practitioners treat any high-risk tick bite with a full month of doxycycline.

If a patient presents with EM or has a positive Lyme test, IDSA guidelines recommend treating with either doxycycline, cefuroxime, or amoxicillin for 10-21 days. All other

Because of the lack of simple culture techniques and the low sensitivity of antibody tests, a negative test for Lyme disease does not rule out infection.

antibiotics are specifically not recommended. After the prescribed amount of time, treatment is discontinued whether symptoms remain or not. However, if symptoms remain severe after the patient has been off the antibiotics for a few months, treatment with another two to four weeks can be considered. One month of IV antibiotics is recommended for severe arthritis or neurologic disease.

IDSA stresses that persistent symptoms do not indicate chronic infection and that prescribing long-term antibiotics to patients unresponsive to the typical two- to four-week course is useless and potentially harmful. "There is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease," the guidelines state. "Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (six months or longer) subjective symptoms after recommended treatment regimens for Lyme disease."

Patients who continue to suffer from persistent fatigue, pain, and cognitive disturbances after a traditional short course of antibiotics are rare, the IDSA panel claims. These patients have developed "post-Lyme syndrome," probably due to an immune system that cannot shut down after the infection is gone. This syndrome can only be treated with symptomatic care and tincture of time.

ILADS, on the other hand, promotes the idea that the Lyme spirochete is very hard to eradicate and persistent symptoms are due to ongoing infection. This organization's approach is to treat with antibiotics as long as symptoms remain. Off-label combinations are often used based on clinical experience. Variable response to antibiotics and occasional antibiotic resistance are thought due to the fact that there are over 100 strains of *B. burgdorferi* in the United States and 300 strains worldwide.

AT A GLANCE

- Lyme disease has been found in every state and should always be considered in the appropriate differential diagnosis.
- While a "bull's-eye" rash is diagnostic, fewer than 50% of patients develop any rash at all.
- Lyme patients should be tested for other tickborne organisms, such as *Ehrlichia*, *Bartonella*, and *Babesia*.
- Eradication of the *Borrelia* spirochete may require use of two to three simultaneous antibiotics for up to three years.

Since the Lyme spirochete is adaptive and morphs to a new cell type when under stress, clinicians who advocate aggressive, long-term treatment support giving two or three different classes of antibiotics at the same time and changing the treatment protocol every two to three months. Higher-than-normal doses of antibiotics are given to achieve better penetration of both the tissue and the blood-brain barrier. IM injections of long-acting penicillin or IV administration of antibiotics are recommended for patients with neurologic disease. Precedent for the safety of long-term antibiotic use has shown that the benefits outweigh the risks.

According to ILADS, treatment is complicated by the frequent presence of coinfections, which can intensify symptoms and prolong treatment. Therefore, antibiotics that target the coinfections are usually prescribed prior to or along with those that treat Lyme disease. *Table 4* lists treatment options used by ILADS clinicians to target the various forms of the *B. burgdorferi* bacterium, and *Table 5* lists treatment options for the most common coinfections.

Occasionally, Jarisch-Herxheimer reactions complicate Lyme disease treatment. These symptom intensifications are due to elevated cytokines and toxins released during *B. burgdorferi* die-off. Many patients notice that symptoms occur cyclically (every 21–28 days). When these intensification reactions occur, the treatment can be temporarily worse than the disease.

It is difficult to decide when to stop treating Lyme disease since there is no test that demonstrates a cure. Because of the lack of simple culture techniques and the low sensitivity of antibody tests, a negative test does not rule out infection. Treatment cessation is based on symptom resolution, which means that symptoms may return if the infection has not been eradicated.

The road ahead

Rather than shy away from the complexities and controversies of Lyme disease, clinicians should welcome the chance to learn about this condition. Lyme disease is much more prevalent than most realize. Clinician education will reduce patient suffering and hopefully put an end to the "Lyme War." ■

For a list of references used in this article, contact the editor via e-mail (editor@clinicaladvisor.com) or telephone (646.638.6077).

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