

Clinical Controversies in Lyme Disease

Case Study and Commentary:

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Lyme disease is currently the most common and frequently reported vector-borne illness in the United States, accounting for more than 95% of cases.¹ The incidence of the disease is 0.5% annually in endemic areas.² The causative tick-borne spirochete, *Borrelia burgdorferi*, and the vector ticks, *Ixodes scapularis* (in the eastern and midwestern United States) and *I. pacificus* (in the western United States), were isolated from blood, skin, and cerebral spinal fluid of infected individuals in the 1980s.^{3,4} Treatment, if given appropriately and in a timely fashion, is effective and has excellent results.⁵

As indicated in the following case study and discussion of Lyme disease, preventive measures are the primary means of avoiding infection with the disease. More specifically, avoiding endemic areas, wearing protective clothing, performing regular body checks, and removing any discovered ticks are the most cost-effective methods of reducing the significant monetary and nonmonetary costs engendered by the morbidity, diagnosis, and treatment of the disease.

Even with these preventive measures, however, the symptoms and costs associated with the disease are sometimes so overwhelming that many have lobbied for effective vaccination against the infection. An effective vaccine has, in fact, been developed, despite arguments that resources allocated to this area of research are less cost-effective in terms of worldwide use.⁶ The vaccine was licensed by the US Food and Drug Administration (FDA) in late 1998 for use in patients age 15 to 70 years to provide greater protection against potential infection. The vaccine is an outer-surface protein vaccine directed against the causative spirochete, *B. burgdorferi*.

The mechanism by which the Lyme disease vaccine works is interesting and unique, because it functions through the tick itself rather than the spirochete. It thus prevents transmission of the infective organism from the tick to the vaccinated person, thereby preventing the action of the spirochete within that person.⁷ However, use of the vaccine is not without difficulties.

In the first place, 3 injections are necessary over 2 years. Clinical trials that follow this protocol have reported the vaccine to be roughly 75% effective, but there are currently no data indicating how long the vaccine's protective effect will last.⁸ Secondly, patients who have received the vaccine subsequently can have false-positive results on enzyme immunoassays performed for diagnostic purposes. This possibility further confuses the treatment picture for physicians facing symptoms that might appear similar to the clinical manifestations of Lyme disease. Hence, use of the vaccine should be considered only as a complementary measure rather than as a substitution for preventive steps.

In addition to concerns about the overuse of vaccines, the limited reliability of serologic testing in general is troubling.^{9,10} Currently, there are roughly 60 assorted serologic tests on the market for detecting the antibody to *B. burgdorferi*; all have been approved by the FDA.¹¹ Although these tests are commercially available, the FDA has issued a public health advisory to physicians and clinical laboratories, alerting them to the potential for misdiagnosis of Lyme disease using these tests only. Because of these reservations about serologic testing, the FDA has recommended a 2-step laboratory testing paradigm for positive or equivocal first-step test results and asked manufacturers of the tests to modify their labeling to reflect this recommendation.¹² This recommendation also is advocated by the Second National Conference on Serologic Diagnosis of Lyme Disease.¹³

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Clinical assessment, including determination of whether erythema migrans was present 2 days to 2 weeks after exposure to the causative agent, is therefore critical in making the diagnosis of Lyme disease and far superior to relying on potentially flawed serologic testing.^{14,15} As more and more patients request serologic testing and expect treatment based on the results of such testing, it is crucial to remember this fact, especially when clinical findings do not support a diagnosis of Lyme disease.^{16,17} There are significantly high error rates in diagnosing the disease,¹⁸ and there is no standardized method of treatment.^{19,20} These considerations not only increase the possibility of medical error and patient injury but can heighten psychological stress in patients whose symptoms do not improve; moreover, they indicate poor cost-effectiveness.^{21,22}

Overall, management of Lyme disease is effective when the condition is diagnosed promptly and correctly and then treated appropriately. The many risks associated with the disease result primarily from inappropriate use of vaccines, imperfect diagnostic technology, and solely empiric treatment. Only by knowing the best methods of preventing Lyme disease can physicians provide their patients with the most cost-effective information about avoiding the disease. Similarly, only by understanding the limitations of available diagnostic and treatment options can they best serve their patients who have the disease and not waste resources best reserved for others in the health delivery system.

DRS. SOOD AND O'DONNELL:

Lyme disease is the most common vector-borne disease in the United States today.¹⁴ Between 1982 and 1998, there was a 25-fold increase in the number of reported cases.²³ In 1998, there were more than 16,000 cases reported to the Centers for Disease Control and Prevention (CDC), and this number is thought to vastly underestimate the actual number of cases that occurred.^{14,23,24} Preliminary data from 1999 suggest a small decrease in reported cases; however, it is too soon to identify whether this will be a trend.²⁵ It is now known that Lyme disease is caused by 3 genospecies of the spirochete *Borrelia*. These 3 genospecies, *B. burgdorferi*, *B. garinii*, and *B. afzelii*, are collectively referred to as *B. burgdorferi sensu lato*.²⁴ Throughout this article, the term *B. burgdorferi* will refer to either the specific genospecies or to *B. burgdorferi sensu lato*.

Although the clinical stages of Lyme disease are well described and several successful treatment strategies have been identified and studied, there is still great

confusion regarding diagnosis. In particular, it is the use of serologic tests that fosters confusion and controversy. Overdiagnosis of Lyme disease continues to be a problem, leading to unnecessary use of antibiotics and increased medical costs. A clear understanding of the currently available serologic tests and their appropriate use is critical to the successful management of patients who are suspected of having Lyme disease or who request testing. Awareness of risk factors and clinical presentation are paramount to appropriate use of the serologic tests and accurate diagnosis.

CASE STUDY

Initial Presentation

An 18-year-old man from southeastern Pennsylvania without past medical history presents to the emergency department in February with a 2-week history of left knee swelling, pain, and erythema.

History

Both the pain and swelling have been worsening over this time period, and range of motion has been moderately limited. He also complains of a 3-week history of flu-like symptoms including fatigue, intermittent fevers, chills, and diffuse myalgias. He has recently been on a hiking trip in the Pocono Mountains in northeastern Pennsylvania, where his family has a vacation home. The patient frequently goes to this area on weekends during the spring, summer, and early fall for various recreational activities. With specific questioning, he recalls removing a tick from his right inner thigh in July of the previous year. He thought the tick appeared large but had no idea how long it had been attached.

The patient has no past surgical history or drug allergies and does not use tobacco, alcohol, or illicit drugs. He is a college freshman and works part-time. Family history is significant for his mother's recent diagnosis of rheumatoid arthritis. He is currently sexually active with one partner, with whom he has been monogamous for the past 4 months. They practice vaginal and oral intercourse but not rectal intercourse. He denies a history of past sexually transmitted diseases and believes his partner to be without symptoms. To his knowledge, his partner does not have any other partners and does not use illicit drugs. They use latex condoms for vaginal intercourse but not for oral intercourse.

Physical Examination

On physical examination, the patient has an oral temperature of 102°F. Vital signs are otherwise stable. The examination is within normal limits except for the left knee, which has increased warmth and erythema

of the surrounding skin and soft tissue, a large effusion, severely limited range of motion, and pain elicited during range of motion testing. Peripheral leukocyte count is $7.2 \times 10^3/\text{mm}^3$, with 68% segmented neutrophils, 22% lymphocytes, and 5% monocytes.

Initial results from an arthrocentesis performed in the emergency department reveal a joint fluid leukocyte count of $42.6 \times 10^3/\text{mm}^3$, with 88% segmented neutrophils and 5% lymphocytes, an erythrocyte count of 5940/ mm^3 , and a Gram stain that shows many neutrophils and no organisms. Crystal examination of the fluid is negative.

QUESTION

- **What is the differential diagnosis of monoarticular arthritis in this patient?**

DISCUSSION

This patient presents with fever and an acute inflammatory monoarthritis of his left knee. The differential diagnosis includes septic arthritis, early rheumatoid arthritis, spondyloarthropathies, sarcoidosis, inflammatory bowel disease, gout, and pseudogout. The absence of systemic features such as rash, back pain, diarrhea, or adenopathy makes psoriatic arthritis, Reiter's syndrome, inflammatory bowel disease, and sarcoidosis all less likely in this patient. Gout and pseudogout usually affect the small joints but may occasionally present as an acute monoarthritis of a large joint such as the knee. These disorders may be easily diagnosed or excluded with examination of joint fluid for crystals. Early rheumatoid arthritis can present with an acute arthritis of 1 joint that eventually progresses to a bilateral symmetric destructive arthritis. The patient's mother was recently diagnosed with rheumatoid arthritis, suggesting a potential genetic predisposition to this disease. At this stage of the patient's illness, further evaluation is required before rheumatoid arthritis can be excluded.

The most important diagnosis to consider in clinical presentations such as this is septic arthritis because it is rapidly destructive and, with early initiation of antibiotic therapy, can be successfully treated and joint destruction averted. The patient's clinical findings and joint fluid studies are consistent with septic arthritis. The absence of organisms on Gram stain should not dissuade clinicians from the diagnosis of bacterial arthritis, as two thirds of patients with septic arthritis will not have organisms identified on Gram stain of their joint fluid. The most likely bacterial pathogens are *Staphylococcus aureus*, group A streptococci, group B streptococci, and *Neisseria gonorrhoeae*, which is the most common cause of septic monoarticular arthritis in adults younger

than 30 years.²⁶ In this young sexually active man, *N. gonorrhoeae* must be strongly considered, and joint fluid, blood, and urethral swabs all should be sent for culture. Finally, among the infectious etiologies, Lyme arthritis due to infection with the spirochete *B. burgdorferi* should be seriously considered because this patient has a compatible clinical presentation as well as epidemiologic risk factors for this diagnosis.

QUESTION

- **Why should the diagnosis of Lyme disease be strongly considered in this particular patient?**

DISCUSSION

This patient has several risk factors in his history that increase his likelihood of having Lyme disease. One is his residence in, and travel to, an endemic area. Three distinct geographic areas of the United States are considered endemic for Lyme disease: the Northeast from Maryland to Massachusetts; the north-central states, like Wisconsin and Minnesota; and the West Coast, particularly northern California. It has been estimated that 30% to 80% of *I. scapularis* ticks, the primary vector for Lyme disease in the northeast and north-central regions, are infected with *B. burgdorferi*, the etiologic agent of Lyme disease.^{27,28}

Although time spent in an endemic area for Lyme disease is an important risk factor, specifically it is the time spent outdoors that is most critical to acquisition of disease.^{29–31} Our patient gives a clear history of engaging in several outdoor recreational activities in an endemic area. Additionally, the patient participated in these activities during the peak season for Lyme disease—late spring, summer, and early fall. The seasonality of Lyme disease is directly related to the life cycle of the tick vectors.³² The *Ixodes* species undergo 3 stages of development: larva, nymph, and adult. Larvae do not transmit *B. burgdorferi* to humans and molt into nymphs in early spring. Nymphs feed on small rodents and other mammals through spring into fall, when they molt into adults. Both the nymph and the adult transmit infection, with the nymph being responsible for 90% of disease transmission to humans.³³

This patient also recalls a tick bite during one of his trips to his family's summer home. Many patients with Lyme disease never remember having an attached tick, in part because the *Ixodes* species ticks are very small. The nymph, which is responsible for the majority of disease transmission, is smaller than the adult and usually less than 2 mm in width. Our patient remembers that the tick was "large." If it were an *I. scapularis* tick, then it may have been easily seen because of engorgement

from a prolonged attachment and feeding. The duration of attachment of the tick is another critical factor in the transmission of Lyme disease. Animal studies have shown that ticks need to remain attached for 36 to 48 hours to transmit *B. burgdorferi*.^{34,35} A retrospective study looking at infected humans showed that risk of infection was between 18% and 25% higher when ticks were attached for more than 72 hours.³⁶ In general, it is thought that at least 24 hours of attachment is necessary before considering someone at risk for Lyme disease.

QUESTION

- **Should this patient have been provided treatment at the time he identified and removed a tick from his thigh?**

DISCUSSION

Even in Lyme-endemic areas, the incidence of infection with *B. burgdorferi* after a deer-tick bite is low, usually estimated to be between 1% and 4%.^{24,37,38} The efficacy of the use of prophylactic antibiotics in this setting remains unproved. In a meta-analysis of 3 prospective randomized blinded trials evaluating the risks and benefits of antibiotic prophylaxis after deer-tick bites, it was estimated that 1 case of Lyme disease would be prevented for every 83 patients treated with antibiotics. Moreover, if penicillin or amoxicillin were the prophylactic antibiotic prescribed, then a 10% incidence of drug-induced rash would be expected.³⁹

Currently, there is no definitive recommendation regarding the management of deer-tick bites. Since the large majority of tick bites do not result in disease transmission, and since early Lyme disease is easily and effectively treated with antibiotics, most experts counsel watchful waiting in patients with a history of recent tick bite.^{38,40} Serologic testing should never be utilized in this setting. Although expert opinion suggests that routine use of antimicrobial therapy for tick bites is unwarranted, exceptions in specific patient subpopulations do exist. For example, patient identification of an engorged tick suggests a prolonged tick attachment (36 to 48 hours), and in this setting the likelihood of infection increases. Such individuals may benefit from antibiotic prophylaxis. Amoxicillin and doxycycline, both administered for 10 days, have been studied as prophylactic regimens. In this particular patient, antibiotic prophylaxis may have been justified.

QUESTION

- **What stage of Lyme disease does this patient most likely have?**

DISCUSSION

Traditionally, Lyme disease was divided into 3 stages. The primary stage manifestation was erythema migrans, followed by neurologic or cardiac involvement in secondary stage Lyme, and finally arthritis or late neurologic manifestations in tertiary Lyme.^{3,41-43} This classification system has more recently been modified to reflect the knowledge that *B. burgdorferi* can disseminate early in the disease and that joint and central nervous system involvement may occur at any time in the illness.⁴⁴⁻⁴⁶ Early Lyme disease is seen within 8 weeks of a tick bite and is divided into early localized and early disseminated disease, whereas late Lyme disease generally occurs more than 8 weeks after a tick bite.⁴⁴ The hallmark of early localized Lyme is the erythema migrans (EM) lesion. EM begins as an erythematous macule or papule at the site of tick bite and becomes a circular erythematous lesion, expanding concentrically over several days. Central clearing may be seen over time, and atypical presentations of the rash of early Lyme have been widely reported.^{44,47} EM may be accompanied by systemic symptoms such as fever, arthralgias, and myalgias. The most common manifestation of early disseminated Lyme is multiple EM lesions, usually seen across the trunk and thighs and usually occurring a few weeks after the initial EM lesion fades.

Other manifestations of early disseminated Lyme include neurologic, cardiac, and joint involvement. Neurologic manifestations in this stage of Lyme disease are usually either aseptic lymphocytic meningitis or a cranial nerve VII palsy. Cardiac involvement most commonly manifests as first-, second-, or third-degree atrioventricular conduction blocks or bundle branch block.²⁴ The arthritis at this stage either is a migratory polyarthritis or one that affects the knees.^{48,49}

Late Lyme disease is manifested as either arthritis or neurologic disease. Joint involvement may initially be polyarticular as noted above; however, as the disease progresses, the attacks become limited to 1 or 2 joints.⁵⁰ The knee is involved in 90% of late Lyme arthritis cases. The involved joint is swollen, painful, and stiff. Synovial fluid has large numbers of leukocytes, the majority neutrophils. The joint effusion often reaccumulates after arthrocentesis, requiring serial joint taps. Left untreated, Lyme arthritis will result in chronic arthritis and destruction of the joint space.

Neurologic manifestations of late Lyme disease may include peripheral neuropathies or chronic encephalopathy manifested by cognitive deficits, memory problems, sleep disturbances, and/or personality changes.⁵¹ Contrary to reports in the popular press, there are no

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definitive data to support that late Lyme disease can manifest as a chronic fatigue syndrome. This patient most likely has late Lyme disease, as manifested by his monarticular arthritis.

Initial Hospital Course

The patient is begun on intravenous ceftriaxone 2 g daily. He becomes afebrile but requires daily arthrocentesis for management of his effusion. Within 48 hours, blood and joint fluid cultures are negative. Urethral swabs for *N. gonorrhoeae* and *C. trachomatis* are also negative. Enzyme-linked immunosorbent assay (ELISA) for Lyme antibodies is reported as positive. A Western blot is still pending.

QUESTIONS

- When are serologic tests for Lyme disease indicated?
- What testing approach is recommended?
- Can the serologic test results be used to monitor disease?

DISCUSSION

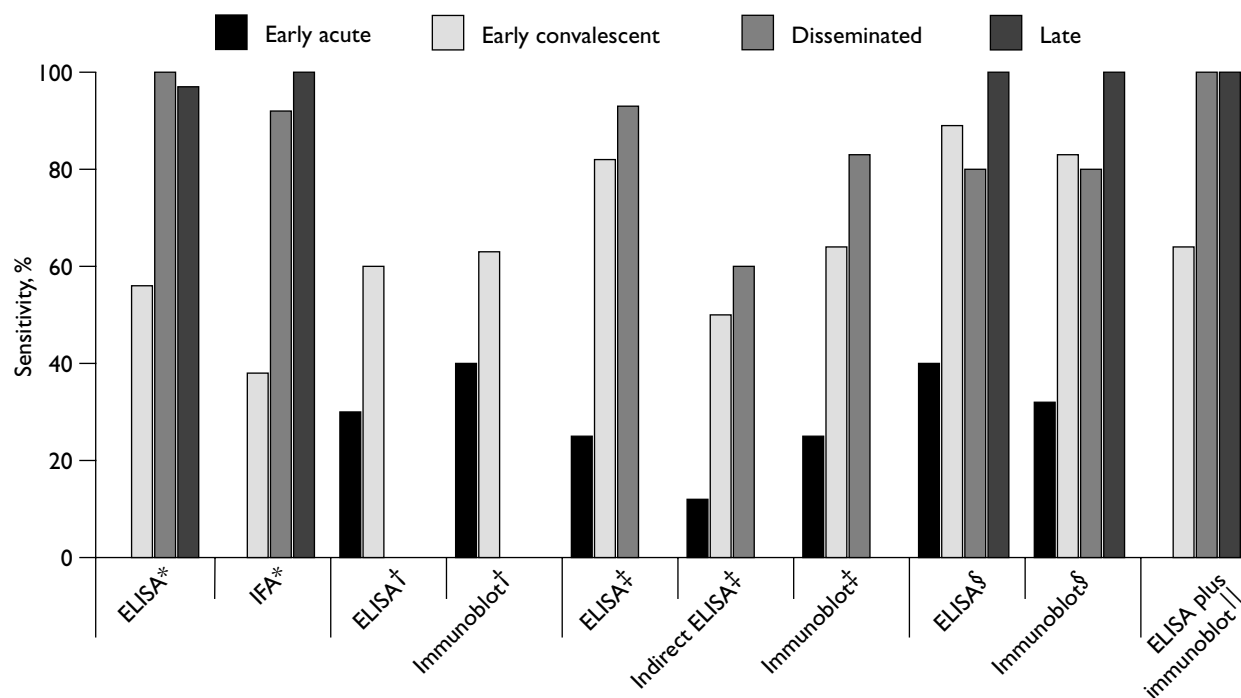
It is important to note that the diagnosis of Lyme disease is never made with serology alone. Rather, it is a clinical diagnosis that can be supported by appropriate serologic test results. Serology should never be used to “screen” patients for Lyme disease who are either asymptomatic or who exhibit nonspecific constitutional symptoms.^{12,15,52} Additionally, there is no need to order serologic tests in the patient who presents with erythema migrans.¹⁵ The diagnosis of Lyme disease is made by the skin manifestations at this stage of infection. Serology should be used in specific settings where the clinical presentation is consistent with early disseminated or late Lyme disease and the patient has had a reasonable possibility of tick contact. **Figure 1** shows the utility of various diagnostic modalities by stage of Lyme disease.

Soon after Lyme disease became a recognized clinical entity, there was a proliferation of different Lyme antibody tests. These early serologic tests were often not standardized and frequently falsely positive, and positive test results became subject to justifiable skepticism and doubt.⁵³ Because of the multitude and lack of standardization of tests, inter- and intralaboratory variability of results, and numerous problems with false-positives, the Second National Conference on Serologic Diagnosis of Lyme Disease and the American College of Physicians began advocating a 2-step approach to serologic diagnosis of Lyme disease in the mid-1990s.^{13,15,52} This 2-step approach (**Figure 2**) is now widely accepted and

consists of an initial ELISA or immunofluorescence assay (IFA) to be followed by Western blotting when the first test is positive or equivocal. If the Western blot is negative, then the patient does not have serologic evidence of Lyme disease and the first-step test should be considered falsely positive. If the Western blot is positive, then the patient has serologic evidence of infection with *B. burgdorferi*. This does not necessarily imply that the patient has active Lyme disease, only that the patient has evidence of either a past or present infection. The ultimate interpretation of the test results can be done only within the clinical context of the patient's presentation. The 2-step protocol, as outlined above, provides better sensitivity and specificity than when either test is used alone.⁵⁴ The sensitivity is approximately 70% in early disease and 100% in late disease, and the specificity is near 90% overall.⁵⁴

It should be noted that although either an ELISA or IFA is suggested as the first-step test, the enzyme immunoassay/ELISA is probably the preferred test. This is because the IFA is more difficult for laboratory technicians to interpret and may be more likely to be read as falsely positive when the technician is not familiar with the test.⁵² Also, humans produce a variety of different IgM and IgG antibodies to proteins of *B. burgdorferi*, and these antibodies are of varying mass as measured in kilodaltons. The Western blot is an immunoblot that separates these specific IgM and IgG antibodies into distinct bands based on mass. Many laboratories automatically report both IgM and IgG antibody Western blot results. After the first 4 weeks of infection, a positive IgM Western blot is not useful and should not be used to support a diagnosis of Lyme disease.^{12,55} Additionally, the IgM antibodies may be falsely positive, and a positive IgM Western blot with a negative IgG Western blot should not be interpreted as a “positive” second-step test.^{12,52,55}

Finally, it is important to understand that all of the serologic tests for Lyme disease are qualitative tests.^{9,55} The absolute number reported by the reference laboratory for the *B. burgdorferi* enzyme immunoassay should be interpreted as positive or negative based on that particular test's defined cut-off point. The absolute number should never be used to assess disease activity. In fact, once a patient is found to have serologic evidence of Lyme disease, there is no reason to repeat Lyme serologies. These tests are not useful for assessing treatment success or for following disease over time. Patients may remain seropositive for Lyme disease for years after infection and treatment. Thus, repeating these tests only adds to the confusion around them and usually leads to inappropriate re-treatment.



*Data from Russell H, Sampson JS, Schmid GP, et al. Enzyme-linked immunosorbent assay and indirect immunofluorescence assay for Lyme disease. *J Infect Dis* 1984;149:465–70.

†Data from Grodzicki RL, Steere AC. Comparison of immunoblotting and indirect enzyme-linked immunosorbent assay using different antigen preparations for diagnosing early Lyme disease. *J Infect Dis* 1988;157:790–7.

‡Data from Berardi VP, Weeks KE, Steere AC. Serodiagnosis of early Lyme disease: analysis of IgM and IgG antibody responses by using an antibody-capture enzyme immunoassay. *J Infect Dis* 1988;158:754–60.

§Data from Dressler F, Whalen JA, Reinhardt BN, Steere AC. Western blotting in the serodiagnosis of Lyme disease. *J Infect Dis* 1993;167:392–400.

||Data from Johnson BJ, Robbins KE, Bailey RE, et al. Serodiagnosis of Lyme disease: accuracy of a two-step approach using a flagella-based ELISA and immunoblotting. *J Infect Dis* 1996;174:346–53.

Figure 1. Sensitivity of serologic diagnostic tests based on clinical stage of disease. ELISA = enzyme-linked immunosorbent assay; IFA = immunofluorescent assay.

QUESTION

- What additional tests may aid in confirming the diagnosis of Lyme disease?

DISCUSSION

A variety of other diagnostic modalities have been utilized in the setting of Lyme disease; however, none can definitively guide diagnosis or management. Both direct culture and polymerase chain reaction amplification (PCR) have been used in the diagnostic evaluation of patients with Lyme disease. Culture of *B. burgdorferi* is both expensive and time-consuming and, with a variable yield, is not a practical service for most laboratories to provide. Direct culture is most likely to yield a posi-

tive result when an erythema migrans lesion is aspirated. In this particular setting, the culture-positivity rate has been as high as 72%.⁴⁵ Yield from blood cultures is variable, with the highest likelihood of a positive blood culture in early disseminated Lyme disease.^{4,44} In all of the other stages, blood has a yield of less than 10%.^{4,56} Although *B. burgdorferi* has been cultured from brain tissue obtained during brain biopsy and has been cultured from joint fluid in 2 case reports, the overall yield from central nervous system tissue/fluid and synovial fluid is extremely low.^{57,58}

PCR assays identify the presence of *B. burgdorferi* DNA in clinical specimens. Blood, skin, synovial fluid, cerebrospinal fluid (CSF), and urine have all been evaluated

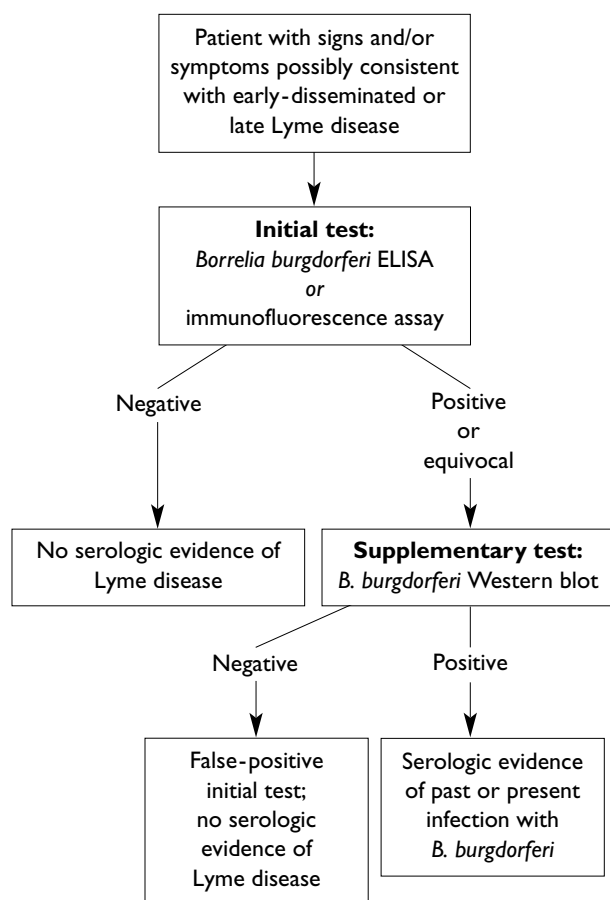


Figure 2. Algorithm for use of Lyme serologies in individuals suspected of having Lyme disease. ELISA = enzyme-linked immunosorbent assay.

by PCR testing for *B. burgdorferi*.^{59,60} Despite reports of overall higher sensitivity than direct culture and good specificity, PCR for the diagnosis of Lyme disease remains of limited value. False-positive PCR results are problematic due to laboratory cross-contamination, and the necessary precautions required to prevent cross-contamination are often impractical for commercial laboratories. False-negative PCR results are also seen, in part because of the low number of spirochetes found in infected individuals.⁵⁹ Additionally, PCR cannot differentiate between live, replicating organisms and dead spirochetes. Thus it cannot routinely be used to monitor all stages of disease or response to treatment. In particular, CSF PCR testing can often be unreliable. In one study, the same specimen tested positive 7 times and negative 6 times.⁶¹ At the present time, PCR for the diagnosis of Lyme disease is not FDA-approved.

Although the role of PCR in the diagnosis of Lyme disease has yet to be completely defined, it may ultimately be most beneficial in 2 particular settings: the evaluation of Lyme arthritis and late neurologic Lyme disease. In the largest study published to date, Nocton and colleagues⁶² showed that in synovial fluid samples of 88 patients with Lyme arthritis, PCR was found to have a sensitivity of 85% and a specificity of 100%. PCR of synovial fluid was shown to both confirm the clinical diagnosis and help identify potential treatment failures in individuals with Lyme arthritis. PCR testing of synovial fluid may be worthwhile when performed on patients with recurrent arthritis after antibiotic treatment and, if positive, may indicate need to treat again. Although the sensitivity of Lyme CSF PCR is variable and often low in the setting of late neurologic Lyme disease, a positive CSF PCR test can be very helpful. As such, it is often recommended that CSF be sent for PCR testing as part of the work-up for late-stage neurologic Lyme disease.

Finally, the use of a T-cell proliferation assay for Lyme disease has been described. In one study, several patients who had clinical evidence of late Lyme disease but who were seronegative for Lyme disease had positive T-cell proliferation assays; the overall sensitivity was 45% and the specificity was 95%.⁶³ The role of these assays in the overall approach to the diagnosis has not yet been defined, and they should not be routinely ordered because they remain very expensive and poorly standardized.⁵²

Additional Follow-up

The patient's Lyme Western blot IgG is positive (10 bands present), and IgM is negative. Synovial fluid is evaluated for *B. burgdorferi* PCR and is positive. The patient requires intraoperative arthroscopy and washout of the involved joint space. He remains hospitalized on intravenous ceftriaxone for 7 days. The patient's girlfriend, who has no symptoms and has not accompanied the patient on his trips to the summer home, is now requesting blood testing for Lyme disease.

QUESTIONS

- What is the appropriate duration of therapy for this patient?
- What are the recommended therapies for the various stages of Lyme disease?

DISCUSSION

Lyme arthritis can be successfully treated with either oral or intravenous antibiotics. Both doxycycline and amoxicillin given for a 28-day treatment course are

Table 1. Recommended Treatment for Lyme Disease by Stage in Adults

Stage	First-Line Therapies	Alternative Therapies	Comments
Erythema migrans (early localized)	Doxycycline 100 mg po bid 14–21 days or amoxicillin 500 mg po tid 14–21 days	Cefuroxime axetil 500 mg po bid 21 days or clarithromycin 500 mg po bid 14–21 days	Doxycycline preferred if concerned about concomitant ehrlichiosis
Early disseminated			
Carditis	Ceftriaxone 2 g IV daily or cefotaxime 2 g IV q8h or penicillin 3–4 million units q4h (all regimens for 14–21 days)	Doxycycline 100 mg po bid or amoxicillin 500 mg po tid (both for 21 days)	Oral regimens should only be used if first-degree block with P–R interval < 0.3 seconds is present. Can change to oral regimen once clinical response maintained.
Facial palsy	Doxycycline 100 mg po bid 21–28 days or amoxicillin 500 mg po tid 21–28 days	Ceftriaxone 2 g IV daily for 21–28 days	Lumbar puncture suggested by some experts to rule out CSF abnormality prior to giving oral regimen
Meningitis	Ceftriaxone 2 g IV daily or cefotaxime 2 g IV q8h (both for 21 days)	Penicillin 20–24 million units/d for 21 days	Should complete therapy with IV agents
Late Lyme disease			
Arthritis	Doxycycline 100 mg po bid for 28 days or amoxicillin 500 mg po tid for 28 days	Ceftriaxone 2 g IV daily for 14–28 days	IV therapy only for recurrent arthritis or oral treatment failures
Neurologic	Ceftriaxone 2 g IV daily for 21–28 days or cefotaxime 2 g IV q8h for 2–28 days	Penicillin 20–24 million units/d for 21–28 days	Treatment for longer than 28 days has not been shown to improve outcome

bid = twice daily; CSF = cerebrospinal fluid; IV = intravenous; po = by mouth; q4h = every 4 hours; q8h = every 8 hours; tid = 3 times daily.

currently accepted as appropriate regimens.⁶⁴ Ceftriaxone in a 2-g daily dose has also been effective and can be given for a total of 14 to 28 days. Large prospective studies comparing oral and intravenous regimens in the treatment of Lyme arthritis have never been done. Most experts recommend an oral regimen as first-line therapy for Lyme arthritis, reserving intravenous ceftriaxone for patients with recurrent Lyme arthritis.^{24,51,65}

Table 1 outlines the suggested regimens for treatment of the various stages of Lyme disease. In general, oral regimens are preferred except in Lyme carditis, neurologic manifestations of Lyme disease (excluding isolated facial palsy), and recurrent Lyme arthritis.⁶⁶ The use of either an oral or intravenous antibiotic for more than 1 month in the treatment of any stage of Lyme disease has never been shown to be beneficial.^{64,67} In fact, prolonged courses of antimicrobials may actually be harmful. Prolonged courses of ceftriaxone in the management of Lyme disease have been associated with biliary complications requiring cholecystectomy.⁶⁸ Patients should be counseled to expect a slow resolution of constitutional symptoms after treat-

ment has been completed and should be informed that prolonged courses of antibiotics or retreatment have not been shown to alleviate such symptoms.

QUESTION

- **How should the patient's girlfriend be counseled regarding her request for Lyme testing?**

DISCUSSION

The patient's girlfriend should not have Lyme serologies performed. As has already been discussed, serologic testing is neither sensitive nor specific enough to make a diagnosis of Lyme disease without clinical correlation. Before Lyme serologies are ordered, there should be an assessment of the patient's pretest probability of having Lyme disease. The girlfriend of this patient has not had significant exposure to the tick vector and has no signs or symptoms suggestive of Lyme disease. Thus, her pretest probability of having Lyme disease is low, and testing is not warranted. If she were to be tested and the ELISA result was reported as positive, it would almost certainly be a false-positive result.

A large decision analysis published in 1998¹⁰ revealed that the most cost-effective approach to the use of serologic tests for Lyme disease was to not test patients with low risk of infection or patients with the highest likelihood of infection. The latter group, the authors recommended, should be presumptively diagnosed and treated with antibiotics. The authors suggested that the 2-step testing approach be used in patients with intermediate likelihood of infection with *Borrelia* species. **HP**

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Adapted from Sood G, O'Donnell JA. Clinical controversies in Lyme disease. JCOM J Clin Outcomes Manage 2000;7(7):47-56.

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