When should you order a Lyme titer?

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EVIDENCE-BASED ANSWER

Lyme titers should be ordered for patients with signs or symptoms of disseminated Lyme disease, but who do not have the pathognomonic erythema migrans rash (strength of recommendation [SOR]: **C**, based on expert opinion). Symptomatic patients with erythema migrans should be treated without being tested, given the high probability of having Lyme disease.

Serologic testing within the first week following potential infection is justified only if antibiotics will be withheld and a repeat serologic study will be performed 8 to 14 days after an initial negative test (SOR: **C**, based on expert opinion).[1] Testing should be 2-tiered, including an initial highly sensitive test (enzyme-linked immunosorbent assay [ELISA]) followed by a supplemental highly specific test (Western blot) (SOR: **C**, based on expert opinion and small case-control study).[2]

CLINICAL COMMENTARY

Strict use of these rules would lead to fewer false positives but would miss atypical forms

The use of testing as described in this article is consistent with the recommendations of the CDC, academic infectious disease experts, and insurance companies. Other indications for ordering a Lyme test include the presence of oligoarthritis, cranial neuropathy (facial nerve palsy is most common), heart block, or meningitis. There is significant controversy about testing, treatment, and even defining late Lyme disease. The universe of people with positive Lyme serology who have fatigue, memory impairment, myalgias, and arthralgias far exceeds those with erythema migrans. A quick Google search reveals numerous patient support groups whose mission is to support those unfortunate people who believe they are afflicted with late Lyme disease. Strict use of these lab-ordering rules would lead to fewer false positives but also risks missing persons with forme fruste (atypical or variant forms) of this disease who may benefit from antimicrobial therapy. This is a highly controversial area of medicine and the limited evidence is conflicting. The cost of the Lyme test is not trivial, with a reflex panel (sensitive ELISA followed by specific Western blot) billed at over $250.

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Evidence summary

Many Lyme disease serologic tests are ordered inappropriately, often influenced by patient demand. In a prospective, cross-sectional survey of Wisconsin physicians, only 20% of ordered tests were appropriate. Tests were classified as inappropriate if ordered (1) for asymptomatic patients, (2) for patients with physician-diagnosed erythema migrans, (3) for patients receiving empiric antibiotic treatment, or (4) as test-of-cure.[3]

The positive predictive value of a test (the likelihood that a person who tests positive actually has the disease) depends on the prevalence of that condition. Available Lyme serology tests vary in their sensitivity and specificity. Selecting patients with signs or symptoms of disseminated Lyme disease theoretically increases the pretest probability, thus improving the positive predictive value of the test.

In a prospective study of 46 treated patients with culture-proven erythema migrans, 91% had a positive ELISA or immunoglobulin M (IgM) immunoblot result at 8 to 14 days after baseline. Peak IgM antibody levels were seen at this time

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TABLE

Pretest probability scenarios for suspected Lyme disease

CLINICAL SCENARIO	TEST?	RATIONALE
Erythema migrans	No	Pretest probability high; clinical diagnosis of Lyme disease (treat without testing)
Signs/symptoms of disseminated Lyme disease, live in endemic region	Yes	Pretest probability intermediate; high prevalence yields high PPV
Signs/symptoms of disseminated Lyme disease, live in non-endemic region	Yes	Pretest probability intermediate; cost-effective
Nonspecific myalgias	No	Pretest probability too low
Asymptomatic patient	No	Pretest probability too low
Empiric antibiotic response; treatment	No	Antibiotic treatment decreases humoral testing not cost effective
Test-of-cure	No	Test remains positive after treatment
Immunized	No	ELISA will be positive (Western blot could assess exposure)

FAST TRACK

Testing should be 2-tiered, with a highly sensitive test (ELISA) followed by a highly specific one (Western blot)

among patients with localized or disseminated disease. Detectable IgM levels appeared within a few days of onset of erythema migrans and were found in most individuals with disease of at least 2 weeks duration.[4] Another small study of 55 treated patients similarly found peak antibody response at 8 to 12 days into treatment.[5]

A recent review article recommends serologic testing for patients with a moderate pretest probability (ie, patients with objective signs of Lyme disease from a highly or moderately endemic area). Patients from highly endemic areas who present with erythema migrans have a high enough pretest probability to make the diagnosis of Lyme disease without serologic testing.[6]

Recommendations from others

The Centers for Disease Control and Prevention (CDC) defines a case of Lyme disease as physician-diagnosed erythema migrans ≥5 cm in diameter, or at least 1 objective manifestation of late Lyme disease (eg, musculoskeletal, cardiovascular, or neurologic symptoms) with laboratory confirmation of *Borrelia burgdorferi* infection using a 2-tiered assay.[7] Thus, the CDC notes that Lyme disease is a clinical diagnosis and accordingly recommends against testing patients who are asymptomatic or who have proven disease (erythema migrans).

The American College of Physicians Clinical Guidelines recommend performing serologic testing for patients with an intermediate pretest probability between 20% and 80%.[8] Low pretest probability scenarios (<20%) include patients with nonspecific symptoms of myalgia such as fatigue, stiffness, and diffuse muscle aches and tenderness. High pretest probability scenarios (>80%) include patients with erythema migrans. Intermediate pretest probability scenarios include patients with possible disseminated Lyme disease findings such as recurrent oligoarticular inflammatory arthritis (**TABLE**). Cost effectiveness analyses support this approach.[9]

Guidelines established by a joint CDC/Association of State and Territorial Public Health Laboratory Directors commission require a 2-tiered laboratory

approach to diagnosis.[2] A highly sensitive initial test (ELISA) is followed by a highly specific supplemental test (Western blot). These guidelines have good clinical applicability (overall sensitivity 50%, specificity 100%).[10] The relatively low sensitivity is likely due to antibiotic treatment of several subjects resulting in reduced humoral response.

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