When should you order a Lyme titer?

Teresa Kulie, MD, Kevin Vogt, MD
Department of Family Medicine, University of Wisconsin-Madison
Erika Sevetsen, MLS
Ebbling Library, University of Wisconsin-Madison

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). 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).

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.

E. Drew Malloy, MD
University of Arizona Campus Health Services, Tucson

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.

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. CONTINUED
**CLINICAL INQUIRIES**

### TABLE

**Pretest probability scenarios for suspected Lyme disease**

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

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 35 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
Evidence-based medicine ratings

The Journal of Family Practice uses a simplified rating system called the Strength of Recommendation Taxonomy (SORT). More detailed information can be found in the February 2003 issue, "Simplifying the language of patient care," pages 111–120.

Strength of Recommendation (SOR) ratings are given for key recommendations for readers. SORs should be based on the highest-quality evidence available.

A Recommendation based on consistent and good-quality patient-oriented evidence.
B Recommendation based on inconsistent or limited-quality patient-oriented evidence.
C Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening

Levels of evidence determine whether a study measuring patient-oriented outcomes is of good or limited quality, and whether the results are consistent or inconsistent between studies.

STUDY QUALITY
1—Good-quality, patient-oriented evidence
(eg, validated clinical decision rules, systematic reviews and meta-analyses of randomized controlled trials [RCTs] with consistent results, high-quality RCTs, or diagnostic cohort studies)
2—Lower-quality patient-oriented evidence
(eg, unvalidated clinical decision rules, lower-quality clinical trials, retrospective cohort studies, case control studies, case series)
3—Other evidence (eg, consensus guidelines, usual practice, opinion, case series for studies of diagnosis, treatment, prevention, or screening)

Consistency across studies
Consistent—Most studies found similar or at least coherent conclusions (coherence means that differences are explainable); or if high-quality and up-to-date systematic reviews or meta-analyses exist, they support the recommendation.
Inconsistent—Considerable variation among study findings and lack of coherence; or if high-quality and up-to-date systematic reviews or meta-analyses exist, they do not find consistent evidence in favor of the recommendation.

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approach to diagnosis. 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%). The relatively low sensitivity is likely due to antibiotic treatment of several subjects resulting in reduced humoral response.

REFERENCES