

JAMA Diagnostic Test Interpretation

Lyme Disease Serology

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A 10-year-old girl developed an annular skin lesion on her anterior neck. The lesion, initially attributed to a bug bite by her mother, enlarged and developed central clearing. The patient lived in North Carolina with no recent travel or known tick bite. She had no symptoms other than mild local itching. After several weeks, the patient's mother applied over-the-counter topical antifungal cream and the lesion faded. After 10 days of antifungal therapy, the patient was evaluated by her pediatrician. Examination results were normal except for a 2.0-cm annular lesion with central clearing and peripheral flaking (Figure). The pediatrician ordered serologic testing for Lyme disease, prescribed 14 days of doxycycline based on the results (Table), and referred the patient to an infectious disease specialist for evaluation.

Table. *Borrelia burgdorferi* 2-Tiered Serologic Test Results

Test Component	Patient Result	Reference Range
First tier: enzyme immunoassay using whole-cell sonicate antigen	1.03	Negative, <0.80 Equivocal, 0.80-1.19 Positive, >1.19
Second tier: immunoblots		
IgM, antibody bands	0	For patients with symptoms ≤30 d only, positive if ≥2 of 3 scored antibody bands present
IgG, antibody bands	1 (41kDa)	For all patients, positive if ≥5 of 10 scored antibody bands present

Answer

D. Discontinue doxycycline and restart topical antifungal cream.

Test Characteristics

This patient had a negative 2-tiered serologic test result for Lyme disease. The first-tier enzyme immunoassay (EIA) was equivocal but second-tier immunoblots were negative. For testing to be positive, both tiers must be positive (ie, the EIA must be positive or equivocal followed by positive IgM or IgG bands). Since the patient's lesion was inconsistent with Lyme disease and there was an alternate etiology (tinea corporis) that responded to antifungal treatment, no further testing or treatment for Lyme disease was indicated.

Approximately 3.4 million Lyme disease tests are performed annually in the United States (cost, ≈\$500 million).¹ The standard of care for Lyme disease testing is 2-tiered serology. The first-tier EIA quantifies potential antibodies against *Borrelia burgdorferi*. If the EIA is positive or equivocal, second-tier immunoblotting is performed to detect antibodies against more specific *B burgdorferi* surface proteins. The Medicare midpoint reimbursement is \$31.32 for first-tier EIA and \$28.49 for second-tier immunoblots.²

Sensitivity during early localized infection is low (<40%), while host immune response is developing but increases to 70% to 100% for patients with disseminated infection. Specificity is 98% to 100%.^{3,4} If 2-tiered serology is negative in patients with possible early

infection, repeat serology 3 to 4 weeks later may demonstrate seroconversion. Because IgM and IgG antibodies can persist for years, serology is not useful to monitor response to treatment.

Testing Guidelines and Interpretation for This Patient

Erythema migrans (EM), the characteristic skin lesion of early Lyme disease, is an expanding circular patch that usually reaches at least 5 cm in diameter (eFigure in the Supplement). Classically EM has a target-like appearance, but it can be confluent. This patient's rash was not consistent with EM since it was present for more than 6 weeks and never exceeded 5 cm. Moreover, EM initially appears at the tick bite site. It is unlikely a parent or child would have missed an engorged tick on the anterior neck for more than 1 day. Residence in a low-incidence state with a rash inconsistent with EM suggests low pretest probability.⁵ Testing in this setting is not useful and risks a false-positive result.⁶

Individually positive bands in the immunoblot are not clinically significant (eg, the 41-kDa antibody band in this patient exists in ≈ one-half of serum samples from healthy blood donors due to cross reaction with flagellar proteins from bacteria such as *Escherichia coli* and oral commensal flora).⁷ Misinterpretation can cause diagnostic errors and unnecessary antibiotic exposure.⁸

What Are Alternative Diagnostic Testing Approaches?

Patients with EM who live in or have traveled to areas endemic for Lyme disease can be diagnosed clinically without testing. For all other patients—those with atypical early disease or signs of disseminated infection—laboratory testing is necessary. Testing patients with low epidemiologic risk is generally not useful, but if pursued, clinicians must recognize the high likelihood of false positives.

WHAT WOULD YOU DO NEXT

- A.** Complete 14 days of antibiotic treatment for Lyme disease. No further testing is indicated.
- B.** Complete 14 days of antibiotic treatment for Lyme disease. Repeat Lyme disease serology in 1 month to evaluate response.
- C.** Obtain skin biopsy for *Borrelia burgdorferi* PCR.
- D.** Discontinue doxycycline and restart topical antifungal cream.



Figure. Lesion on Anterior Neck of Case Patient

Using EIA or immunoblot alone is insufficient for diagnosing Lyme disease because of reduced specificity and potential for false positives.³

Polymerase chain reaction (PCR) assay of blood has low sensitivity because of the short duration of spirochetemia. PCR of synovial fluid or skin biopsy samples may be useful in certain clinical situations if specimens are available.³

Laboratory-developed tests for Lyme disease are offered by some commercial laboratories claiming to specialize in Lyme

disease testing. These nonstandardized tests lack adequate clinical validation and FDA clearance and are not recommended.¹⁰

Patient Outcome

The patient was evaluated by an infectious disease consultant 1 week after beginning doxycycline. Based on a clinical diagnosis of tinea corporis and very low likelihood of Lyme disease, discontinuance of doxycycline and resumption of topical antifungal therapy were recommended. Four weeks later, the lesion faded and the child was well.

Clinical Bottom Line: Lyme Disease Serology

- Testing is generally not recommended for patients unlikely to have Lyme disease (inconsistent illness or lack of plausible exposure). In this setting, false-positive results are more likely than true positives.
- A lesion consistent with erythema migrans in a region known to be endemic for Lyme disease does not require diagnostic testing.
- The recommended 2-tiered serology for Lyme disease begins with an EIA. If the EIA is positive or equivocal, immunoblotting should be performed. Both a positive or equivocal EIA and sufficient number of immunoblot bands (≥ 2 of 3 IgM or ≥ 5 of 10 IgG) are required for a positive test.
- Clinicians interpreting test results should not focus on individual positive bands as these have no diagnostic value on their own.
- Patients with Lyme disease symptoms (>30 d) require positive IgG immunoblot results to confirm diagnosis.
- Nonstandard tests for Lyme disease and alternative immunoblot interpretations offered by some specialty laboratories lack clinical validation and are not recommended.

ARTICLE INFORMATION

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