EDITORIAL COMMENTARY

Laboratory Testing for Lyme Disease: Time for a Change?

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(See the article by Steere et al. on pages 188–95)

Laboratory testing for Lyme disease by the measurement of antibodies to Borrelia antigens using ELISA and Western immunoblot in a 2-tier fashion remains essential to diagnosing this disease [1, 2]. However, this diagnostic methodology is not always necessary, sufficient, properly used, or properly interpreted.

An erythema migrans (EM) rash is recognized in 80% of patients with early Lyme disease [3]. As Steere et al. [4] have confirmed in the prospective clinical-laboratory study reported in this issue of Clinical Infectious Diseases, the frequency of a test result positive for Lyme disease remains very low among patients with EM alone (17%), although it increases to ~50% in the convalescent phase, after antibiotic therapy. However, this anemic diagnostic sensitivity for patients with early Lyme disease who have isolated EM is less important than the sensitivity of the test for patients with other clinical features associated with Lyme disease, because the presence or history of an expanding EM rash is often sufficiently characteristic to make laboratory testing unnecessary for therapeutic decision-making [5]. On the other hand, patients with prolonged exposure to Borrelia burgdorferi who exhibit extracutaneous clinical features have positive IgG immunoblot results, which have high specificity and a strong positive predictive value for Lyme disease [6, 7]. However, even a positive immunoblot result is insufficient to diagnose current infection in the absence of current symptoms that are consistent with active Lyme disease, because test positivity may reflect prior infection due to Borrelia species or asymptomatic seroconversion [8–10]. In the study by Steere et al. [4], 11 (79%) of 14 patients with prior Lyme disease had a positive result on 2-tier testing.

The 2-tier serological test performs optimally for patients with clinical symptoms that are compatible with disseminated or late Lyme disease manifestations; in such patients, the sensitivity and positive predictive value of a positive IgG immunoblot result are very high [11]. In the study by Steere et al. [4], >90% of patients with disseminated Lyme disease and 100% of patients with late Lyme disease had a positive 2-tier test result. Despite the confirmation of the value of this diagnostic methodology in the appropriate clinical setting, it is used inappropriately >25% of the time [12]. Even more important is the misinterpretation of test results. This relates both to the technical peculiarities of the immunoblot test in general and to the interpretation of a positive IgM immunoblot result for Lyme disease in particular. Immunoblots are only semiquantitative, and faint bands are commonly observed and subjectively interpreted. This may result in interlaboratory variability and was a consideration in the recommendation not to use immunoblotting as a single-tier test. IgM immunoblot results are particularly subject to errors in interpretation because of false-positive results for patients who have symptoms that are likely to invoke Lyme disease testing [7, 13–16]. This partly reflects the lesser stringent criteria for a positive test result, compared with the criteria for a positive IgG immunoblot result (IgM immunoblot requires only 2 of 3 positive bands), and it is the major reason for the recommendation that the appropriate use of IgM immunoblotting is for individuals who have exhibited symptoms for <4 weeks, for whom the true-positive rate is greater than the false-positive rate [1].

This dilemma of misuse and misinterpretation of Lyme disease tests has persisted for over a decade, despite numerous scholarly articles reemphasizing the appropriate application of 2-tier testing [2, 3, 5]. The study by Steere et al. [4] provides an alternative that warrants further study in the population at large. Measurement by ELISA of IgG antibodies to the variable major protein-like sequence, expressed, (commonly abbreviated VlsE) antigen of B. burgdorferi or its sixth invariant region peptide (C6 peptide ELISA) has been pre-
viously shown to compare well with 2-tier testing for the diagnosis of Lyme disease [17–19]. In the study by Steere et al. [4], the C6 peptide ELISA performed as well as—and, in some cases, better than—2-tier testing. The C6 peptide ELISA had positive results more frequently than did IgG immunoblots among patients with EM who had acute-phase and convalescent-phase disseminated disease (38% vs. 15% and 63% vs. 20%, respectively) and among patients with late Lyme disease (100% vs. 85%). These differences were not apparent when positive IgM immunoblot results were also included, and there were no statistically significant differences between the 2 test systems [4].

The excellent results for both testing methods have been obtained in a highly controlled research laboratory with many years of experience in Lyme disease testing and interpretation. Consequently, the performance of 2-tier testing in this study does not necessarily reflect the general clinical experience with frequent Lyme disease testing using commercial laboratories in both appropriate and inappropriate clinical situations. Alternatively, the C6 peptide ELISA as a single, primary test for Lyme disease would have the advantage of providing an objective, quantitative measurement that could be standardized within and between laboratories. Furthermore, this study and others support the overall equivalent performance of C6 peptide ELISA and 2-tier testing in all stages of Lyme disease [4, 18, 19]. Steere et al. [4] expressed concern regarding the possible lower specificity of the C6 peptide ELISA, based on 1 false-positive result (2%) in a healthy subject from an area in which Lyme disease was not endemic. However, it seems likely that the C6 peptide ELISA would have negative results in the numerous instances in which false-positive IgM immunoblot results are seen in clinical practice. Thus, the results of this study [4] should stimulate the research community involved in Lyme disease testing to further research this question. If the commercial C6 peptide ELISA is shown to outperform 2-tier testing as it is currently used in clinical practice, its adoption as the primary diagnostic test for Lyme disease will eliminate one of the major causes of the misdiagnosis of Lyme disease.

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References