Preliminary Falsification of EIA Screening Is Cost-Effective in the Two-Step Serodiagnosis of Lyme Disease

To the Editor—We read with great interest the article by Trevejo et al. [1] that described a simplified procedure for the laboratory diagnosis of Lyme disease (LD). The authors assumed as “certain” the clinical diagnosis of LD and on this basis calculated the sensitivity of 3 different diagnostic approaches. We suggest that there is some bias in the assumption that 25 EIA-positive serum samples plus 2 more Western immunoblot (WB)-confirmed samples, among equivocal results, sum up to a sensitivity of 41%, by the authors’ simplified method, in the early phase of LD. Similarly, the assumption was made that 39 EIA-positive sera, with no WB confirmation of equivocal results, give a sensitivity of 71% in the convalescent phase. The authors ignore that 6 (22%) of 27 and 23 (59%) of 39 EIA-positive results were disproved by WB. We cannot understand what scientific reasoning allows the omission of the WB-unconfirmed, EIA-equivocal results and the inclusion of WB-unconfirmed but EIA-positive cases.

As far as we know, the “etiologic certainty” of a given infection can be determined only by the isolation of a causative organism, which is difficult to do for LD. At present, the best available parameter of relative certainty seems to be WB confirmation, on the basis of which the sensitivity of other diagnostic approaches should be calculated. It is possible, of course, for the scientific community to decide that a physician-diagnosed erythema migrans rash ≈5 cm is the most sensitive determination of early LD. If so, a further simplified and cost-effective approach would be not to do any EIA screening.

The discrepancies between the screening tests and WB confirmation indicate that in the serodiagnosis of LD a major problem is specificity, since some unrelated disease conditions other than spirochetes and flagellated bacterial infections interfere with the results [2]. This is of great concern for the diagnosis of patients with symptoms compatible with late LD who live in geographic areas in which LD is not known to be endemic. We were very surprised that Trevejo et al. [1] reported an EIA-screening specificity of 97%, which we believe was likely due to use of a small control group.

In a setting of unknown endemicity for LD, we carried out a large case-control study with subgroups including healthy and sick subjects. Tests with the same commercial polyvalent EIA (Vidas; BioMérieux Vetik, Hazelwood, MO) used by Trevejo et al. [1] resulted in negative findings for 167 (88%) of 189 subjects. Only 2 (9%) of 22 positive or equivocal EIA were confirmed by Western blot. Major sources of interference included acute phase and asymptomatic infectious mononucleosis (specificity, 78%) and polyclonal hypergammaglobulinemia (specificity, 87.5%) [3]. Recently, in various acute infections of viral or bacterial etiology, we found a specificity of 78%. When we included the results for our case patients, 21 serum samples were unequivocally WB negative whereas 40 were either EIA positive (19 samples) or EIA equivocal (21 samples) (EIA vs. WB specificity, 47.5%). In the series presented by Trevejo et al. [1], the specificity of EIA versus WB was 75% in the early LD serum specimens but only 37% in the convalescent samples. In our experience, 22.5% of positive/equivocal EIA results were due to Epstein-Barr virus (EBV) viral capsid antigen (VCA) IgM interference. Thus, in view of the low (or perhaps absent) endemicity in our setting, we decided to routinely falsify positive/equivocal EIA tests with EBV VCA IgM, to reduce the waste of resources. Immunoblot confirmation was done only on specimens for which falsification failed. If the suspicion of LD is high, we suggest that WB should be postponed until the interfering factor is cleared, if this is possible; if it is not, an immunoblot, however performed, can be interpreted with the knowledge that an interfering factor is present. When possible, polymerase chain reaction using biologic fluids could provide a further interpretative key [4].

In our country the cost per specimen of the approach recommended by the Centers for Disease Control and Prevention, calculated for reagents only, is $84.70; the cost per specimen of the falsification approach is $9.12. Until better-standardized and less cross-reactive reagents are marketed [5, 6], the falsification approach (by EBV IgM in our study but perhaps by other approaches in different settings) allows cost savings and, most importantly, avoids laborious immunoblots—the results of which often cannot be interpreted—and, at least in part, misdiagnosis of LD.

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