Reviewer's report

Title: Utilization of serology for the diagnosis of suspected Lyme borreliosis in Denmark: Prospective survey of patients seen in general practice

Version: 1 Date: 22 February 2010

Reviewer: Mary Petzke

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Early diagnosis of Lyme disease is mainly based on clinical manifestations including a characteristic skin lesion, erythema migrans (EM), which is present at the site of the tick bite in up to 80% of patients. Unlike most bacterial diseases that can be diagnosed by direct microscopic observation, cultivation or PCR, clinical diagnosis of Lyme disease is supported by serological assays, primarily ELISA and Western immunoblot. However, these assays suffer from a number of limitations, including inter- and intra-laboratory variability, subjective interpretation and lack of both high sensitivity and specificity. The flagellin-based ELISA assay used for serodiagnosis in the present study has a false positive rate of 2% (98% specificity). In areas highly endemic for Lyme disease, the false positive rate is compensated for by the high incidence of Lyme borreliosis cases. However, in areas in which the incidence of Lyme disease approaches the limit of sensitivity of the test (low pretest probability), the demand for serological testing can lead to incorrect diagnosis and unnecessary treatment. In this study by Dessau et al, the authors assessed the utility of serological testing for Lyme disease in three counties of Denmark, where the background seropositivity is 1.6%. Serological testing was performed by three laboratories using the same commercial ELISA assay. The results (IgM and IgG titers) from 2,647 patients, performed over one year, were compared with both the presence of clinical indicators of Lyme disease and the decision to treat. Rigorous statistical and experimental methods were employed. The authors determined that age (0-15 years) and suspected EM, or suspected acrodermatitis, were significant predictors of IgM or IgG seropositivity, respectively. Due to the low pretest probability, serological testing was not recommended for the diagnosis of Lyme arthritis. This study concluded that EM is a distinct clinical entity and an indicator for treatment, without the need for laboratory testing. While the authors were careful to note that the results of this study may not be extrapolated to areas where the epidemiology of Lyme disease and diagnostic methods may differ, they concluded that the use of serological testing is of limited utility in certain patient groups and in areas with low rates of pretest probability.

Only a few minor modifications to this excellent and well-written manuscript are suggested:

Discretionary Revisions:
1. Page 9, paragraph 2, sentence 7; Page 9 paragraph 3, first sentence: both
sentences should be rewritten for clarity.

Minor Essential Revisions:
1. In Table 1, footnotes should be added to explain the following:
   a) items in bold font
   b) the reference population used for determination of the odds ratio in the lower half of the table

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.