Reviewer's report

**Title:** Probable Late Lyme disease: An atypical manifestation of untreated Borrelia burgdorferi infection.

**Version:** 1  **Date:** 8 October 2011

**Reviewer:** Brian Fallon

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Comments to the Authors

The authors have conducted a retrospective case review of patients with “probable late Lyme Disease”. This review was prompted by the newly defined category of ‘probable’ Lyme disease which is now part of the epidemiologic surveillance criteria in the United States. This is a valuable contribution to the literature as the clinical profile of these patients is uncertain and they may represent a neglected group of patients who may benefit from antibiotic therapy. This article is well-written and methodologically sound. Specific comments to the authors follow:

1. The authors provide a helpful discussion regarding the definitional differences among post-treatment Lyme syndrome, late Lyme disease, and probable late Lyme disease.

2. As noted in the article, patients who present with “subjective symptoms” of widespread musculoskeletal pain, fatigue, and/or cognitive dysfunction warrant serologic testing for Lyme disease as otherwise these patients would not be recognized as having “probable” Lyme disease and they also would then not receive the possible benefit of a course of antibiotic therapy.

3. Page 5, bottom, Methods. Were all patients in this consecutive series referred for the evaluation or consideration of Lyme disease? If so, this needs to be stated clearly at the start of the methods section.

4. Page 6 and 7 list different categories for patients as defined by Feder et al. There is no category in this list however for those who met criteria for probable late Lyme disease and who got treated but who then over the course of the next 6 months relapsed. It might be helpful in the discussion for the authors to opine as to whether this group should be considered as a PLDS subtype?

5. Category d on page 7 is unclear. How is the group stated in the second line of category d different from the group in the first line. The authors state this group is less stringently defined – this is not clear.

6. End of page 7 – is Azithromycin included here because it was only a 5 day course? In that case, it’s not that the antibiotic is not recommended but rather that the duration is insufficient.

7. Do the authors have any comment about the fact that 7 patients with persistent symptoms and well-defined prior disease were excluded from the PLDS category
cause onset duration was more than 6 months out. Do they suggest any changes in the PLDS definition? What was the range of onset for these patients?

8 Top of page 9. It is surprising that only 3% of PLDS patients recall an EM rash? Or, is it that more had it objectively documented but these wouldn’t be considered here. If so, then the groups differ partly based on definition.

9. Page 9. The authors state that 83% of the 12 treated patients had some improvement. What does ‘some’ mean? IS that consistent with “clinically meaningful”? How many of these patients were treated by one of the authors? If most were treated by the authors, then it wouldn’t be just to conclude in the discussion that this “demonstrates current community practice” More detail would be helpful.

10. Page 9. Rather than say “borderline significantly different”, it is preferred to say at “a trend level”.

11. Table 1 would be enhanced if info from the other Lyme groups could be included for comparison with the probable LD group.

12. page 11. “By definition,...”. This sentence states that Probably late Lyme disease is not defined by laboratory findings – that must be a typo as isn’t a positive IgG WB part of the definition?

Also, a positive IgG WB doesn’t necessarily mean a person has late, untreated infection. This could merely be a sign of a good immune response against the initial infection that is now no longer present. This needs to be corrected on page 12.

13. The discussion on page 14 about pre-test probability and the importance of testing for suspected LD in the absence of objective symptoms is quite important.

14. What other variables or clinical assessments might the authors suggest to compare the different groups for future studies?

15. The Conclusion is stated twice. Please correct.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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

Declaration of competing interests:

I have no competing interests.