Author’s response to reviews

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

Authors:

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Version: 2 Date: 10 January 2012

Author’s response to reviews:

Dear Miss Pangilinan: Thank you for the opportunity to revise our manuscript, MS: 2079895125620863, Probable Late Lyme disease: An atypical manifestation of untreated Borrelia burgdorferi infection. We have change the terminology of Post Lyme disease Syndrome to Post-Treatment Lyme Disease Syndrome (PTLDS) in concordance with the currently terminology used by the CDC. To respond to our reviewers’ requests for more information on our patients, we have added a new table 2 to show more details of the Probable late Lyme patients treatment history and outcomes. In addition, the original table 1 has been expanded to show comparison of symptoms across all groups. We also have added a photo of a patient rash to illustrate the difficulty with diagnosis of early Lyme disease with the progression to probable late Lyme disease in one of our reported patients.

We have also made the following specific changes in response to the helpful comments of the reviewers.

Version: 1 Date: 8 October 2011
Reviewer: Brian Fallon
Reviewer’s report:

1. The authors provide a helpful discussion regarding the definitional differences among post-treatment Lyme syndrome, late Lyme disease, and probable late Lyme disease. No response required
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. No response required
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. The methods section of the manuscript has been changed to reflect the fact that the patients were referred for evaluation of Lyme disease.

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? We have added a point in the discussion about what % of patients have recurrent symptoms after antibiotic treatment and how they may then be considered to have PLDS.

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. We have clarified in the manuscript that these less stringently defined patients would be excluded from the IDSA guideline definition because of pre-existing conditions or because of falling outside of the window of symptom onset.

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. We agree and have changed the manuscript to reflect that.

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? We have added the mean duration of onset for these patients into the results section.

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. We have clarified that the percentages refer to those instances where the patient identified a rash but there was no resulting physician diagnosis of EM. In patients with PLDS the majority of patients did receive a physician diagnosis of EM in addition to their own recognition of the rash.

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. We have provided details in the text regarding that 66% of patients that were treated received treatment by other physicians prior to their evaluation by the author (page 14). We have provided more detail on treatment outcomes by adding a second table that focuses on the patients with probable post Lyme syndrome and there treatment history.

10. Page 9. Rather than say “borderline significantly different”, it is preferred to say at “a trend level”. The manuscript has been altered to state 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. We have expanded Table 1 to show data for the other groups.

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? Correct, we have removed laboratory from the manuscript. 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. We have expanded the text to discuss the possibility of exposure and seroconversion without the subsequent development of illness.

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. No response required

14. What other variables or clinical assessments might the authors suggest to compare the different groups for future studies? We have added to the discussion on page 15 suggestions to compare the overlap of PLDS to fibromyalgia and chronic fatigue syndrome as well as the need to find biomarkers that are sensitive to the presence of prior exposure to Lyme disease in patients with medically unexplained symptoms.

15. The Conclusion is stated twice. Please correct. Corrected

Reviewer’s report
Title: Probable Late Lyme disease: An atypical manifestation of untreated Borrelia burgdorferi infection.
Version: 1 Date: 22 September 2011
Reviewer: Raphael Stricker

Major Comments
1. The authors cite the revised CDC surveillance case definition for Lyme disease (Reference 6) with objective symptoms supported by "positive IgG
serology”. It should be noted that Reference 6 refers to "IgG immunoblot seropositivity", and this term should be used throughout the manuscript. The problem with the revised CDC case definition is that the standard commercial laboratory approach involves two-tier testing with a screening IFA or ELISA followed by a confirmatory immunoblot. Thus it is unclear how the authors obtained the IgG immunoblot positivity in their patients. Were all patients screened with IFA or ELISA? Did the screening test have to be positive for an IgG immunoblot to be run? Or was the IgG immunoblot run without a screening test, contrary to the CDC-approved commercial test method? This needs to be clarified in the Methods section. We have changed the manuscript using the preferred term IgG immunoblot throughout the manuscript. The serologies were obtained by chart review of patients medical records and were ordered in some cases by the referring physicians without utilized a 2-tier reflex testing strategy. We have clarified the methods section to reflect that we accepted the results of IgG immunoblots whether or not a IFA or ELISA was done.

2. Assuming that screening tests were run, patients had commercial Lyme testing by "laboratories utilizing CDC interpretive criteria". It is important to note that the CDC-sanctioned two-tier test algorithm has a sensitivity of 46% or less in the USA (Stricker & Johnson, Minerva Med 2010;101:419-25, Table 1) and Europe (Ang et al, Eur J Clin Microbiol Infect Dis 2011;30:1027–32, Table 4). Thus the testing used in this study probably missed more than half the patients with Lyme disease. This should be stated somewhere in the Discussion. We have added a discussion point regarding the insensitivity of early serology and its impact on disease misclassification.

3. The gender distribution in the five diagnostic categories is intriguing. As shown in Figure 2 and discussed in the manuscript, a male predominance was seen in the "Lyme groups", while a female predominance was seen in the "non-Lyme" and "indeterminate" groups. This distribution is consistent with the observation that commercial Lyme testing discriminates against women, who are less likely to achieve the level of reactivity required for CDC surveillance positivity on the commercial Lyme immunoblot (Schwarzwalder et al, Gend Med. 2010;7:320–329; Stricker & Johnson, J Womens Health 2009;18:1717-18). This test bias may skew the results of the study, which might have been quite different if "gender neutral" testing was used (Engstrom et al, J Clin Microbiol 1995;33:419-27; Ma et al, J Clin Microbiol 1992;30:370-6). We have added a discussion point regarding the sex based differences in test performance and the impact on disease classification.
4. The age distribution of patients is also of interest. The age of patients in the male-dominated "Lyme groups" appeared to be significantly higher than in the larger female-dominated "indeterminate" group (median 51 vs 42 years old). However, the median age in the "indeterminate" group matches the mean age reported in predominantly female patients with chronic neurologic Lyme disease (Stricker et al, Minerva Med 2010:101:1-7; Stricker et al, Int J Gen Med 2011;4:639-46). Thus there may be a larger group of younger, predominantly female Lyme patients who are not recognized by the diagnostically inappropriate CDC surveillance criteria and insensitive commercial Lyme testing. It follows that the 6% of patients who fall into the "probable late Lyme disease" category may be dwarfed by the missed cases of Lyme disease in the "indeterminate by CDC criteria" category. We agree although we feel that discussion of this point is beyond the scope of this paper.

5. The authors failed to report other Lyme-related information such as IgM immunoblot seropositivity and the results of coinfection testing. Positive IgM immunoblot results have been noted in patients with late Lyme disease (Porwancher et al, Clin Vaccine Immunol 2011;18:851-9, Table 3), and this testing would be helpful to confirm the etiology of "probable late Lyme disease" cases. Likewise the detection of other tickborne agents such as Babesia, Anaplasma, Ehrlichia, Bartonella and Rickettsia would support the presence of Lyme disease in these patients. We agree that a positive IgM can be found in patients with late Lyme disease. However, in the current schema, a positive IgM immunoblot by itself without a corresponding (+) IgG immunoblot is also seen in PLDS and in patients who may have had Lyme disease but do not meet any case definitions as so end up defined as medically unexplained symptoms. Because of this we have chosen not to focus on the additional complexity of what information is added by the IgM immunoblot. We have included a statement in the discussion that data on co-infections were not generally available for this retrospective cohort and were not able to be reported.

Minor Comments

1. The Conclusion is duplicated at the end of the Discussion section and should be deleted in that section. Done

2. Table 1: Male sex The table has been change to reflect this

Thank you for your consideration,
John Aucott, MD