Reviewer's report

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

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Reviewer: Raphael Stricker

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Re-review
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Probable Late Lyme disease: An atypical manifestation of untreated Borrelia burgdorferi infection.
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BMC Infectious Diseases

General Comments
The authors have not adequately responded to the reviewer comments and concerns. For starters, in the absence of Track Changes it would be helpful if the authors would state where exactly in the manuscript they have addressed specific concerns, ie "we have addressed this issue in the Discussion on page so-and-so". This would make it easier to assess the revisions that have been made, which appear to be minimal.

In re-reading this manuscript, I am reminded of the man who is cleaning the windows of his house while an elephant is knocking it down. The windows are the 12 patients who fit the new CDC surveillance case definition for "probable Lyme disease". The elephant is the 163 patients with SOD (some other disease but never never not ever Lyme disease) who are misclassified and ignored in this study. First, the authors do not state what the 35 patients with "other diagnosis" actually have, although they hint that it may be fibromyalgia or chronic fatigue syndrome, two "garbage can" diagnoses that describe symptoms that are extremely common in Lyme disease. Second, the 128 younger predominantly female patients with "medically unexplained symptoms" should really be the focus of this article. These are patients with negative commercial Lyme testing who do not fit the CDC surveillance case definition that misses up to 90% of Lyme cases, as stated in the Introduction on page 4. Saying that discussion of these issues is "beyond the scope" of this article (author response to Point 4) is basically saying that Lyme disease is beyond the scope of this article, which it is.

What is missing here is a clear statement by the authors of the very limited scope of their work (analyzing 12 out of 175 potential and probable undiagnosed Lyme patients) due to the continued abuse of the CDC surveillance case definition as a diagnostic tool for Lyme disease. The CDC continues to say that the surveillance
case definition is not appropriate for diagnosis of Lyme disease (http://www.cdc.gov/osels/ph_surveillance/nndss/casedef/lyme_disease_current.htm). What then is the significance of this article? It shows that there may be a few patients who fit some modified version of the CDC surveillance case definition. Perhaps more importantly, it shows that the CDC surveillance case definition is not clinically useful to diagnose Lyme disease and should be abandoned in favor of clinical judgment and better testing.

Other problems abound. In the Title, it is inaccurate to say that "probable late Lyme disease" is an "atypical" manifestation of untreated Bb infection because (1) it represents 36% of patients with confirmed or probable late Lyme disease, as noted in the Discussion on page 12, and (2) the word "atypical" connotes "rare", which it may not be. It may be appropriate to say it is a "variant manifestation of untreated Bb infection", but that's about it.

On page 3, the authors state that up to 16% of Lyme patients do not present with a rash. This number is more like 50% when taken from non-CDC sources (Donta, Clin Infect Dis. 1997;25(Suppl 1):S52-6; Kudish et al, Del Med J. 2007;79:51-8; Clarissou et al, Med Mal Infect. 2009;39:108-15). Even the CDC puts the rash incidence at about 70% in their circular assessment (ie, rash used to diagnose LD, mainly patients with rash get LD diagnosis, most LD patients have rash).

In the Discussion on page 14, the authors repeat the misconception that the pathophysiology of "antibiotic-refractory" late Lyme disease is due to an autoimmune response in the absence of ongoing infection. This misconception is now particularly untenable in light of the recent monkey study showing persistent Bb infection despite antibiotic therapy (Embers et al, PLoS ONE 2012;7: e29914). Basing any statement regarding pathophysiology on the 12 patients that are the focus of this article is inappropriate. Nevertheless it is of interest that 9/12 patients with follow-up improved with further antibiotic therapy. This suggests that longer treatment may be useful in these patients, as suggested in a recent study (Stricker et al, Int J Gen Med. 2011;4:639-46).

Figure 4 would be a good starting point to rewrite this manuscript. It shows how bad the CDC Western blot IgG criteria really are. Perhaps when a useful culture technique becomes available, the results of this study could be re-evaluated in light of a "gold standard" for Lyme disease diagnosis. Until then, the category of probable Lyme disease remains a marginal clinical entity with limited diagnostic utility for the vast majority of Lyme disease patients.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**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