LETTER

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Potential Benefits of Retreatment Highlight the Need for Additional Lyme Disease Research

To the Editor:

We are responding to Klempner et al[1] regarding our statistical review of the National Institutes of Health–sponsored antibiotic retreatment trials for Lyme disease.[1,2] Our primary finding is that the trials did not prove retreatment is ineffective.[2] A basic concept in statistical science regarding randomized controlled trials is that one can only conclude treatment is ineffective when the treatment effect and confidence interval exclude and are below the minimum clinically important difference. None of the trials showed this. Two trials actually demonstrated evidence of improvement in patients with severe symptoms at baseline. The trials without significant findings did not incorporate interactions between treatment and baseline severity in their statistical analysis. The only valid conclusion is that treatment *may* be beneficial, which is the conclusion we drew.

Our review used a common definition of minimum clinically important difference—the smallest difference that patients perceive as beneficial and that would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management. The published minimum clinically important difference literature for the Short Form-36 Health Survey is robust, including anchor-based physical and mental component score estimates relevant to our study population, and studies by a coauthor of the trials by Klempner et al.[1,3-5] These published minimum clinically important difference estimates, calculated *apart* from risks, are intended for use in clinical trials. Minimum clinically important difference estimates for the trial by Krupp et al[6] also were examined. Although research on minimum clinically important difference estimates for the Fatigue Severity Scale (FSS-11) and Alphabet Arithmetic (A-A) test is limited, the few studies estimating the Fatigue Severity Scale 11 minimum clinically important difference supported Krupp et al's fatigue effect size choice (references available on request). We are unaware of literature supportive of tripling the observed placebo effect for a minimum clinically important difference.

Our objective was to evaluate biostatistical elements of the randomized controlled trials; we purposefully omitted risk–benefit analyses as attempted by Klempner et al.[1] Such analyses are performed after all data are collected and results are validated, are subjective, and deserve their own careful and transparent analysis.

Contrary to the authors' suggestion, no support exists for a placebo effect in the trials. Because similar proportions of patients taking placebo worsened and improved in the trials by Klempner et al,[1] it is impossible to disentangle placebo effects from natural variability. Significant changes in placebo arms simply may be due to practice effects or desire to please the study team. Defensible estimates of placebo effects compare randomized, blinded placebo groups with unblinded control groups (references available on request).

Our careful statistical analysis of the antibiotic retreatment trials demonstrates a lack of scientific support for claims that retreatment was ineffective. Furthermore, we identified groups that clearly benefitted from retreatment. Given the heterogeneous patient population, the limited number of trials, and the need for safer, less costly regimens, we not only stand by our conclusions, but also renew our call for additional research. That is, after all, how science is supposed to work.

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References

1. Klempner MS, Baker PJ, Shapiro ED, et al. Treatment trials for post-Lyme disease symptoms revisited. *Am J Med*. 2013;126:665-669.
2. Delong AK, Blossom B, Maloney EL, Phillips SE. Antibiotic retreatment of Lyme disease in patients with persistent symptoms: a biostatistical review of randomized, placebo-controlled, clinical trials. *Contemp Clin Trials*. 2012;33:1132-1142.

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3. Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med*. 2001;345:85-92.
4. Kosinski M, Zhao SZ, Dedhiya S, et al. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. *Arthritis Rheum*. 2000;43:1478-1487.
5. Coteur G, Feagan B, Keininger DL, Kosinski M. Evaluation of the meaningfulness of health-related quality of life improvements as assessed by the SF-36 and the EQ-5D VAS in patients with active Crohn's disease. *Aliment Pharmacol Ther*. 2009;29:1032-1041.
6. Krupp LB, Hyman LG, Grimson R, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. *Neurology*. 2003;60:1923-1930.