REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Treatment Trials for Post-Lyme Disease Symptoms Revisited

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ABSTRACT

The authors of 4 National Institutes of Health–sponsored antibiotic treatment trials of patients with persistent unexplained symptoms despite previous antibiotic treatment of Lyme disease determined that retreatment provides little if any benefit and carries significant risk. Two groups recently provided an independent reassessment of these trials and concluded that prolonged courses of antibiotics are likely to be helpful. We have carefully considered the points raised by these groups, along with our own critical review of the treatment trials. On the basis of this analysis, the conclusion that there is a meaningful clinical benefit to be gained from retreatment of such patients with parenteral antibiotic therapy cannot be justified.
 • *The American Journal of Medicine (2013) 126, 665-669*

KEYWORDS: *Borrelia burgdorferi*; Clinical trials; Lyme disease; Post-Lyme disease syndrome

The authors of 4 National Institutes of Health–sponsored antibiotic treatment trials of patients with persistent unexplained symptoms despite previous antibiotic treatment of Lyme disease determined that retreatment provides little—if any—benefit and carries significant risk.[1-4] In an analysis of these studies, Delong et al[5] concluded that retreatment can be beneficial and that the study findings are consistent with continued infection, which is in contrast to the conclusions drawn by the authors of these 4 treatment trials. Although Delong et al[5] present their analyses as a rigorous, independent evaluation of the results of the reported clinical trials, they are based on questionable assumptions, and the authors fail to disclose their support of long-term treatment with antibiotics and alternative treatments for Lyme disease.[6]

Fallon et al[7] also have provided their own "reappraisal" of these studies, including the study for which Dr Fallon was the lead investigator.[4] Fallon et al's[7] interpretation of these

Funding: None.

Conflict of Interest: MSK has received research grants from the Centers for Disease Control and Prevention and the National Institutes of Health. PJB has no conflicts of interest. EDS is a board member of the American Lyme Disease Foundation, for which no compensation is received, and has received compensation from UpToDate for reviewing medical records for the Metropolitan Life Insurance Company and for providing medicolegal testimony. AM is co-inventor on a patent application for a test for the detection of anti-*Borrelia burgdorferi* antibodies in which one of the antigens is based on the IR6 peptide: VOVO LIPS test for Lyme disease US Provisional Application No. 61/312,520 filed March 10, 2010 (HHS Reference No. E-036-2010/0-US-01). No money has been paid to her or to her institution. She is supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, and National Institutes of Health (NIH). RJD has received research grants from the NIH; is part owner of and has stock in Biopeptides Corp, no product of which is referred to in this article; has received payment for providing expert testimony in malpractice cases; and holds patents on vaccine and diagnostic technology with SUNY at Stony Brook and Biopeptides Corp. JJH has served as an expert witness in several medicolegal cases concerning Lyme disease and has equity in Abbott Laboratories, Bristol-Myers Squibb, Johnson & Johnson, and Merck; no products from these companies are referred to in this article. GPW has received research grants from the Centers for Disease Control and Prevention, the NIH, Immunetics, Inc, BioRad, DiaSorin, Inc, and bioMérieux, Inc; holds equity in Abbott Laboratories; is an expert witness in malpractice cases involving Lyme disease; is an unpaid board member of the American Lyme Disease Foundation; was an expert witness regarding Lyme disease in a disciplinary action for the Missouri Board of Registration for the Healing Arts; and is a consultant to Baxter for Lyme vaccine development.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2013.02.014

studies is that intravenous ceftriaxone is moderately efficacious for chronic fatigue after treatment for Lyme disease and that such therapy might be prescribed after a careful discussion with the patient of the risks involved. In what follows, we address the issues raised by Delong et al[5] and Fallon et al[7] and provide additional commentary on the treatment trials of patients with Lyme disease with persistent symptoms.

Delong et al[5] state that post-treatment symptoms of Lyme disease are of the same severity as those of multiple sclerosis or congestive heart failure, based on the severity of the symptoms of some patients in the trials.[1-4] Although their statement may be true for the study patients, the design of these studies specifically required enrollment of only the subsets of post-treatment patients with functionally disabling symptoms. Thus, the patient populations in the studies purposely comprised only individuals with severe symptoms rather than with the full spectrum of post-Lyme disease symptoms. In prospective studies of patients with well-documented Lyme disease, functionality has rarely been affected by the presence of subjective symptoms.[8,9] Rather, it seems that the majority of patients with symptoms of this level of severity have an unconvincing history of having had Lyme disease.[10-12] The lack of credible evidence for Lyme disease is one of the reasons that recruitment of subjects was so difficult in all of the trials (**Table 1**).[1-4] Indeed, of the 5457 individuals screened for the trials, only 221 (4.0%) were randomized, with recruitment periods varying from 2.6 to 4.3 years. At least 40% were excluded because of lack of documentation of previous Lyme disease (**Table 1**).

Delong et al[5] claim that the criteria used to judge clinical improvement were "unrealistic" in the trials by Klempner et al[1] and that, in accordance with clinical trials on noninfectious chronic conditions such as rheumatoid arthritis, the studies should have been powered to detect a smaller effect of treatment. Delong et al[5] seem to have a fundamental misunderstanding of the effects of antibiotic therapy in active infections (acute, subacute, or chronic), which are far from subtle. The concept of a minimal clinically important difference has been defined as the smallest difference in treatment effect that patients perceive as beneficial, given the side effects, costs, and inconveniences. This concept, although appealing, also is subjective; how to define the minimal clinically important difference for a particular disease and intervention is often not straightforward. In addition, focusing exclusively on a global assessment scale value without consideration of the potential drawbacks of the treatment modality, including, but not limited to, economic costs and adverse events, is ill advised. The risk/benefit ratio of an intervention should be an important, if not essential, factor in determining the minimal clinically important difference. The trials by Klempner et al[1] and Krupp et al[3] (which had similar durations of the intravenous treatment with ceftriaxone) had a 1.6% and 7.3% incidence of life-threatening complications, respectively. The number of life-threatening complications in a similar trial with 800 individuals (as suggested by Delong et al[5] to be able to detect a difference of 2 points in the Short Form-36 physical component summary) could range from 13 to 58. The frequency of severe adverse events was larger in the study by Fallon et al[4] (26.1% for those who were randomized to receive ceftriaxone), as expected, because this trial had a longer course of intravenous therapy. In addition, there are other adverse events and costs associated with intravenous therapy that include not only the monetary costs of the intervention but also the additional time and inconvenience of intravenous treatment.

CLINICAL SIGNIFICANCE

- Some patients given recommended antibiotic therapy for Lyme disease have nonspecific symptoms, believed—but not proven—to be caused by a persistent Borrelia infection.
- Four clinical trials report that extended antibiotic therapy is of little or no benefit; however, others claim that these trials are flawed.
- The present analysis of all 4 trials reaffirms that extended antibiotic therapy provides no meaningful benefit.

Furthermore, in the studies by Klempner et al,[1] 36% of the placebo-treated patients met the purported "unrealistic" standard used to judge improvement, a value that is virtually identical to the 40% success rate for the antibiotic-treated patients. Because 32% of the antibiotic-treated group actually worsened, even if a substantially lower threshold for improvement had been used, at most only the remaining 28% of antibiotic-treated patients (who were judged to be unchanged) conceivably could have been reclassified as improved. Even with modified outcome criteria, it is highly unlikely that there could have been a sufficiently large effect in this small subgroup to have substantially changed the results. Moreover, it would be expected that a lower standard for improvement also would result in a larger number of patients with improvement in the placebo-treated group; this would further diminish any difference between the groups and make a different result extremely unlikely.

Delong et al[5] seem less focused on choosing the proper minimal clinically important difference when evaluating the trial by Krupp et al.[3] In the study by Krupp et al,[3] severe fatigue was defined as a score of $\geq$4.0 on a fatigue severity scale. Krupp et al[3] selected a 0.7-point change from the baseline score as an end point. This end point was believed to be clinically significant partly on the basis of the investigators' experience with multiple sclerosis in which the mean placebo effect was only 0.2 points. The 0.7-point change was chosen because it "represented an improvement approximately three times as large as that observed in a placebo-treated group" with multiple sclerosis.[13] However, in the study by Krupp et al[3] on post-treatment

Table 1 Recruitment Efforts in Retreatment Trials of Lyme Disease

Study	Recruitment Period	Duration of Recruitment	Screened	Reasons for Exclusion	Okay for Inclusion	Randomized	% Enrolled
Klempner et al[1]	July 24, 1997, to November 14, 2000	40 mo	1577	At least 647 for inadequate documentation of Lyme disease, 800 because of other exclusion criteria as defined in the clinical protocols†	130*	129	8.2%
Krupp et al[3]	January 1997 to July 1999	31 mo	512	Most because of the absence of documented Lyme disease	56	55	10.7%
Fallon et al[4]	January 2000 to April 2004	52 mo	3368	1316 excluded for not fulfilling criteria for Lyme disease	38	37	1.1%

*One subject dropped out of the study before randomization.

†See clinical protocols for the Klempner et al[1] study at http://www.aldf.com/pdf/Klempner_Seronegative_Clinical_Protocol.pdf and http://www.aldf.com/pdf/Klempner_Seropositive_Clinical_Protocol.pdf.

symptoms of Lyme disease study, 23% of the placebo-treated patients had a change of ≥0.7 points below their baseline fatigue severity scores at 6 months, with a mean reduction of 0.5 points in the entire placebo-treated group. At 1 month, the reduction in fatigue among placebo recipients was even greater, and the results were indistinguishable from those in the antibiotic-treated group. Thus, using Krupp et al's[3] reasoning for setting a standard for benefit, the minimal clinically important difference actually would have been higher (>1.5).

Delong et al[5] failed to mention that in the study by Krupp et al,[3] one third of the placebo recipients did not complete the study as originally designed. Of the 27 patients randomized to receive placebo, 3 withdrew before receipt of any treatment, 3 in retrospect who did not meet entry criteria for the study, and 3 developed intravenous catheter sepsis and treatment was prematurely discontinued. Losses of >20% are believed to invalidate most trials and jeopardize both intent-to-treat and on-study analyses.[14] The sensitivity analysis done by Krupp et al[3] also can be criticized because it did not exclude the 3 ineligible subjects who mistakenly were enrolled in the study.

In the study by Krupp et al,[3] 69% of the ceftriaxone-treated patients had a ≥0.7-point reduction in fatigue score at 6 months, resulting in a mean total score at this time of 4.4. Thus, the ceftriaxone-treated patients on average still had severe fatigue and met the original entry criteria. The ceftriaxone-treated patients had a 22% reduction in fatigue score from baseline, whereas the placebo group had a 9.1% reduction. In the study by Fallon et al,[4] the percentage reduction in the same fatigue severity index score among placebo recipients was even higher (15%). Thus, fatigue as measured by this scale can decline by as much as 15% among placebo recipients with post-treatment symptoms of Lyme disease.

Other evidence also indicates that Krupp et al[3] may have underestimated the placebo effect in their study. At the 6-month time point in the study by Krupp et al,[3] 68% of the placebo-treated subjects believed that they were on active therapy versus 69% of the ceftriaxone-treated patients. This observation certainly suggests the possibility of a marked placebo effect in the study population or the presence of some other factor interpreted by the patients to mean they had received an active treatment.

The clinical significance of a 22% reduction in the fatigue severity index is highly questionable. When subjects in the study by Krupp et al[3] were asked at the 6-month time point to record the intensity of their fatigue for the past 2 weeks using a visual analogue scale, the difference in scores between those who received antibiotics and those who did not was not statistically significant ($P = .08$); nor did antibiotic treatment have a significant effect on perceived health status.

Delong et al[5] also failed to mention other important issues related to the Krupp et al trial.[3] The study by Krupp et al[3] hypothesized that fatigue was due to residual *Borrelia burgdorferi* infection of the central nervous system specifically. This was so fundamental to the rationale for their study that they designated 3 co-primary end points, improvement of fatigue along with both cognitive improvement and clearance of a borrelial antigen from cerebrospinal fluid. Delong et al[5] try to discount the lack of cognitive improvement in the study by Krupp et al,[3] emphasizing that cognitive impairment was not an entry criterion; however, on entry into the study, patients clearly "showed slower mental speed than…healthy controls" using the objective metric selected for the study. There also was no impact on clearance of a borrelial antigen from cerebrospinal fluid, because the experimental assay for this antigen was positive in only a few patients before retreatment with antibiotics.

In the study by Fallon et al,[4] the baseline fatigue score was 5.2 in the ceftriaxone-treated patients, which decreased by 15% to 4.4 after 6 months. Likewise, the baseline score in the placebo group was 5.5, which decreased to 4.7 after 6 months, also by 15%. Contrary to the assertions of Delong et al,[5] on the basis of this assessment of fatigue there was no benefit from 10 weeks of intravenous ceftriaxone in the study by Fallon et al.[4] In their post hoc analysis,[4] a reduction of 0.7 points in the fatigue score was observed in 66.7% of ceftriaxone-treated patients versus 25% of placebo-treated patients. Fallon et al[4] cite a P value of .05; this is

misleading, not only because it is a post hoc analysis but also because no statistical correction was made for the multiple post hoc comparisons that were performed by the authors. The questionable value of relying on borderline *P* values throughout the article by Fallon et al[4] is well illustrated by the observation that in the assessment of joint pain between weeks 12 and 24, the placebo-treated patients improved more than the patients treated with ceftriaxone. This difference was associated with a *P* value of .052.

Delong et al[5] also failed to mention contradictions between the study by Krupp et al[3] and the study by Fallon et al.[4] In the study by Krupp et al,[3] differential improvement was most evident at 6 months but not at 1 month after entry. In contrast, in the study by Fallon et al,[4] treatment effect on cognition was most evident 2 weeks after the end of treatment, but not 3 months later. On the basis of this observation, Fallon et al[4] concluded that long-term treatment might have a real but unsustained benefit. If true, this would require that fatigue and cognitive slowing respond to treatment in opposite ways: On the one hand, long-term treatment briefly improves cognition beyond a placebo effect, but this benefit soon disappears. On the other hand, the response of fatigue to long-term treatment with ceftriaxone is initially indistinguishable from that of treatment with placebo, but at 6 months it is superior. Another contradiction between the 2 studies is that in the Krupp et al study,[4] exploratory analyses revealed a larger treatment effect for fatigue in patients with less pain, whereas in the study by Fallon et al,[4] post hoc analyses showed an interaction effect favoring ceftriaxone over placebo as a function of baseline severity of the patients' symptoms. These inconsistent results illustrate the limitations inherent in basing conclusions on post hoc analyses and on results with marginal statistical significance. This point cannot be overemphasized.

Delong at al[5] mention that the study by Fallon et al[4] found, among the secondary outcomes, that patients with worse baseline pain and physical functioning who received antibiotics were improved at week 12, and this was sustained to week 24. The validity of this post hoc analysis also is questionable, and not simply because it was post hoc. No information was provided regarding the use of analgesics and anti-inflammatory drugs by the patients in the different treatment groups. Clearly, the use of these agents can confound the assessment of these parameters.

All of the patients enrolled in the 4 retreatment studies of patients with post-treatment symptoms of Lyme disease had already been treated for Lyme disease, often with extensive courses of antibiotics (**Table 2**).[1,3,4] Thus, it is hardly surprising that neither microbiologic nor molecular evidence for residual infection was found at any site in any of the 4 trials.[1-4] The retreatment antibiotic regimens invariably included ceftriaxone, a drug that crosses the blood–brain barrier and that is commonly used to treat bacterial meningitis because of the possibility of residual borrelia in the central nervous system. Cerebrospinal fluid analysis was performed in all 4 trials but failed to show evidence of inflammation; this finding was consistent with the negative microbiologic testing and with the fact that symptoms had persisted despite prior treatment with ceftriaxone in 33% to 100% of the patients enrolled (**Table 2**).[1,3,4] Because the smallest proportion of study subjects who had been previously treated with ceftriaxone was in the Klempner et al trials,[1] it might have been predicted that their studies had the greatest chance of supporting a role for retreatment if central nervous system infection were the cause of the patients' symptoms. The Klempner et al trials[1] failed to show any benefits of retreatment despite a 12-week course of antibiotics (4 weeks of intravenous ceftriaxone followed by 8 weeks of oral doxycycline), the longest retreatment regimen that was used among the trials. Furthermore, the assumption that prior use of oral antibiotics would have been ineffective in clearing a central nervous system infection may be questionable, at least as it relates to doxycycline, which is probably the most commonly used oral antibiotic for the treatment of Lyme disease in adults. Since publication of the retreatment studies, numerous clinical trials have shown that doxycycline is highly effective for neurologic Lyme disease.[15,16]

It should be further emphasized that even if there are residual spirochetes in patients who have been treated for Lyme disease, this fact alone, although necessary, is not sufficient to justify additional antibiotic therapy. Residual organisms have to be playing a role in causing illness. A

Table 2 Antibiotics Used for Patients in Retreatment Trials of Lyme Disease

Study	Antibiotic Inclusion Criteria	Antibiotic Exclusion Criteria	Past Use of Antibiotics	Antibiotic Use in the Clinical Trial
Klempner et al[1]	Must have received a course of antibiotics for Lyme disease	Allergy; ≥60 d of parenteral antibiotics	33% prior IV antibiotics for mean of 30 d; median duration of prior total antibiotic use >50 d	IV ceftriaxone 2 g/d × 30 d followed by doxycycline 100 mg twice daily × 60 d
Krupp et al[3]	Must have been treated for Lyme disease with ≥3 wk of oral or IV antibiotics	Allergy	47.3% prior IV ceftriaxone for ≥3 wk; mean duration of prior total antibiotic use >50 d	IV ceftriaxone 2 g/d × 28 d
Fallon et al[4]	Must have been treated for Lyme disease with ≥3 wk of ceftriaxone completed ≥4 mo before study entry	Allergy	100% prior IV antibiotics for a mean of 69 d plus a mean of 216 d of oral antibiotics	IV ceftriaxone 2 g/d × 70 d

IV = intravenous.

consistent observation has been that patients with long-term subjective symptoms after treatment do not eventually develop an objective late clinical manifestation of Lyme disease, such as Lyme arthritis.[8] In comparison, 60% of patients with untreated erythema migrans will develop Lyme arthritis within a 2-year period from onset of infection despite spontaneous resolution of the skin lesion.[17] Patients with objective evidence of treatment failure are rare with currently recommended antibiotic regimens, but this can occur. Arthritis, meningoencephalitis, carditis, and other objective manifestations of Lyme disease are clear evidence of treatment failure and require antibiotic therapy as outlined in the 2006 Infectious Diseases Society of America Treatment Guidelines.[18] These patients should not be grouped with patients with post-treatment symptoms of Lyme disease or identified by using the ill-defined term "chronic Lyme disease."[10] Patients also can acquire a new infection that should be retreated with antibiotics. Indeed, approximately 15% of patients treated for erythema migrans may develop recurrences of this skin lesion over a 5-year period.[7] A recent detailed analysis of this phenomenon has shown that such recurrences are due to reinfections from another tick bite rather than relapse of a residual skin infection.[19]

Moreover, to justify intensive retreatment with antibiotics, an additional criterion needs to be met—that retreatment both resolves the infection and relieves the symptoms. Those who argue that antibiotics cannot fully eradicate *Borrelia burgdorferi* from animals or patients[18,20] never provide evidence for why, if this were true, longer courses of antibiotic therapy would overcome this limitation.

CONCLUSIONS

Delong et al[5] fail to provide credible or convincing evidence that the methodology, findings, and conclusions of the study by Klempner et al[1] are invalid or that the other National Institutes of Health−sponsored retreatment trials show any evidence that post-treatment symptoms of Lyme disease are due to persistent infection. Neither of the analyses provided by Delong et al[5] or Fallon et al[7] justify a conclusion that there is a meaningful clinical benefit to be gained from retreatment with parenteral antibiotic therapy.

ACKNOWLEDGMENTS

The authors thank Lisa Giarratano and Shantale Williams, of the office support staff of NY Medical College, for expert assistance in editing and preparing the text of this article. EDS receives support from CTSA Grant Numbers KL2 TR000140 and UL1 TR000142 from NCATS. The contents of this paper are solely the responsibility of the authors and do not necessarily represent the official view of NCATS or the NIH.

References

1. 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.
2. Kaplan RF, Trevino RP, Johnson GP, et al. Cognitive function in post-treatment Lyme disease. Do additional antibiotics help? *Neurology*. 2003;60:1916-1922.
3. 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.
4. Fallon BA, Keilp JG, Corbera KM, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology*. 2008;70:992-1003.
5. 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.
6. Stricker RB, Delong AK, Green CL, Savely VR, Chamallas SN, Johnson L. Benefit of intravenous antibiotic therapy in patients referred for treatment of neurologic Lyme disease. *Intl J Gen Med*. 2011;4:639-646.
7. Fallon BA, Petkova E, Keilp JG, Britton CB. A reappraisal of the U.S. clinical trials of post-treatment Lyme disease syndrome. *Open Neurol J*. 2012;6(Suppl 1-M2):79-87.
8. Nowakowski J, Nadelman RB, Sell R, et al. Long-term follow-up of patients with culture-confirmed Lyme disease. *Am J Med*. 2003;115:91-96.
9. Cerar D, Cerar T, Ruzic-Sabjlic E, Wormser GP, Strle F. Subjective symptoms after treatment of early Lyme disease. *Am J Med*. 2010;123:79-86.
10. Feder HM Jr, Johnson BJ, O'Connell S, et al. A critical appraisal of "chronic Lyme disease." *N Engl J Med*. 2007;357:1422-1430.
11. Hassett AL, Radvanski DC, Buyske S, et al. Role of psychiatric comorbidity in chronic Lyme disease. *Arthritis Rheum*. 2008;59:1742-1749.
12. Hassett AL, Radvanski DC, Buyske S, Savage SV, Sigal LH. Psychiatric comorbidity and other psychological factors in patients with "chronic Lyme disease". *Am J Med*. 2009;122:843-850.
13. Krupp LB, Coyle P, Doscher C, et al. Fatigue therapy in multiple sclerosis: results of a double blind, randomized, parallel trial of amantadine, pemoline, and placebo. *Neurology*. 1995;45:1956-1961.
14. Schulz KF, Grimes DA. Sample size slippages in randomized trials: exclusions and the lost and wayward. *Lancet*. 2002;359:781-785.
15. Ljostad U, Skogvoll E, Eikeland R, et al. Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial. *Lancet Neurol*. 2008;7:690-695.
16. Wormser GP, Halperin JJ. Oral doxycycline for neuroborreliosis. *Lancet Neurol*. 2008;7:665-666.
17. Steere AC, Schoen RT, Taylor E. The clinical evolution of Lyme arthritis. *Ann Intern Med*. 1987;107:725-731.
18. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;43:1089-1134.
19. Nadelman RB, Hanincova K, Mukherjee P, et al. Differentiation of reinfection from relapse in recurrent Lyme disease. *N Engl J Med*. 2012;367:1883-1890.
20. Wormser GP, Schwartz I. Antibiotic treatment of animals infected with Borrelia burgdorferi. *Clin Microbiol Rev*. 2009;22:387-395.