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Treatment Trials for Post-Lyme Disease Symptoms Revisited

Mark S. Klempner, M.D.[1], **Phillip J. Baker, Ph.D.**[2], **Eugene D. Shapiro, M.D.**[3], **Adriana Marques, M.D.**[4], **Raymond J. Dattwyler, M.D.**[5], **John J. Halperin, M.D.**[6], and **Gary P. Wormser, M.D.**[7]

[1]University of Massachusetts Medical School, 460 Walk Hill Street, Boston, MA 02126

[2]American Lyme Disease Foundation, P.O. Box 466, Lyme, CT 06371

[3]Departments of Pediatrics, of Epidemiology and Public Health, and of Investigative Medicine, Yale University, New Haven, CT, 06520

[4]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, 20892

[5]Division of Allergy, Immunology and Rheumatology, Department of Medicine, New York Medical College, Valhalla, NY, 10595

[6]Department of Neurosciences, Overlook Medical Center and Atlantic Neuroscience Institute, Summit, New Jersey, 07902

[7]Division of Infectious Diseases, Department of Medicine, New York Medical College, Valhalla, NY, 10595

Corresponding Author: Phillip J. Baker, Ph.D.; American Lyme Disease Foundation, P.O. Box 466, Lyme, CT 06371; 203-233-6463; Executivedir@aldf.com.

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Abstract

The authors of four National Institutes of Health (NIH)-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. Recently, two groups have 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. Based on 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.

Keywords

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

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The authors of four National Institutes of Health (NIH)-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 contrast to the conclusions drawn by the authors of these four treatment trials, DeLong et al.[5] in their analysis of these studies concluded that retreatment can be beneficial and that the study findings are consistent with continued infection. 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 as well as alternative treatments for Lyme disease[6].

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

DeLong et al.[5] state that post-treatment symptoms of Lyme disease (PTSLD) are of the same severity as those of either multiple sclerosis or congestive heart failure, based on the severity of the complaints 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 were composed only of individuals with severe symptoms rather than with the full spectrum of post-Lyme disease complaints. In prospective studies of patients with well documented Lyme disease, functionality has rarely been impacted 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 years to 4.3 years. At least 40% were excluded due to 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 Klempner et al. trials[1] and that, in accordance with clinical trials on non-infectious chronic conditions such as rheumatoid arthritis, the studies should have been powered to detect a smaller effect of treatment. DeLong et al.[5] appear 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, while appealing, is also very subjective; how to define the minimal clinically important difference for a particular disease and intervention is often not straight forward. 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 Klempner et al. trials[1] and the Krupp et al. trial[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 SF-36 physical component summary) could range from 13 to 58. The frequency of severe adverse events was larger in the Fallon et al.[4] study (26.1% for those who were randomized to receive ceftriaxone), as expected, since 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.

Furthermore, in the Klempner et al. studies[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. Since 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 would also 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 Krupp et al. trial[3]. In the Krupp et al. study[3] severe fatigue was defined as a score of ≥ 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 endpoint was believed to be clinically significant based in part on 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 Krupp et al. post-treatment symptoms of Lyme disease study[3], 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 one 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 Krupp et al. study[3] one-third of the placebo recipients did not complete the study as originally designed. Of the 27 patients randomized to receive placebo, three withdrew prior to receipt of any treatment, three in retrospect did not meet entry criteria for the study, and three 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] can also be criticized because it did not exclude the three ineligible subjects who mistakenly were enrolled in the study.

In the Krupp et al. study[3] 69% of the ceftriaxone-treated patients had a ≥0.7 point reduction in fatigue score at six 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 Fallon study[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 Krupp et al. study[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 Krupp et al. study[3] were asked at the six month time point to record the intensity of their fatigue for the past two weeks using a visual analogue scale (VAS), the difference in scores between those who received antibiotics and those who did not was not statistically significant ($p = 0.08$); 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 Krupp et al. study[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 three co-primary endpoints, 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 Krupp et al. study[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 was also no impact on clearance of a borrelial antigen from cerebrospinal fluid, since the experimental assay for this antigen was positive in only a few patients before retreatment with antibiotics.

In the Fallon et al. study[4], the baseline fatigue score was 5.2 in the ceftriaxone-treated patients that fell by 15% to 4.4 after six months. Similarly, the baseline score in the placebo group was 5.5 that fell to 4.7 after six months, also by 15%. Contrary to the assertions of DeLong et al.[5], based on this assessment of fatigue there was no benefit from 10 weeks of IV ceftriaxone in the Fallon study[4]. In Fallon et al.'s *post-hoc* analysis[4], a reduction of 0.7 points in the fatigue score was observed in 66.7% of ceftriaxone-treated patients vs. 25% of placebo-treated patients. Fallon et al.[4] cite a p value of 0.05; 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 Fallon et al. paper[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 did the patients treated with ceftriaxone. This difference was associated with a p value of 0.052.

DeLong et al.[5] also failed to mention contradictions between Krupp et al.'s[3] and Fallon et al.'s[4] studies. In the Krupp et al. study[3], differential improvement was most evident at six months but not at one month after entry. In contrast, in the Fallon et al. study[4], treatment effect on cognition was most evident two weeks after the end of treatment, but not three months later. Based on 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 six months it is superior. Another contradiction between the two studies is that in the Krupp et al. study[4], exploratory analyses revealed a larger treatment effect for fatigue in patients with less pain, while the Fallon et al.[4] study's *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 Fallon et al. study[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 is also 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 four retreatment studies of patients with post-treatment symptoms of Lyme disease had been already 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 four trials[1–4]. The retreatment antibiotic regimens invariably included ceftriaxone, a drug that crosses the blood brain barrier and is commonly used to treat bacterial meningitis, because of the possibility of residual borrelia in the central nervous system. Cerebrospinal fluid analysis was done in all four 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]. Since 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 (four weeks of IV ceftriaxone followed by eight 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, while necessary, is not sufficient to justify additional antibiotic therapy. Residual organisms have to be playing a role in causing illness. A consistent observation has been that patients with long-term subjective symptoms following 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 can also 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, that longer courses of antibiotic therapy would overcome this limitation.

In conclusion, DeLong et al.[5] fail to provide credible or convincing evidence that the methodology, findings and conclusions of the Klempner et al. studies[1] are invalid or that the other NIH-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 by Fallon et al.[7] justify a conclusion that there is a meaningful clinical benefit to be gained from retreatment with parenteral antibiotic therapy.

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Clinical Implications

- Some patients given recommended antibiotic therapy for Lyme disease complain of non-specific 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 four trials re-affirms that extended antibiotic therapy provides no meaningful benefit.

Table 1

Recruitment Efforts in Re-Treatment Trials of Lyme Disease

Study authors (Ref)	Recruitment period	Duration of recruitment	Screened	Reasons for exclusion	OK for inclusion	Randomized	% Enrolled
Klempner et al. (1)	07/24/97 to 11/14/2000	40 months	1577	At least 647 for inadequate documentation of Lyme disease. 800 because of other exclusion criteria as defined in the clinical protocols[2]	130[1]	129	8.2%
Krupp et al. (3)	01/97 to 07/99	31 months	512	Most because of the absence of documented Lyme disease	56	55	10.7%
Fallon et al. (4)	01/2000 to 04/2004	52 months	3368	1316 excluded for not fulfilling criteria for Lyme disease	38	37	1.1%

[1] One subject dropped out of the study before randomization.

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

Table 2

Antibiotics Used for Patients in Re-Treatment Trials of Lyme Disease

Study authors (Reference)	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 days of parenteral antibiotics	33% prior IV antibiotics for mean of 30 days; median duration of prior total antibiotic use >50 days	Ceftriaxone 2 g IV/day × 30 days followed by doxycycline 100 mg twice daily × 60 days
Krupp et al. (3)	Must have been treated for Lyme disease with ≥3 weeks of oral or IV antibiotics	Allergy	47.3% prior IV ceftriaxone for ≥3 weeks; mean duration of prior total antibiotic use >50 days	Ceftriaxone 2 g IV/day × 28 days
Fallon et al. (4)	Must have been treated for Lyme disease with ≥3 weeks of ceftriaxone completed ≥4 months before study entry	Allergy	100% prior IV antibiotics for a mean of 69 days plus a mean of 216 days of oral antibiotics	Ceftriaxone 2 g IV/day × 70 days