Evaluation of antibiotic treatment in patients with persistent symptoms of Lyme disease: an ILADS position paper

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EVALUATION OF ANTIBIOTIC TREATMENT IN PATIENTS WITH PERSISTENT SYMPTOMS OF LYME DISEASE: AN ILADS POSITION PAPER


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ABSTRACT

Background and Objective:
The history of Lyme disease has been characterized by intense controversy over the diagnosis and treatment of this spirochetal infection. A recent high-profile article by Klempner et al. [1] focused attention on the optimal antibiotic treatment for chronic Lyme disease. Because this research study has generated significant conflict and confusion in the medical community, we undertook a critical analysis of its methodology and conclusions.

Methods:
The International Lyme and Associated Diseases Society (ILADS) reviewed the article according to established standards of evidence-based medicine. Study design and scientific objectivity were analyzed in light of peer-reviewed medical literature on chronic Lyme disease and associated tickborne illnesses.

Results:
Numerous methodologic weaknesses are noteworthy in the study. These include inappropriate study design with respect to the antibiotic treatment regimen; inappropriate selection and inadequate randomization of study patients; failure to explain positive cerebrospinal fluid findings, and failure to report objective neurocognitive assessments; failure to assess coinfection status of study participants; exclusion of pertinent findings from the final report, with inadequate follow-up of study participants; and failure to recognize that spirochetal infection cannot be excluded without adequate culture techniques.

Conclusions:
The study by Klempner et al. contains a series of interrelated errors. It fails to achieve its stated goal of being a long-term, properly randomized, placebo-controlled treatment trial. The study appears to be scientifically invalid and risks harming patients if its flawed conclusions are accepted uncritically by physicians. In view of the uninterpretable results of this study, further research into the use of long-term antibiotic therapy for chronic Lyme disease is warranted.
INTRODUCTION

Lyme disease is a multi-system illness caused by infection with the spirochete *Borrelia burgdorferi*. Although Lyme disease was officially recognized in the United States in 1975 in the Connecticut town from which it derives its name, the disease had been discovered almost a century before in Europe, where the “bullseye” rash known as erythema migrans (EM) and the late stage rash and deformity of acrodermatitis chronicum atrophicans (ACA) were first recognized [2].

Rudolph Scrimenti first documented the EM rash in the United States in 1970, five years before the official labeling of Lyme disease [2]. Scrimenti noted a striking similarity between his patient’s expanding ring-shaped skin lesion and the “erythema chronicum migrans” lesions he knew, in part, from the writings of Sven Hellerstrom [3]. Scrimenti published *Erythema chronicum migrans* in the July 1970 issue of the *Archives of Dermatology*, stating that this lesion was sometimes associated with significant neurologic symptoms [2]. Further, he postulated that spirochetes and/or rickettsiae caused the illness, which he thought was likely transmitted by ticks. His work established him as the actual discoverer of the disease that later came to be called Lyme disease. Yet both Scrimenti and Hellerstrom were openly ridiculed for their beliefs [4].

In the ensuing years, following Polly Murray’s report in 1975 of an epidemic of multi-system illness including (but not limited to) arthritis in the now famous Connecticut town of Lyme [4], chronic and persistent sequellae of tick bites became common knowledge in both the scientific and lay communities. Those notably convinced included researchers such as Allen Steere, who in his early work wrote copiously on the subject of chronic neurologic and arthritic manifestations of Lyme disease, even in cases following antibiotic treatment [5]. In 1982, the spirochetal etiology of the disease was proven by Willy Burgdorfer [6], but this was only the beginning of what has since become a monumental task in understanding the pathogenesis of Lyme disease and its chronic manifestations, as outlined below.

A major problem with the diagnosis of Lyme disease stems from the variable results of serologic testing for its causative agent, *B. burgdorferi*. Indeed, well documented but seronegative Lyme disease has been widely reported in the medical literature [7–12], and the existence of seronegative infection is substantiated by the observation that the great majority of repeatedly infected deer remain seronegative for *B. burgdorferi* [13]. These observations raise doubt about the reliability of negative results using current Lyme disease tests, particularly when testing is aimed at the diagnosis of chronic as opposed to acute *B. burgdorferi* infections.

Just as seronegative but active Lyme disease has been documented in the scientific literature, so has active central nervous system (CNS) infection despite negative spinal fluid tests for *B. burgdorferi*[14,15]. Negative results are often obtained on cerebrospinal fluid (CSF) of known Lyme patients, including normal cell count and chemistry evaluations and absent Lyme antibody titers [14,15]. Consequently the absence of antibodies against *B. burgdorferi* in CSF cannot be relied on to rule out CNS infection with this organism. Given the foregoing, the diagnosis of *B. burgdorferi* infection should be made primarily on clinical grounds, with current serologies playing only supportive roles.
In addition to problems with diagnosis, it has been almost impossible to obtain a definition of cure for this illness due to inherent problems in culturing the organism. Without an easy method for culture, there has been no “gold standard” to assess treatment efficacy. Despite this uncertainty, some physicians insist that 30–day courses of antibiotic therapy are curative even for later stage Lyme disease. This belief persists despite seminal studies documenting that 30-day courses of antibiotics do not eradicate disseminated *B. burgdorferi* infection from mice, chimps and dogs [16–18]. Although animal data must be interpreted with caution, it is not surprising that many humans with late stage Lyme disease also are not cured of their symptoms with 30-day courses of antibiotics.

Indeed, there have been a number of peer reviewed publications demonstrating persistent infection with *B. burgdorferi* in humans despite multiple and extended courses of antibiotic therapy [19]. Persistent infection has been demonstrated repeatedly by both polymerase chain reaction (PCR) and histopathology [20–23]. Chronic infection has also been demonstrated by culture despite the well-known difficulties in harvesting *B. burgdorferi* from Lyme patients, and culture positivity has even been found in patients who are seronegative for the Lyme spirochete [24–30]. In light of such data, it would be illogical to assume that persistent symptoms in chronically ill Lyme disease patients are not related to active infection with *B. burgdorferi*. Ironically, and in direct opposition to the extensive body of published data, some researchers have attributed chronic symptoms compatible with Lyme disease to alternative vague diagnoses, such as “post-Lyme syndrome,” fibromyalgia, or chronic fatigue syndrome [31,32]. The recent article by Klemperer et al. [1] amplified the dispute between widely differing medical factions and prompted the current analysis.

**METHODS**

The International Lyme and Associated Diseases Society (ILADS), an international multi-specialty medical organization, reviewed the article by Klemperer et al. [1] in an objective and didactic fashion. The review was accomplished using principles of evidence-based medicine [33]. Specifically, the study design, patient selection criteria, data reporting and outcomes analysis were all subjected to scrutiny. The conceptual framework of the study was also analyzed with reference to the published medical literature on chronic Lyme disease and associated tickborne illnesses, which includes more than 12,000 articles in the peer reviewed medical literature [19].
RESULTS

In reviewing the article by Klempner et al [1], it became apparent that there are multiple serious methodological flaws inherent in the fabric of the work. First and foremost is the initial contention that the study was intended to be a double blind, placebo-controlled trial of long-term antibiotic treatment for chronic Lyme disease patients of both seronegative and seropositive status. The authors used a treatment regimen consisting of one month of intravenous ceftriaxone at 2 gm daily followed by two months of oral doxycycline at 200 mg daily [1]. These antibiotics differ markedly in their mode of action and bioavailability, with no scientific evidence backing the assumption that their effect is additive or that the combination qualifies as “long-term” treatment. Consequently the trial amounted to a short-term ceftriaxone protocol for re-treatment of patients who had, without apparent success, experienced comparable treatment in the past, thereby undermining the principal objective of the study. Furthermore, the doxycycline dose used in the study (200 mg daily) was inadequate for CNS penetration [34]. Since the study population had neurocognitive symptoms, it is puzzling that the authors would use a medication dosage that achieves only marginal CNS concentration. To make matters worse, the acceptable medication compliance rate was 75%, reducing the doxycycline dose to sub-therapeutic levels. This was a regrettable oversight because enforcing a better compliance rate using the correct dosage would have been simple, inexpensive, and safe.

A related problem with the study derived from participants’ prior antibiotic treatment. If this truly had been a long-term antibiotic treatment trial, one could have compared short and long term antibiotic treatment efficacy given the participants’ prior “failure” with short-term antibiotics. However, since this was in reality a short-term ceftriaxone re-treatment study, it fell prey to obvious selection bias in that many of the patients had already “failed” treatment with a short course of ceftriaxone, thus increasing the odds that they would do so again. This approach introduced significant selection bias into the study.

Selection bias was a key problem throughout the trial. For example, evaluated patients were excluded from participation if they tested positive by polymerase chain reaction (PCR) for the presence of B. burgdorferi DNA, barring from the study the very patients who may have been most likely to benefit from antibiotics. In addition, despite the fact that PCR negativity was obligatory for inclusion in the study population, PCR was then reported in the body of the work as if it were a new “finding”. This may mislead readers to conclude that chronic Lyme disease patients do not frequently have intermittently positive PCR reactivity following treatment with antibiotics.

Criticism over the exclusion of PCR positives was voiced in published correspondence by Bransfield et al. [35], to which Weinstein and Klempner replied, “We screened over 1800 patients for this study, and no patient was excluded for this reason, since no patient was found to have a positive PCR assay or culture for borrelia—a result that confirms the absence of evidence of active infection in this clinical syndrome” [36]. However, the fact that the authors did not find even a single positive B. burgdorferi PCR out of the 1800 previously identified Lyme disease patients is in direct contrast to prevailing medical experience [20–30]. Although B. burgdorferi PCR has clinical disadvantages in sensitivity (see Discussion), it has been shown to be a valuable tool for the documentation of persistent infection in chronic Lyme disease patients [20–22,28].
Because the authors failed to find, even once, what other researchers have demonstrated repeatedly, doubt is raised as to the accuracy of their PCR methods. In sum, the statement by Klempner et al. that they had confirmed the absence of active infection in this chronically ill population was patently inaccurate, as ample evidence has verified the persistence of *B. burgdorferi* infection in antibiotic-treated patients with chronic Lyme disease [20–30].

Additionally, randomization seems to have been insufficient in this research. Bransfield et al. state, “Furthermore, at baseline, the placebo and antibiotic groups appeared to have significantly different scores on the primary outcome measures. These observations suggest that randomization may have been inadequate, thereby invalidating the results of the study” [35]. Weinstein and Klempner respond, “The randomization protocol was adequate, since baseline values for the primary outcome measures in all patients were statistically equivalent in the placebo and antibiotic groups” [36]. However, the published data was in direct disagreement with their own statement because the authors report a number of significant pre-test differences between the placebo- and antibiotic-treated patients in the seronegative and seropositive groups. For example, among seropositive patients the baseline scores on the MOS Cognitive Scale were significantly worse in the antibiotic-treated cohort than in the placebo cohort. Furthermore, within the seronegative group of patients, the placebo cohort had significantly poorer baseline scores on the SF-36 Mental Component, the MOS Pain Scale and the Fibromyalgia Impact Questionaire than the antibiotic-treated cohort. These baseline differences could have biased the outcome of the study.

Weinstein and Klempner further stated, “Moreover, each patient served as his or her own control, since the clinical response was measured by calculating a change in health status for each patient” [35]. This argument is unconvincing because the authors did not address their reported pre-test differences. In addition, since the trial was conceived as a randomized, placebo-controlled study, analysis of covariance in the randomized groups would have been more appropriate than analysis of intrapatient variation to address the issue of inadequate patient randomization [37]. This type of analysis was apparently not performed.

While the study focused intensely on subjective neuropsychological testing, some noteworthy objective findings were reported succinctly without any discussion. For example, Klempner et al. found that over 25% of the enrollees had elevated CSF protein and that 8 had intrathecal production of *B. burgdorferi* antibodies. In patients with a history of well-documented Lyme disease and such CSF findings, these clinical parameters may be consistent with active neuroborreliosis. Instead, the authors focused on measurements of questionable utility in assessing chronic Lyme disease. Bransfield et al. criticized the authors in this regard by writing, “The neuropsychological scales used in the study were insufficient to assess the cognitive impairments in executive functioning and the psychiatric dysfunctions that are seen in patients with persistent Lyme disease. The SF-36 is a subjective assessment scale, based on the patient's self-perception. There was a paucity of objective measures to assess the patient's status” [35]. Weinstein and Klempner replied that the enrollees were given an “extensive battery of neurocognitive tests in addition to the SF-36. A forthcoming analysis of these data should help to demonstrate any cognitive impairment, should it exist” [36]. Yet the question arises as to
why this “extensive battery” of neurocognitive tests was not discussed in this paper, where it might have aided in the serial analysis of the patients’ neurocognitive dysfunction during antibiotic treatment.

Such omission raises the question as to what other data collected during this study was excluded from the formal report. For example, Klempner publicly alluded to his testing for CSF matrix metalloproteinases in these patients (Klempner MS, 11th Annual Diseases of Summer Conference, South County Hospital, Wakefield, RI, 2001), but this was not reported in the study. Since Klempner previously published on the presence of these markers both in vitro and in vivo in active neuroborreliosis [38,39], we anticipated that the paper might have included this important objective data. Had it been revealed, it could have provided additional clues regarding the presence or absence of active neuroborreliosis, and thus might have added significantly to the study.

A final problem with the study’s data analysis is the exclusion of possible Jarisch-Herxheimer reactions. As in syphilis, another spirochetal infection, Lyme disease patients frequently experience this symptom intensification upon initiation of antibiotic therapy [40–42], yet this was not evaluated. Failure to discuss this symptom complex is a serious oversight, since any assessment of interval change in patient status could not be conducted properly without consideration of such a common phenomenon. Indeed, for patients with active B. burgdorferi infection, worsening symptoms due to Jarisch-Herxheimer reactions potentially could have been troublesome enough to prompt their withdrawal from the study unless this complication had been discussed with them in advance.

DISCUSSION

The methodologic deficits described above reflect the fact that the complexities of B. burgdorferi pathogenesis were not fully taken into consideration by Klempner et al. As a result, the authors ignored the critical context for exploring diagnostic factors and treatment responses in chronic Lyme disease. For example, B. burgdorferi has the ability to survive in divergent conditions of mammals and ticks by existing in a variety of forms that are ultrastructurally and metabolically distinct. Even in the tick, altered morphologic forms of B. burgdorferi are present [43], but in the mammal, selective pressure from mammalian immune surveillance results in these altered forms becoming more common. These “host adapted” forms generally display altered morphology to varying degrees and are referred to collectively as L-forms or spheroplasts. B. burgdorferi spheroplasts, of which cystic forms and granules are sub-types, have been extensively documented in vitro and in vivo [44–53], both extracellularly and intracellularly [27,47,54–57]. Their ability to revert from host-adapted forms back to helical forms under appropriate conditions has been demonstrated in vitro [47,58,59].

To the uninitiated, it may be tempting to infer that B. burgdorferi cystic forms are degenerative bacterial fragments. This is not the case, since researchers have demonstrated protein synthesis requirements for spirochetal conversion into the spheroplast form [44]. Indeed, it has been unequivocally proven that B. burgdorferi cystic forms are virulent and infectious. Their infectivity, survival under extreme environmental conditions, and ability to revert back to helical forms in vivo have all been demonstrated by inoculation of B. burgdorferi cysts into mice and subsequent recovery of helical
spirochetes from the animals [60]. As such, host-adapted forms of \textit{B. burgdorferi} are considered to be major factors in the relapsing and persistent nature of Lyme disease [61–63].

Just as \textit{B. burgdorferi} spheroplasts have altered metabolic requirements for growth, so too, do they have unique antibiotic sensitivities, altered surface protein expression, dramatically reduced surface area presented for immune surveillance, and the ability to cause multiple potential problems for PCR analysis. All of the foregoing helps to explain observations of antibiotic resistance, seronegativity, and even frequent PCR negativity in active disease [51,54,59,63,64]. The failure to address the complexities of the borrelial life cycle in the work by Klempner et al. is a serious error. For example, the fact that cystic forms demonstrate sensitivity to metronidazole while their helical kin are resistant, illustrates the point that \textit{B. burgdorferi} spheroplasts have altered antibiotic resistance [65]. Attention to these forms during the initial study design might have resulted in different treatment decisions, with consideration that a cell wall-attacking cephalosporin may not have been the ideal antibiotic choice for treatment of cell wall-deficient organisms in patients with late-stage Lyme disease.

In addition, had the authors addressed the intracellularity of \textit{B. burgdorferi}, this might have broadened their choices of antibiotic therapy. Although the utility of ceftriaxone for Lyme disease has been documented, it has been similarly documented that this agent frequently does not fully eradicate human \textit{B. burgdorferi} infections [19]. Cephalosporins do not achieve intracellular penetration, a fact that may partially explain well-known treatment failures associated with late stage Lyme disease. Indeed, \textit{B. burgdorferi} has been documented within a variety of cell types, including but not limited to endothelium, fibroblasts, lymphocytes, macrophages, keratinocytes and synovial cells [17,51,54,66–70]. These findings are critically important since chronic infections are highly dependent on intracellular asylum as a mode of persistence, and localization within eukaryotic cells protects \textit{B. burgdorferi} from antibiotics [71,72]. It is particularly surprising that the lead author agreed to use ceftriaxone in this study, since he previously authored a paper on the fibroblast-mediated protection of \textit{B. burgdorferi in vitro} from concentrations of ceftriaxone achieved \textit{in vivo} for the treatment of Lyme disease [71].

Another conceptual oversight in this study was the lack of consideration in the body of the manuscript of co-infections commonly found in Lyme disease patients. In addition to \textit{B. burgdorferi}, Ixodes ticks transmit other pathogens that may have infected the study patients, such as \textit{Babesia}, \textit{Ehrlichia} and \textit{Bartonella} species [73–80]. These tickborne coinfections apparently were not considered in the evaluation of patients but could well have been clinically relevant and affected outcomes in the study, since they occur in approximately 10\% to 66\% of Lyme disease patients [73–78]. As with most tickborne illness, the clinical spectrum of these coinfections spans sub-clinical to life threatening presentations [75,76], and they are underdiagnosed in all age groups [73].

Despite the severity of illness documented in this study’s chronic Lyme disease patients, and the fact that neither ceftriaxone nor doxycycline effectively treats certain coinfections, this potential drawback was not mentioned in the body of the paper. Furthermore, aside from non-spirochetal co-infections that can be tested for, there are other tickborne spirochetal infections for which there is no commonly available testing [81,82]. These unknowns also should have been mentioned in the body of the study since
it is not clear to what extent they may cause or prolong illness or to what extent they are amenable to antibiotic therapy.

In summary, the methodologic problems of the study reflect an apparently inadequate appreciation of Lyme disease pathogenesis and persistence in patients with chronic symptoms of tickborne disease.

CONCLUSIONS

In our analysis, the study by Klempner et al. fell prey to a series of interrelated errors. The study began by missing its initial design goal of being a long-term, properly randomized, placebo-controlled antibiotic treatment trial for patients with chronic Lyme disease, simply because the treatment provided was not long-term. Many methodologic and conceptual aspects of the work were flawed, resulting in patient selection bias, suboptimal antibiotic treatment regimens, faulty analysis and/or exclusion of data, and disregard for *B. burgdorferi* microbiology and pathogenesis.

Based on its many errors, much of the article by Klempner et al. is, in our opinion, scientifically invalid and risks harming patients if it is accepted uncritically by physicians who may not have the time or the expertise to analyze the work. Indeed, a majority of medical practitioners may, after reading this paper, inappropriately withhold treatment from patients with persistent Lyme disease [83]. This would be especially troubling since other peer reviewed medical research demonstrates that extended treatment with months of the correct choice of antibiotic therapies can be remarkably beneficial for patients with late-stage Lyme disease [84–86]. Certainly, long-term antibiotic treatment is medically accepted and approved for other chronic infectious diseases such as tuberculosis and leprosy [87–89]. We hope that future studies of long-term treatment of Lyme disease will be designed, implemented and analyzed in a more appropriate manner.

AUTHOR CONTRIBUTIONS

Dr Phillips wrote the initial manuscript, researched the initial references, initially coordinated the project and participated in many editing reviews. Dr Bransfield wrote the initial outline, wrote and researched sections of the article, participated in many editing reviews and coordinated completion of the article. Dr Sherr wrote and researched sections of the article, served as a liaison to the ILADS board and participated in many editing reviews. Dr Brand wrote and researched a section of the article related to research design and participated in some reviews. Dr Smith wrote sections of the article, participated in many editing reviews, rewrote one of the revisions and checked for the accuracy of the references. Kathleen Dickson wrote sections and participated in editing reviews. Dr Stricker wrote a section on the study protocol, edited the section on coinfections, contributed assistance with the references, participated in final review of the manuscript and coordinated completion and submission of the article.
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