Perspectives on "Chronic Lyme Disease"

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Abstract

There is much controversy about the treatment of Lyme disease with respect to two poorly defined entities, "chronic Lyme disease" and "post treatment Lyme disease syndrome". In the absence of direct evidence that these conditions are due to a persistent infection, some mistakenly advo cate extended antibiotic therapy (6 months or more) , which can do great harm and has resulted in at least one death. The purpose of this brief report is to review what is known from clinical research about these conditions to assist both practicing physicians and law-makers in making sound and safe decisions with respect to treatment.

During the 2007 session of the Maryland House of Delegates, legislation was proposed that would have compelled health insurance companies to pay for extended antibiotic therapy for the treatment of "chronic Lyme disease", and prohibited local medical boards from disciplining physicians who administered such therapy. Similar legislation was proposed in Pennsylvania, Connecticut, Massachusetts, and New York where Lyme disease is endemic. This is all part of an orchestrated campaign by some who mistakenly believe that "chronic Lyme disease" is due to a persistent infection requiring 6 months or more of antibiotic therapy to cure. The purpose of this document is to review what is known about "chronic Lyme disease" and examine the impact of such therapy on the public health.

Lyme disease is easy to cure with a short course of oral antibiotics such as doxycycline or amoxicillin. What is less well-recognized is that late manifestations also are responsive to 3 to 4 weeks of treatment with doxycycline, amoxicillin, or ceftriaxone. Despite the proven efficacy of these regimens, there still is much controversy about the treatment of two poorly defined entities, "chronic Lyme disease" and "post treatment Lyme disease syndrome", which occur in a small percentage (<5%) of individuals previously treated for correctly diagnosed early Lyme disease. To address this issue, the National Institutes of Health (NIH) funded three placebo-controlled clinical trials on the efficacy of prolonged antibiotic therapy for these conditions; the results obtained have been published in major scientific journals and thus were subjected to rigorous peer review. Two large studies provided no evidence that prolonged antibiotic treatment is beneficial [1]. In the third study, the score for severity of fatigue improved in both the antibiotic-treated and the placebo groups [2]; however, the improvement was greater by 13% in those who received antibiotic (22% *vs* 9%). No significant benefit was found for other symptoms and unblinding may have occurred. Because of the high frequency of serious adverse effects noted, the investigators concluded that "repeated courses of antibiotic treatment are not indicated for persistent symptoms following Lyme disease, including those related to fatigue and cognitive dysfunction…" [2].

Several key factors were considered in the design of these clinical trials. They included:

- the susceptibility of *Borrelia burgdorferi*, the causative agent of Lyme disease, to the antibiotics used,
- the ability of the antibiotics used to access the central nervous system and to persist –at effective levels—during the course of therapy,
- the ability of the antibiotics used to penetrate mammalian cells, even though there is much evidence to indicate that Borrelia are extracellular, rather than intracellular, pathogens,

- the possibility that various co-infecting agents could influence the expression and severity of symptoms, and
- the safety of patients enrolled in the trials.

Since the experimental protocols used addressed all of these issues, there is no reason to believe that different results would be obtained using other antibiotics – given singly or in combination by different routes—for longer periods of time. The results obtained are consistent with the findings of more than 20 years of basic research on the pathogenesis and treatment of Lyme disease supported by the NIH and the Centers for Disease Control and Prevention (CDC).

Despite the convincing results obtained, some continue to claim -- in the absence of relevant peer-reviewed experimental data -- that "chronic Lyme disease/post treatment Lyme disease syndrome" is due to a persistent infection with *Borrelia burgdorferi* , requiring several months of antibiotic therapy to be cure. Such a regimen, which is unprecedented for a disease that is not life-threatening, is harmful and exposes patients to great risks that may result in:

- death from fulminating fungal infections [3];
- obstruction of the gall bladder often requiring its removal [4];
- outbreaks of severe *Clostrium difficile* infections with significant mortality [5]; and,
- the generation of new antibiotic resistant strains of bacterial pathogens that are an increasing and serious public health problem [6].

Obviously, extended antibiotic therapy for the treatment of "chronic Lyme disease/post treatment Lyme disease syndrome" is not warranted unless there is clear evidence of a persistent infection which proponents of this view have yet to provide.

To be accepted by the medical and scientific community, the validity of any therapeutic regimen proposed must be supported by the results of carefully designed and critically reviewed clinical trials. This has always been the norm and is the foundation of sound evidenced-based medical practice where the burden of proof is on those recommending a particular therapeutic approach. They must provide unequivocal evidence that their approach is justified, effective, and safe. In this context, those advocating extended antibiotic therapy for the treatment of "chronic Lyme disease/post treatment Lyme disease syndrome" have failed to address the following key issues:

- "Chronic Lyme disease/post treatment Lyme disease syndrome" must be defined in terms of well-established diagnostic criteria, so that it can be distinguished from other non-infectious medical conditions with similar symptoms, e.g., fibromyalgia, and chronic fatigue syndrome. This issue was a matter of great concern in developing the criteria for enrollment in the aforementioned NIH-supported clinical trials to ensure that those enrolled had a high probability of having this condition; otherwise, the results obtained would have been inconclusive. In the trials conducted at the New England Medical Center (NEMC), more than 1,500 individuals claiming to have chronic Lyme disease were screened in order to obtain the 129 subjects (8.6%) enrolled [1]. An enrollment rate of about 5% was noted in another treatment study [2]. This indicates that "chronic Lyme disease/post treatment Lyme disease syndrome" is not common.
- Direct evidence must be provided that "chronic Lyme disease/post treatment Lyme disease syndrome" is due to a persistent bacterial infection in patients being considered for treatment. Without such evidence, prolonged antibiotic therapy is not justified, can result in great harm, and contributes to the emergence of new strains of antibiotic resistant bacterial pathogens.
- Evidence must be provided, from the results of placebo-controlled studies, that prolonged antibiotic therapy is beneficial and safe. Testimonial observations and anecdotal reports are not reliable, since a placebo effect of 40% was noted in the published studies cited above [1], and other investigators have noted periodic improvements in the symptoms of patients given only placebo during the course of their studies.
- Adjustments must be made in the experimental design to compensate for the unanticipated beneficial effects of antibiotics that are unrelated to their antimicrobial properties. The anti-inflammatory properties of macrolides, doxycycline and other tetracyclines are well-known; however, these – as well as several other beta lactam and cephalosporin antibiotics, including ceftriaxone often used to treat "chronic Lyme disease/post treatment Lyme disease syndrome" – have profound neuroprotective properties that might ameliorate neurological symptoms [7,8,9]. Such pharmacologic effects, rather than the elimination of a presumed persisting infection *per se*, might account for the short-lived beneficial effects sometimes seen. In the absence of evidence for a persisting infection, some have suggested treatment with gabapentin to alleviate symptoms associated with "chronic Lyme disease/post treatment Lyme disease syndrome". Although promising results were obtained in one small clinical trial [10], this approach requires much more study. Recently, the Food and Drug Administration (FDA) approved the use of pregabalin for the

treatment of fibromyalgia, a condition with symptoms very similar to those ascribed to "chronic Lyme disease/post treatment Lyme disease syndrome".

The results of NIH-supported studies acknowledge that some patients with "chronic Lyme disease/post treatment Lyme disease syndrome" indeed have deficits with respect to their physical health status [1]. No doubt such patients experience significant pain and therefore require appropriate medical attention and care. However, since there is no evidence to indicate that their symptoms are caused by a persistent *Borrelia burgdorferi* infection, other options must be considered to determine their cause and how such patients might be treated to relieve their symptoms. Without direct evidence for a persistent infection, it is clear that extended antibiotic therapy is not the answer; it remains an unproven and unsafe therapeutic approach that is neither justified nor in the best interest of the public health. This is in accord with the views expressed by many outstanding experts in infectious disease [11,12,13].

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