

"Ending the Lyme Disease Wars"

Much of the confusion and misinformation being disseminated about Lyme disease can be attributed to the failure to make several key distinctions:

The terms Lyme disease and "chronic Lyme disease", although often used interchangeably, refer to two different medical conditions. In the United States, Lyme disease is a tick-borne bacterial infection, transmitted by *Borrelia burgdorferi sensu stricto*. We know a great deal about its transmission, diagnosis, and treatment (1). By contrast, there is considerable controversy about "chronic Lyme disease," which has not been defined as a distinct clinical entity to distinguish it from other medical conditions with similar symptoms. Without a precise case definition, it is impossible to determine who has it, much less develop a rational approach for treating it. In this commentary, the term "chronic Lyme disease" is used to describe a condition in which individuals have an array of non-specific persistent symptoms of which pain is a major component; here, there is no objective evidence of a persistent *B. burgdorferi* infection. In those who have evidence of a correctly diagnosed and treated previous infection, the more preferred term is post-treatment Lyme disease symptoms (PTLDS), rather than "chronic Lyme disease". In this way, no assumptions are made on the possible existence of a persistent infection.

In the 4 NIH-supported clinical trials showing no benefit of extended antibiotic therapy for the treatment of persistent symptoms following the treatment of Lyme disease, only patients with a past history of well-documented active Lyme disease, diagnosed in accordance with criteria established by the Centers for Disease Prevention and Control (CDC), were enrolled (2,3,4). This did not guarantee that all enrolled patients actually had a persistent *B. burgdorferi* infection; however, it at least made such an assumption much more probable and excluded those not likely to derive any benefit from antibiotic therapy. Of the more than 3,000 patients who volunteered for enrollment because they believed they had "chronic Lyme disease", only 5-8% met this criterion for enrollment. This suggests that the number of individuals who believe they have "chronic Lyme disease" far exceeds those with documented evidence of a prior *B. burgdorferi* infection who have persistent symptoms.

It has been suggested that the total number of patients enrolled in the above mentioned clinical trials was too small for one to draw

meaningful conclusions about the efficacy of retreatment, despite the fact that the data obtained were subjected to appropriate statistical analysis and rigorous peer-review. However, based on the enrollment data cited above, one would have to survey more than 10,000 prospective subjects in order to enroll 500 patients to do a comparable study. To conduct a clinical trial of such magnitude for an infectious disease that is neither fatal nor life-threatening (5) would be enormously expensive in terms of the almost "Herculean" recruitment efforts required. So, in the absence of convincing objective evidence of a persistent infection, is there any wonder that many individuals, who believe that they have "chronic Lyme disease" fail to respond to months -- or in some cases even years -- of antibiotic therapy, and often sadly conclude that "chronic Lyme disease" is incurable? Admittedly, the majority of such individuals experience real pain; but, there is just no evidence that most of them have -- or ever had -- a *B. burgdorferi* infection.

Instead of acknowledging the very real and distinct possibility that no *B. burgdorferi* infection actually exists, the failure to respond to extended antibiotic therapy is often attributed to the ability of *Borrelia* to form protective cysts, or to form antibiotic-impermeable biofilms, or to occupy intracellular niches in the body where they are sheltered from the action of antibiotics or antibody. However, there is no evidence that any bacteria form cysts, or that *Borrelia* secrete extracellular biofilms in mammalian host tissue during infection. Recent studies indicate that *Borrelia* localize, not intracellularly, but preferentially to the extracellular matrix (6).

B. burgdorferi produces a variety of adhesins that enable it -- or their cell surface components-- to bind tenaciously to the extracellular matrix (7). This enables dead *Borrelia* cells and/or their fragments to persist in the extracellular matrix for long periods of time after antibiotic therapy (8,9). Since such spirochetal debris contains pharmacologically active lipoproteins that can stimulate the production of inflammatory and/or proinflammatory cytokines (8,9), it could contribute to the expression of the pain associated with antibiotic-refractory Lyme arthritis, and perhaps other symptoms ascribed to "chronic Lyme disease". Although the expression of such symptoms no doubt decline with time, treating with antibiotics until symptoms disappear is not a prudent strategy and is not likely to hasten the elimination of such pharmacologically active debris. Obviously, more clinical research on this phenomenon and its implications with respect to pain and other symptoms associated with "chronic Lyme disease" is needed. In this context, it is interesting to note that the number of

annual episodes of antibiotic-refractory arthritis has been shown to decline progressively with time and eventually disappear, several years after initial antibiotic therapy and without additional antibiotic treatment (10).

In the largest of the clinical trials mentioned above (2), a placebo effect of 38% was noted. This means that, without a well designed placebo-controlled study, the claims of efficacy for various unorthodox remedies advocated by Lyme literate physicians (LLMDs) are not credible. We often hear of some patients who have “benefited” from such therapies; however, we are never told about the many more that have experienced no tangible benefit or have suffered great harm from such therapy. Obviously, it is incumbent upon those who advocate unorthodox remedies to document the results obtained for all treated patients to demonstrate a statistically significant benefit beyond that of a placebo effect. Those who place their trust in such unproven remedies do so at their own peril.

The Institute of Medicine (IOM) issued a comprehensive report on pain in the United States (11). It asserts that “Acute and chronic pain affect large numbers of Americans with at least 116 million U.S. adults – about 30% of the population—burdened by chronic pain alone. The annual economic cost associated with chronic pain is estimated to be \$560-635 billion”. It notes the tortuous and frustrating experiences of those seeking relief from such pain; they often consult several physicians, who are unable to identify the cause of their medically unexplained symptoms (MUS) or suggest a remedy.

Patients with symptoms believed to be caused by “chronic Lyme disease” might easily be included in this large group of 116 million Americans. It also might include patients with symptoms often attributed to “chronic Lyme disease” even though such patients are seronegative and have no past history of Lyme disease. Some have consulted as many as 7 different physicians, often to no avail. Eventually, they are persuaded to consult a LLMD, who “specializes” in the treatment of “chronic Lyme disease” and are claimed to have “special insights” on its treatment. In so doing, they are often promised relief through a variety of unproven therapeutic approaches, some of which may be harmful -- at great personal expense. In most cases, they are sadly disappointed.

The IOM report provides a multidisciplinary blueprint for dealing with the pain of “chronic Lyme disease” and MUS in a constructive and non-contentious manner. Since primary care physicians in endemic

areas may see many “chronic Lyme disease” patients, they surely would welcome new insights on how best to manage and treat this condition. Implementation of this blueprint would be an excellent first step in achieving these worthy goals and perhaps ending the Lyme disease wars – once and for all.

Phillip J. Baker, Ph.D.
Executive Director
American Lyme Disease Foundation

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