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EDITORIAL

Lyme borreliosis: the challenge of accuracy

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'The challenge of Lyme disease: tired of the Lyme wars', a recent editorial by Kullberg *et al.* in the Netherlands Journal of Medicine,[1] is presented as a plea for balance and reason in the ongoing 'wars' concerning this infectious disease. The editorial, in part, contrasts a review article on Lyme borreliosis published in the same issue[2] with anticipated revisions of the 2004 Dutch CBO Treatment Guidelines for Lyme Disease, developed in conjunction with a Lyme advocacy group from the Netherlands, and expected to be published in late 2011.

All can agree with Kullberg *et al.*[1] that the field would be well-served by a dispassionate and reasoned consideration of the evidence and that physicians must listen carefully to their patients, reach rational conclusions based on evidence and then recommend appropriate treatment. Unfortunately, the editorial contained a number of statements that fall short of these standards.

Kullberg *et al.*[1] use misleading dualities to advance their arguments. The second sentence sets the tone– 'whether or not persisting fatigue, cognitive dysfunction, and musculoskeletal pain are "real disease" and related to persistent infection....' Such a statement juxtaposes two distinct concepts. Patients with such symptoms have a clinically important disorder, and they need appropriate management. However, one or more of such symptoms occurs on a chronic basis in a sizable proportion of the adult population (>20%), which for the vast majority cannot be explained on the basis of a chronic infection; this is well-illustrated by the many studies on the aetiology of chronic fatigue.[3] Evidence also indicates that persistent infection is not the explanation for similar kinds of subjective symptoms in patients who have been previously diagnosed and treated for Lyme borreliosis [see below].

Kullberg *et al.*[1] also make statements that are incorrect. They assert that little is known about treatment success rates among patients with a delay in either the diagnosis or initiation of treatment for *Borrelia burgdorferi* sensu lato infection. However, most patients with Lyme arthritis have a delay in diagnosis, since the average time from onset of infection with *B. burgdorferi* sensu stricto to development of this late clinical manifestation is six months.[4] Nevertheless, the outcome of antibiotic treatment is generally very good and well understood, as documented extensively in many clinical reports, most of which are summarised in the 2006 clinical practice treatment guidelines for Lyme disease developed by the Infectious Diseases Society of America (IDSA).[5] Of course, no drug, including antibiotics, would be able to reverse permanent tissue damage of joints, nerves or skin. Earlier rather than delayed treatment is presumably desirable,[5,6] as shown by the success in prevention of Lyme arthritis when patients with erythema migrans, the most common manifestation of early Lyme borreliosis, are treated with antibiotics.[5]

Kullberg *et al.*[1] state that it is unknown whether long-term antibiotic treatment of patients with unexplained symptoms after standard therapy for Lyme borreliosis is beneficial. This is not true in North America, since the published results of four NIH-sponsored placebo-controlled treatment trials either showed no benefit at all, or a benefit so modest or ambiguous that the investigators themselves felt that any potential benefit was outweighed by the risks associated with the treatment.[7-10] Although

the species of Lyme *Borrelia* are more diverse in Europe compared with North America, it is not expected that these conclusions would be any different in Europe, as suggested by the findings of a Finnish study of prolonged antibiotic treatment.[11]

Kullberg *et al.*[1] dismiss the findings of the Klempner trials,[7,8] in which retreatment with 30 days of parenteral ceftriaxone (2 grams/day) followed by an additional 60 days of oral doxycycline (200 mg/day) provided no benefit compared with placebo. To explain away these important findings, Kullberg *et al.*[1] assert that the trials were discontinued prematurely due to slow recruitment and thereby had inadequate enrolment, and that they failed to report the primary endpoint of success in the intent-to-treat population. Both assertions are incorrect. The trials were ended based on the recommendations of an independent Data and Safety Monitoring Board, after a ***planned* interim analysis** of the first 107 patients enrolled indicated that it was highly unlikely (<5%) that a significant difference in treatment efficacy between the groups would be observed with the planned full enrolment of 260 patients. In the publication of their findings, Klempner *et al.*[7] explicitly stated that: 'The primary clinical endpoint was the proportion of patients whose condition was categorised as improved, unchanged, and worse on the basis of the summary scores for the mental and physical components of the SF-36 at 180 days. Patients who withdrew from the study were categorised as having worsened health status on both of these scales'. Thus, it was the ***intent-to-treat*** analysis specifically that showed no significant differences in the primary outcome measure in the prolonged retreatment groups compared with the groups who received placebo. Furthermore, consistent with these findings and perhaps equally important, Klempner *et al.* did not find any evidence, based on over 700 samples from 129 patients that were examined by culture and polymerase chain reaction (PCR) assays, for persistent *B. burgdorferi* sensu stricto infection in patients with persistent symptoms after treatment for Lyme borreliosis.[7,12] They also found no evidence of an *Ixodes scapularis*-transmitted co-infection with *Anaplasma phagocytophilum* or *Babesia microti* to explain the symptoms.[7] Kullberg *et al.*[1] omitted any mention of these findings in their editorial, although they stressed the importance of making 'reasonable attempts to rule out relapse or persistent infection.'

Kullberg *et al.*[1] suggest that serological assays for detection of antibodies to *B. burgdorferi* sensu lato are suboptimal by citing a recent paper from the Netherlands that showed inconsistent results among the various assays tested.[13] Unfortunately, that study had a number of potentially significant methodological concerns, not the least of which is that the patient population was poorly defined, as has already been pointed out by other investigators from the Netherlands.[14] However, if the comments and conclusions of Kullberg *et al.*[1] on serological testing are to be interpreted as providing support for the need for proper validation of diagnostic tests before they are used in routine patient care, we are in complete agreement. Use of appropriately validated tests, in conjunction with considerations of pre- and post-test probabilities, is extremely important in the serological diagnosis of most of the clinical manifestations of Lyme borreliosis other than erythema migrans in both the United States and Europe.[15]

Lastly, Kullberg *et al.*[1] consider use of the term 'post-Lyme disease syndrome' as 'deceitful,' an unusual, if not inappropriate, choice of words for an editorial in a medical journal. The term, 'post-Lyme disease syndrome,' for which there is a published definition,[5] is widely used in the medical literature and in international guidelines[16] and is generally meant to describe this particular medical condition, without making any assumptions as to the mechanism(s) involved. In contrast, the term, 'chronic Lyme disease – which clearly needs to be distinguished from well-defined late manifestations of Lyme borreliosis such as acrodermatitis or late neuroborreliosis – is undefined, means quite different things to different people, and is based on the assumption of a persistent infection for which there is no valid scientific evidence in this patient group.[7,10,12] The definition of post-Lyme disease syndrome was developed to provide a framework for future research and to reduce diagnostic ambiguity in study populations. Evidence of having had *B. burgdorferi* infection at some point is an **absolute** requirement of the case definition.[5] Such an inherently sensible standard is quite different from that used for 'chronic Lyme disease' by many of the healthcare providers who argue for this term. Indeed, in the United States the majority of patients being treated with indefinite courses of antibiotic therapy for 'chronic Lyme disease' have no valid evidence of ever having had *B. burgdorferi* sensu stricto infection.[17,18]

Lyme disease activists in the United States[19] often take issue with the term 'post-Lyme disease syndrome,' since they believe it conveys the message that there is no active infection to explain persistent symptoms. Actually, it is the microbiological and clinical evidence gathered by Klempner *et al.*[7,8,12] and corroborated by other investigators,[10,20] rather than the term per se, that warrants such a conclusion.

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