A Commentary on the Treatment of Early Lyme Disease

Raymond J. Dattwyler
Department of Medicine and Microbiology/Immunology, New York Medical College, Valhalla

(See the article by Kowalski et al, on pages 512–20.)

The question of how long to treat Borrelia burgdorferi infection is a topic that provokes confusion among a large number of physicians. As pointed out by Kowalski et al [1] in this issue of Clinical Infectious Diseases, many physicians tend to use longer courses of antibiotics for Lyme disease than they would for other bacterial infections. A few physicians advocate prolonged courses of antibiotics, claiming that Lyme disease is responsible for an array of vague subjective clinical concerns and a cause of chronic infection [2, 3]. One has to question why a reasonable physician would treat a patient this way and more importantly what has led to this confusion.

In large part, one can look to the treatment trials of Lyme disease for an answer. How Lyme disease is defined and how “cure” is determined stands at the crux of the issue. The only clinical manifestation of B. burgdorferi infection that is diagnostic is erythema migrans (EM), a characteristic skin lesion associated with early infection [4, 5]. In contrast to most bacterial diseases in which infection is defined microbiologically by direct observation, culture, or polymerase chain reaction of the pathogen, Lyme disease is defined indirectly, by EM or in its absence, by serologic testing, and by the presence of objective clinical manifestations [6, 7]. Serologic testing is useful as an adjunct to diagnosis but has no role in the definition of cure. Antibodies against B. burgdorferi can be present years after successful treatment and like many serologic assays are best used to demonstrate exposure to a microorganism, not active infection. Because there is no standard microbiologic or laboratory definition of infection, the definition of cure is by necessity indirect.

There is limited availability of culture at some medical centers, but culture is not useful in Lyme arthritis or nervous system infection because of its extremely poor sensitivity [2]. Thus, all the major studies on the treatment of Lyme disease have used clinical definitions of cure.

Early Lyme disease is the easiest phase of the disease to study. The fact that there were 9 prospective, randomized trials of antibiotic treatment for early Lyme disease performed in the United States reflects this [2]. Each trial used EM to define infection. The use of EM as the definition of infection virtually guarantees that the patient in fact had early B. burgdorferi infection. However, given the state of the art, the definitions of cure and treatment failure used in these studies cannot grant a similar guarantee. Because most researchers are cautious in designing and performing clinical trials, there is a strong tendency to have a liberal definition of failure and a conservative definition of cure. The difficulty in defining failure is reflected by the variability in the definition of treatment failure in these studies. They are by no means uniform or for that matter clear-cut. Some used the persistence or emergence of objective clinical manifestations as the definition, whereas others also included the persistence of subjective symptoms. One thing is consistent, though: they all overestimate true treatment failures.

The cause of this overestimation is multifaceted. There are 3 aspects that were largely ignored in all of these studies. The first and most important is that, although all 9 studies were performed in regions endemic for multiple tickborne infectious diseases, none of these studies considered that 2 other tickborne infectious diseases, Babesia and Anaplasma infections, commonly carried by the same ticks that carry B. burgdorferi, could be the cause of continued symptoms [2]. Second, because patients in these studies live in areas of endemicity, subsequent infection rather than treatment failure has to be considered but was not in most studies. Third, further complicating the interpretation of these studies is that many of the clinical manifestations used to define failure are common complaints in the general population. Such complaints as fatigue, stiff neck, arthralgia, myalgia, palpitations, abdominal pain, sleep disturbance, poor concentration, irritability, depression, back pain,
headache, dizziness, and other nonspecific symptoms are reported fairly commonly in otherwise healthy members of the general population [8, 9]. None of the studies took the common occurrence of these concerns into consideration in their definition of treatment failure.

Of these 9 EM treatment trials, only 1 specifically addressed the question of duration of treatment. In that study, patients with EM were prospectively randomized into a double-blind, placebo-controlled trial that compared 3 different treatments: oral doxycycline for 10 days, a single 2-g intravenous dose of ceftriaxone followed by oral doxycycline for 10 days, and oral doxycycline for 20 days [10]. No difference in the response to treatment was seen between the groups.

With this background, the article by Kowalski et al [1] in this issue of the journal makes a particularly important contribution to our understanding of the treatment of early Lyme disease and its outcome. Their study is notable for several reasons. It is the largest study of its kind, with 607 patients meeting the criteria for inclusion. The patient population is similar to that in the other published studies, as are the clinical presentations (75% had local disease and 25% had early disseminated disease). In addition, there was the long mean follow-up of 2.9 years [1]. A refreshing aspect of this article is that the authors are cognizant of and appropriately point out the problems associated with defining cure and failure. The study used definitions similar to the prior early Lyme disease studies cited herein with some notable and key differences. First, the authors recognize that the patients live in an area of endemicity; thus, subsequent infection can occur. Second, patients with only subjective symptoms were classified as having possible treatment failure not true treatment failure. The likelihood that the definition of possible failure was too broad because it included patients subsequently treated with antibiotics for a positive serologic test result was also pointed out.

Subsequent infection occurred in 4% of the patients and was far more common than treatment failure. Although this number is undoubtedly higher than some previous studies because of the longer duration of this study, it clearly points out this issue. Another striking and welcome aspect is that the authors included data on the incidence of common vague complaints in their study population. Not surprisingly, it was high, but rather than being a reflection of B. burgdorferi infection, it reinforces just how universal these concerns are in our society. Diagnosing Lyme disease simply on the basis of the presence of subjective complaints is unjustifiable.

I fully support the authors’ conclusion that early Lyme disease, both local and acute disseminated, can and should be treated for 10 days with an appropriate antibiotic, either doxycycline or amoxicillin. Although spirochetemia occurs in nearly 45% of patients presenting with EM [11], disseminated disease is effectively treated orally [12]. Only 6 of the 607 patients met the study definition of treatment failure, and of those, 4 had subsequent infection and 1 was initially given an inappropriate antibiotic. The unavoidable conclusion is that treatment failures are exceedingly rare. All physicians should reconsider their treatment of patients presenting with EM. The failure rate observed in this study makes longer courses of antibiotics unsustainable considering the risks and benefits. These investigators should be praised for this important contribution.

**Acknowledgments**

*Potential conflicts of interest.* R.J.D. is an officer of Biopeptides Corporation. Biopeptides Corporation is developing new laboratory diagnostics for Lyme disease.

**References**


522 • CID 2010:50 (15 February) • EDITORIAL COMMENTARY