EDITORIALS

Time for a Different Approach to Lyme Disease and Long-Term Symptoms

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The condition of most patients with Lyme disease improves after initial antibiotic therapy; however, 10 to 20% of treated patients may have lingering symptoms of fatigue, musculoskeletal pains, disrupted sleep, and lack of customary mental functions. The plausible idea that additional antimicrobial therapy for potentially persistent bacterial infection would foster improvement has been a touchstone of hope in the 40 years since discovery of the disease in the mid-1970s. Patients with long-standing symptoms and well-documented, previously treated Lyme disease have been the focus of a number of randomized, placebo-controlled studies in North America that assessed whether additional antibiotic therapy offers a reduction in symptoms.[1] Because molecular or culture methods did not find evidence of persistent infection in the enrolled patients, it was perhaps not surprising that additional antimicrobial therapy yielded neither clinically significant nor durable reductions in symptoms as compared with placebo.

Despite these findings, proponents of longer-term antibiotic therapy prescribe them for people living with stubborn symptoms — whether the symptoms are called the post-treatment Lyme disease syndrome or the more nebulous chronic Lyme disease that is often not associated with customary, objective measures of *Borrelia burgdorferi* infection.[2] Weaker evidence, including findings from observational studies that suggest an improvement driven by antibiotic treatment, are commonly cited as a rationale for longer-term therapy, though such conclusions should be moderated to take into account the placebo response of 36% that was observed in the randomized, controlled trials.[3]

In this issue of the *Journal*, Berende and colleagues report the results of the Persistent Lyme Empiric Antibiotic Study Europe (PLEASE) trial, which again investigated whether longer-term antibiotic therapy provides relief for subjective symptoms (lasting an average of more than 2 years) attributed to Lyme disease.[4] The trial design is interesting in several respects. First, the trial involved a European population, and the species of *B. burgdorferi* sensu lato that circulate in Europe, including *B. afzelii* and *B. garinii*, differ from those that circulate in North America. The infections associated with these species can manifest differently than do infections from North American species, such as with a longer initial duration of illness.[5] Second, only 96 of 280 participants (34%) had objective evidence of Lyme disease such as the characteristic rash, erythema migrans. This means that nearly two thirds of their study population had nonspecific symptoms that were attributed to Lyme disease solely on the basis of positive IgM or IgG (or both) immunoblot assays for *B. burgdorferi*. Such laboratory findings do not necessarily imply causation and could represent either false positive results or remote infection, since antibody titers can remain elevated for decades.[6,7] Finally, all patients in the three study groups that were included in this trial received intravenous ceftriaxone for 2 weeks before the 12-week randomized phase, which means that there was no true placebo component; the two active oral study regimens (doxycycline and clarithromycin with hydroxychloroquine) that were used in the 12-week randomized phase are both known to produce antiinflammatory effects in addition to their antimicrobial properties.

The takeaway from this well-performed study is that 12 weeks of therapy with either doxycycline or clarithromycin plus hydroxychloroquine yielded no additional benefit over placebo with respect to serial mental and physical health-related quality-of-life measures that spanned the duration of the study through 38 weeks after the active study drugs or placebo were discontinued. Although some may attribute the improvement seen in all three study groups to the initial 2 weeks of ceftriaxone received by everyone, this improvement might be explained by the 11% of patients who had not received any previous antibiotic therapy before study entry.

Critics may rightly say that this trial does not truly capture with certainty the consequences of bona fide Lyme disease. However, studies with more stringent inclusion criteria have already been conducted, and the approach used by Berende and colleagues probably reflects the common practice in ambulatory care settings, in which patient presentations of fatigue or nonspecific pain prompt serologic checks for Lyme disease, despite evidence suggesting that these tests will not identify a probable cause or result in a treatment benefit.[8] Because antibiotics that target infection generally return a benefit before 12 weeks, arguments for a favorable delayed-onset outcome with even longer courses are weak. Moreover, although the side effects were mostly minor, 68.6% of the patients reported at least one adverse reaction that was thought to be drug related, which should lessen the temptation among physicians to prescribe longer courses of antibiotics just in case they might help.

Where does this leave patients who are living with symptoms possibly related to Lyme disease, and where does this lead their clinicians? The report by Berende et al. is an important contribution and contains a simple message, regardless of the diagnosis given to those enrolled in the trial. Patients with subjective, vexing symptoms attributed to Lyme disease should not anticipate that even longer courses of antibiotics will produce relief, a finding that is in concert with results from previous trials. These patients may, however, take small comfort in a recent study of longer-term outcomes after culture-confirmed Lyme disease that showed that mental and physical health scores had returned to baseline scores similar to those of the age-adjusted U.S. population.[9]

Though prolonged antibiotic therapy is not the answer, we do not know what is truly helpful. Our personal approach is centered on making thorough assessments for alternative diagnoses such as sleep disorders and providing recommendations borrowed from practices in general medicine. Such a patchwork approach should make it clear that chronic health problems such as fatigue and pain that afflict millions of people worldwide urgently require answers with respect to the causal mechanisms and better approaches for a quicker recovery, regardless of whether the problems were triggered by *B. burgdorferi* or by some other process. One example of an innovative investigation is the recent finding of differential gene expression suggesting post-infectious cytokine or metabolic changes after Lyme disease, as compared with other acute infections.[10] Future research efforts should continue to explore such different strategies that may lead to proven options for helping our patients.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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