What Constitutes Appropriate Treatment of Post-Lyme Disease Symptoms and Other Pain and Fatigue Syndromes?

Allen C. Steere and Sheila L. Arvikar
Division of Rheumatology, Allergy and Immunology, Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, Harvard Medical School, Boston

(See the Major Article by Lantos on pages 1776–82.)

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Lyme disease, which is caused by the tick-borne spirochete *Borrelia burgdorferi*, is estimated to cause over 300,000 cases annually in the United States, primarily in northeastern and mid-Atlantic States [1]. In untreated patients, the infection typically occurs in stages with different manifestations at each stage [2]. It usually begins during summer with an expanding skin lesion, erythema migrans, sometimes followed weeks later by neurologic or cardiac abnormalities, and often followed months later by arthritis, or rarely a subtle encephalopathy or polyneuropathy. With late stage abnormalities, patients often have few, if any, systemic symptoms. Most patients respond well to appropriate antibiotic regimens for the stage of disease, as recommended by the Infectious Diseases Society of America (IDSA) [3]. However, despite antibiotic therapy, some patients experience post-infectious signs or symptoms, which can be quite disabling.

The only post-infectious picture with a well-defined pathologic correlate (proliferative synovitis) is antibiotic-refractory Lyme arthritis [4]. In such patients, inflammatory arthritis persists for months or several years after apparent spirochetal killing with oral and intravenous (IV) antibiotics. Excessive inflammation, immune dysregulation, and infection-induced autoimmunity are thought to play a role in this disease outcome [5]. After antibiotic therapy, treatment with disease modifying antirheumatic drugs, such as methotrexate or synovectomy, is often beneficial [4].

However, the term post-Lyme disease symptoms or syndrome usually refers to subjective pain, neurocognitive, or fatigue symptoms that persist after antibiotic therapy. At one end of the spectrum, one or a few subjective symptoms such as malaise and fatigue or minor joint symptoms may persist for several months after antibiotic treatment of erythema migrans [6]. In a recent study, a subgroup of such patients had persistently high levels of interleukin 23, suggesting that hyperactive Th17 immune responses may have a role in their delayed recovery from the disease [7]. At the other end of the spectrum, and often after a gap of several months after treatment of the infection, patients may develop chronic, disabling joint and muscle pain, neurocognitive difficulties, and incapacitating fatigue that persist for years after antibiotic treatment for Lyme disease [8]. This chronic pain and fatigue syndrome may have different pathogenic mechanisms than those involved when symptoms resolve rather soon after antibiotic therapy.

This chronic syndrome, which sometimes meets criteria for fibromyalgia or chronic fatigue syndrome, is not specific for Lyme disease [8]. Such symptoms may follow other infections or physical or emotional trauma, or the inciting cause may not be apparent. Moreover, using the serologic criteria of the Centers for Disease Control and Prevention [9], most patients with the diagnosis of “chronic Lyme disease” have little or no evidence of past or present *B. burgdorferi* infection [8]. Thus, in general usage, the term “chronic Lyme disease” has come to have a different and broader meaning than evidence-based descriptions of *B. burgdorferi* infection, and only a minority of patients with this diagnosis has evidence of preceding *B. burgdorferi* infection.
Some patients diagnosed with “chronic Lyme disease” are treated with months or years of antibiotic therapy, often with multiple antibiotics, which have the potential for harmful adverse effects. Antibiotics are usually prescribed based on the idea that these patients have persistent spirochetal infection. However, antibiotics have other effects than spirochetal killing. Interestingly, preclinical studies with minocycline and ceftriaxone have shown efficacy in neuropathic pain models [10]. Both of these antibiotics increase glutamate transport across neural membranes, which help to protect neuronal cells [11]. Thus, improvement with antibiotics may result from other mechanisms than spirochetal killing.

Yet, in patients with chronic, disabling post-Lyme pain, neurocognitive or fatigue symptoms, 4 double-blind, placebo-controlled trials of 4 to 10 weeks of intravenous ceftriaxone, in 2 instances followed by 8 weeks of oral doxycycline, showed similar results in antibiotic-treated and placebo-treated patients [12–14]. In 2 trials, no significant differences were found between the antibiotic and placebo groups [12]. In the third trial, a significant difference was noted only in fatigue for 1–6 months after therapy [13]. In the fourth trial, significant differences were initially observed in pain and fatigue, but beneficial effects were not sustained [14]. Moreover, in all 4 trials, microbiologic measures of infection were negative. Thus, IDSA expert panels recommend against months or years of antibiotic therapy for Lyme disease, concluding that any possible benefit is outweighed by the risk of potentially harmful adverse effects [3, 15].

Current research suggests that chronic pain and fatigue syndromes may be part of a central sensitization syndrome, which may follow Lyme disease or other infections [16] or other noninfectious stimuli. In such patients, intense, sustained activity in first-order peripheral neurons elicits neuronal and biochemical processing at central synapses, known as central sensitization. When central sensitization is associated with infection, hyperalgesia (pain hypersensitivity) may not reset appropriately after the infection, and the increased sensitization to pain signals may last for months or years. Additionally, central sensitization may result in an array of other symptoms including lethargy, sleep disorder, neurocognitive difficulties, anxiety, and depression, which can be further debilitating. In such patients, the lack of objective findings or abnormal test results and difficulty in treatment are often frustrating to both patients and physicians, and this has led to an industry of unorthodox therapies.

The article by Lantos and colleagues in the current issue of Clinical Infectious Diseases demonstrates the scope of this problem, revealing a wide array of more than 30 unorthodox alternative therapies that are marketed for the treatment of “chronic Lyme disease” [17]. The authors highlight the lack of scientific evidence behind most of these therapies and their potential for harmful effects. However, in preliminary studies, naltrexone, which was included here, has shown some benefit in fibromyalgia [18]. In addition, fish oil may have anti-inflammatory properties, but its utility in pain syndromes is less clear.

Then, how do we help such patients? We try to begin by remembering the Hippocratic Oath, which states, “first, do no harm.” Borrowing from treatment studies of fibromyalgia, multidisciplinary approaches that combine medications with nonpharmacologic therapies are usually best [19]. Possible medications for reducing pain signals include gabapentin, pregabaline, dual serotonin and norepinephrine reuptake inhibitors, or tricyclic antidepressants, such as amitriptyline, which may also aid in restoring sleep cycles. In addition, selective serotonin reuptake inhibitors may help in the control of coexistent mood disorders.

Nonpharmacologic approaches include cognitive behavioral therapy in groups with other patients, under the guidance of a trained health professional, which is a valuable way to learn coping skills, particularly stress reduction. Moreover, a number of safe alternative therapies, can be helpful, and in some cases, they may be as or more effective than pharmacotherapy [20]. For example, 2 randomized, controlled trials showed the effectiveness of tai chi, a mind-body practice, in improving fibromyalgia symptoms [20, 21]. Other complementary therapies include meditation, yoga, qi-gong, acupuncture, massage, or low-impact aerobic exercise programs, which include walking or aquatic exercise. Finally, as with the treatment of any disease, empathetic engagement by the patient’s physician is a vital component of a successful outcome.