Point: Antibiotic Therapy Is Not the Answer for Patients with Persisting Symptoms Attributable to Lyme Disease

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(See the counterpoint by Stricker on pages 149–57)

It is not well understood why some patients develop a subjective syndrome that includes considerable fatigue, musculoskeletal aches, and neurocognitive dysfunction after receiving standard antibiotic courses for the treatment of Lyme disease. Some practitioners use the term "chronic Lyme disease" and order prolonged courses of oral and parenteral antibiotics, believing that persistent infection with *Borrelia burgdorferi* is responsible. However, well-performed prospective studies have found neither evidence of chronic infection nor a benefit worthy of long-term antibiotic therapy for these patients. Such extended antibiotic therapy poses hazards and cannot be viewed as acceptable. The term "chronic Lyme disease" should be discarded as misleading; rather, the term "post–Lyme disease syndrome" better reflects the postinfectious nature of this condition. Further research is necessary to understand possible mechanisms of these chronic symptoms following Lyme disease as well as to find effective therapies.

INTRODUCTION

> There are two kinds of light—the glow that illuminates, and the glare that obscures.
>
> —James Thurber

Considerable public debate has arisen regarding the role of antibiotic therapy for patients who have persisting symptoms attributed to Lyme disease. The profile of Lyme disease has become prominent in part as a result of its emergence as the most common vectorborne disease reported in the United States since its first description 30 years ago [1, 2]. The causative spirochete, *Borrelia burgdorferi*, is transmitted by the bite of the *Ixodes* tick in North America.

Early Lyme disease may be localized, such as in erythema migrans (the characteristic round or ovoid expansile rash at the site of the tick bite), or disseminated, as indicated by spread from the original focus; the most familiar manifestations include multiple erythema migrans and musculoskeletal, CNS, and cardiac involvement. Antibiotics such as doxycycline or amoxicillin are effective therapy for the majority of patients with early Lyme disease, with courses of 10–21 days. Parenteral drug therapy (most commonly ceftriaxone) is reserved for involvement of the CNS, for symptomatic cardiac involvement, or in late Lyme disease, such as in cases of oral antibiotic–refractory chronic Lyme arthritis [3]. These recommendations for Lyme disease treatment have been challenged, but they are not the focus of this article [4].

Instead, the contested stage is rather confusingly populated by cases that some persons label "chronic Lyme disease." A small set of practitioners have advanced the notion that patients with chronic, subjective symptoms, such as fatigue, musculoskeletal aches, and neurocognitive symptoms, have ever-present infection

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with *B. burgdorferi* that requires treatment, with months to years of antibiotics often prescribed in combination or by parenteral administration [4, 5]. Although a small minority of patients with bona fide Lyme disease have persisting, subjective symptoms despite receipt of antibiotic treatment, realistic evidence that active infection accounts for this adverse outcome is lacking [6].

Because use of the term "chronic Lyme disease" by some groups has blurred the exact role played by *B. burgdorferi,* an alternative description, "post–Lyme disease syndrome," has been advocated to better separate patients who have resolution of objective symptoms of infection yet continue with these subjective complaints for many months or even years [3]. This helps avoid potential confusion with late Lyme disease, which requires antibiotic treatment for such objective symptoms as chronic Lyme arthritis and neuroborreliosis. The proposed definition of post–Lyme disease syndrome includes Lyme disease as defined by Centers for Disease Control and Prevention criteria [7]; conclusion of an appropriate course of antibiotics, with resolution or stabilization of objective manifestation(s) of Lyme disease; presence of symptoms (such as fatigue, widespread musculoskeletal pain, cognitive problems, and substantial reduction in functional activities) >6 months after Lyme disease diagnosis, while excluding patients with documented coinfections, such as *Babesia* or *Ehrlichia* coinfection; presence of objective evidence of active Lyme disease; or presence of preexisting conditions, such as fibromyalgia or chronic fatigue syndrome, or an underlying condition that can simulate the symptom complex of Lyme disease (e.g., thyroid disease, psychiatric conditions, and anemia) [3].

The recently updated, evidence-based guidelines released by the Infectious Diseases Society of America (IDSA) have introduced few changes to the recommended Lyme disease treatments, compared with the first version, which was released in the year 2000 [3, 8]. Among the most fundamental changes regarding Lyme disease was the addition of high-quality evidence to reinforce certain advice, such as the duration of antibiotic therapy. Curiously, these strengthened recommendations have been greeted by some with heated debate, including a demand to retract the IDSA guideline [9]. This article will not provide an exhaustive review of the topic; rather, it will reflect on relevant evidence and arguments why long-term use of antibiotics for persistent Lyme disease symptoms hews neither to good science nor the best interest of patients.

LYME DISEASE: OUTCOMES AFTER INITIAL ANTIBIOTIC THERAPY

Untreated Lyme disease may progress to cause later symptoms of disease [10]. Use of antibiotic treatment for Lyme disease tends to be highly successful, with resolution of objective and subjective complaints in most patients who are treated for early disease [11, 12]. Uncommon objective problems after therapy are few and include either meningitis or facial palsy, which often develop within the first week of oral therapy [11, 13]. Persisting problems that occur despite antibiotic therapy may afflict ~10% of patients with late Lyme arthritis [13]. This persistent, chronic Lyme arthritis does not seem to be due to active infection with *B. burgdorferi* but, rather, to immunological responses that may have a basis in certain human histocompatibility leukocyte antigen haplotypes [14, 15].

Subjective problems, such as fatigue and musculoskeletal aches, may linger after treatment for erythema migrans, the frequency of which may result in part from when therapy was initiated after the symptom onset. In one prospective study, 24% of patients complained of mild symptoms at 3 months after treatment of erythema migrans, whereas 17% still had symptoms at 12 months [13]. Observation of a group with culture-confirmed Lyme disease found that up to 10% of patients had symptoms that persisted beyond 1 year (the patients were observed for a mean of 5.6 years), but only 4% of patients reported complaints at every visit [16]. This slow improvement appears to be more common in patients with disseminated disease and may be due to residual inflammatory mechanisms or, perhaps, alternative disease processes unrelated to *B. burgdorferi* infection.

The duration of initial antibiotic therapy for Lyme disease has been studied in several situations and does not appear to correlate with any differential in the resolution of these chronic, subjective complaints. Prospective studies of early Lyme disease failed to find a benefit associated with longer courses of antibiotic therapy [13, 17]. Examination of management of late Lyme disease found no statistical difference between groups that received either 14 or 28 days of ceftriaxone therapy [18].

Several confounding factors bedevil the evaluation of patients with subjective symptoms after receiving a diagnosis of and treatment for Lyme disease. First, many patients who are told that they have Lyme disease may not have this diagnosis. For example, 788 patients presenting to a tertiary care center with the complaint of Lyme disease found that 57% did not have Lyme disease but, rather, a symptom complex better explained by fibromyalgia or chronic fatigue syndrome, whereas 20% were found to have prior Lyme disease without need for additional antibiotics [19]. Some patients are told they have chronic Lyme disease based on unexplained symptoms without objective or valid laboratory evidence of infection [5]. Moreover, other patients are advised improperly they have Lyme disease based on Lyme IgM western blot assays which should not be relied on for diagnosis of vague chronic symptoms because of high rates of false-positive results [20]. Others are investigated using certain unvalidated assays, such as the Lyme urine antigen, or are

evaluated employing tests such as a *B. burgdorferi* PCR on inappropriate specimens, perhaps leading to erroneous diagnoses of active *B. burgdorferi* infection [21, 22].

Second, the presence of subjective symptoms in the normal background population creates considerable "noise" that may be difficult to separate from patients who truly have a new symptom set after experiencing Lyme disease, compared with those who may have had similar preexisting symptoms or who would have developed problems regardless of recent *B. burgdorferi* infection. Fatigue, neurocognitive dysfunction, and musculoskeletal aches can often be found in the so-called "normal" populations at rates as high as or higher than what has been described in relation to Lyme disease. Some guidance may be derived from large surveys, such as a study of a group of nondeployed military personnel used as a control for investigation of the Gulf War syndrome, among whom rates of depression (10.9%), anxiety (1.8%), alcohol abuse (12.6%), and fibromyalgia (9.6%) were substantial [23]. Other population surveys have included findings of chronic fatigue (20%–30%), arthritis (21.5%), serious pain (3.7%–12.1%), and fibromyalgia (2%) [24–28]. Even if substantial overreporting of symptoms occurred, the basic point is that background problems in the population make interpretation of any subjective symptoms complex difficult, whether the symptoms are due to Lyme disease or to another disorder. In part, this is also why there have been long-standing directives not to perform Lyme diagnostic testing for subjects with only subjective complaints—because of the high potential for false-positive results [21, 29, 30].

Finally, use of the "chronic Lyme disease" tag for some patients, especially when there has been a questionable diagnosis of *B. burgdorferi* infection, could be seen as a labeling of a functional syndrome that medical science cannot easily explain or solve [31, 32]. Over the years, other attempted explanations for the etiology of chronic fatigue and other subjective complaints have included Epstein-Barr virus infection, chronic candidiasis, and even immunization [33–35]. Use of a medical definition such as "chronic Lyme disease" for these problems can be self-perpetuating, as it can reinforce symptoms.

EVIDENCE REGARDING TREATMENT OF CHRONIC SYMPTOMS ATTRIBUTED TO LYME DISEASE

In an effort to address the role of antibiotic therapy for patients with subjective symptoms of post–Lyme disease syndrome, a large, multicenter, prospective trial investigated both *B. burgdorferi*–seropositive and –seronegative patients, all of whom had well-documented Lyme disease and had received prior antibiotic therapy [36]. These patients had persistent complaints of musculoskeletal pain, with neurocognitive symptoms, fatigue, and dysesthesia, that averaged 4 years. They were randomized to receive 2 g of ceftriaxone daily for 30 days, followed by doxycycline (200 mg daily for 60 days), compared with a matched placebo group. The primary outcome was the health outcomes score SF-36 used to assess the responses to the intervention. The study was halted early by the data monitoring board when no statistical difference was seen between the 2 groups that were observed through day 180 after treatment. This study has been criticized by those who favor long-term antibiotic therapy as being insufficient in duration and antibiotic dosage, despite the inability to find any objective evidence of active *B. burgdorferi* infection [4, 36].

The only other prospective trial published was a smaller, single-center study that enrolled 55 patients with post–Lyme disease syndrome symptoms who experienced severe fatigue, as assessed by an 11-item questionnaire [37]. Three primary outcomes examined at the end point of 6 months included changes in the fatigue score, mental processing speed, and clearance of an experimental borrelial marker in the CSF after receiving either 28 days of ceftriaxone (2 g per day) or placebo. The results have to be analyzed in light of the fact that full study blinding was not achieved, and more patients were lost from the placebo arm than from the treatment arm. The investigators found that there was a modest benefit with a lower fatigue score among those receiving ceftriaxone, although there was no change in the other end points, such as neurocognitive function or the CSF biomarker. Because of serious adverse effects, 4 (7%) of 55 patients were hospitalized with complications of intravenous therapy; study investigators concluded that parental antibiotic therapy could not be recommended, because the single subjective improved measure could not be justified against the considerable complication rate.

Why is there a belief in some quarters that patients benefit from antibiotic therapy for the persisting symptoms of Lyme disease, despite these 2 prospective studies that failed to show worthwhile benefit? Some published data suggest benefit from long-term administration of treatment, but these studies suffer from open-label design and nonstandard applications of the Lyme disease diagnosis and serologic testing that make it difficult to understand whether enrollees truly had Lyme disease or merely benefited from placebo effects or time [38–40]. Because prospective studies suggest that approximately one-third of patients find improvement over time, regardless of intervention [36], practitioners who routinely administer long-term antibiotics could be falsely encouraged by their own clinical observations as they witness only antibiotic administration. Moreover, antibiotics could have their own immunomodulatory activities independent of anti-infective effects, and indeed, short-term benefit at 3 months was identified using a drug such as doxycycline in a prospective study of Gulf War syndrome, although this effect waned at 6 months [41, 42].

BIOLOGICAL PLAUSIBILITY

Studies designed to investigate prospectively whether *B. burgdorferi* can be recovered after antibiotic therapy have found evidence of the organism neither by skin biopsy culture in the area of prior erythema migrans nor by culture or PCR evidence with multiple samplings of plasma or CSF, in the largest study of patients with post–Lyme disease symptoms [36, 43, 44]. Other studies said to show such persistent evidence of *B. burgdorferi* suffer from inability to replicate findings, inappropriate specimen testing, use of unvalidated tests, or inability to exclude reinfection or test contamination (see Wormser et al. [3] for a review). Suggestions that *B. burgdorferi* can survive despite antibiotic therapy by adopting a cystic form has only been seen in certain in vitro conditions and is unproven in humans [45]. Another hypothesis—that *B. burgdorferi* becomes latent during an intracellular phase of infection—remains without solid proof and stands in counterpoint to its known extracellular lifestyle [46, 47].

From a general perspective, no other spirochetal disorders appear to require long-term therapy for successful treatment, including tertiary syphilis or neurosyphilis. Both conditions respond to 2-week courses of parenteral penicillin therapy, with objective measures in cases of relapse [48, 49]. Description of antibiotic resistance in *B. burgdorferi* has not yet been documented in vitro or as evidence for treatment failure [50]. For other infectious diseases that require long-term therapy—for example, tuberculosis or chronic Q fever—recommendations have evolved, because shorter-course therapy yields insufficient resolution and leads to objective relapse of infection [51, 52]. The rationale to use antibiotics in these scenarios is buttressed by supportive evidence, such as results of culture, serologic testing, or other quantitative measurements, in contradistinction to patients who experience posttreatment symptoms of Lyme disease.

Postinfectious fatigue syndromes are not unique to Lyme disease, and at least with our current understanding, they are defined by the lack of evident active infection. A recent prospective cohort study performed with patients who had acute Epstein-Barr virus infection, Ross River virus infection, or acute Q fever found that ~12% experienced fatigue, musculoskeletal problems, mood disturbances, or neurocognitive problems at 6 months after the initial onset, regardless of infection [53]. Other described infections that can yield a chronic fatigue-like syndrome afterwards include *Brucella* infection, parvovirus infection, viral hepatitis, and even toxin-mediated processes [54–57]. Although the cause for postinfectious fatigue is unknown, some recent investigations have focused on neurohumoral mechanisms or mitochondrial dysfunction, as opposed to an actively infectious explanation [58, 59]. Whether microbiologic debris or other changes immunologically drive these problems in certain individuals is unknown.

CONCLUSIONS

The 2 existing placebo-controlled trials do not support the use of long-term antibiotics for the treatment of chronic subjective symptoms attributable to Lyme disease [36, 37]. Given the weight of this evidence, the burden of proof regarding human persistent *B. burgdorferi* infection, or the benefit of long-term antibiotic therapy must rest with those advocates who now use debatable theory and less robust data to argue their points. Protracted courses of antibiotics for post–Lyme disease syndrome do not result in the kind of efficacious benefit normally associated with the resolution of infection, and they may be injurious, with complications related to catheters, biliary disease, *Clostridium difficile* infection, and promotion of antibiotic resistance [60–62].

Unfortunately, prospective studies with other therapies have not been performed for patients with persisting symptoms after Lyme disease. Understanding why some patients continue with symptoms after receiving antibiotics for Lyme disease clearly deserves more study, to elucidate mechanisms and to develop beneficial therapies. For now, the best medical care should only rest on thorough exclusion other treatable disorders, use of individualized symptomatic treatment, and the foundation of an empathetic and trusting patient-physician relationship.

This highly vocal debate probably more reflects the unmet needs of many patients and the frustrations of our incomplete understanding of post–Lyme disease syndrome. Passions will likely run high until progress can assuage this uncertainty and provide proven, effective therapy for these patients.

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