IDSA LECTURE

Counterpoint: Long-Term Antibiotic Therapy Improves Persistent Symptoms Associated with Lyme Disease

Raphael B. Stricker

International Lyme and Associated Diseases Society, Bethesda, Maryland

(See the point by Auwaerter on pages 143–8)

Background. Controversy exists regarding the diagnosis and treatment of Lyme disease. Patients with persistent symptoms after standard (2–4-week) antibiotic therapy for this tickborne illness have been denied further antibiotic treatment as a result of the perception that long-term infection with the Lyme spirochete, *Borrelia burgdorferi,* and associated tickborne pathogens is rare or nonexistent.

Methods. I review the pathophysiology of *B. burgdorferi* infection and the peer-reviewed literature on diagnostic Lyme disease testing, standard treatment results, and coinfection with tickborne agents, such as *Babesia, Anaplasma, Ehrlichia,* and *Bartonella* species. I also examine uncontrolled and controlled trials of prolonged antibiotic therapy in patients with persistent symptoms of Lyme disease.

Results. The complex "stealth" pathology of *B. burgdorferi* allows the spirochete to invade diverse tissues, elude the immune response, and establish long-term infection. Commercial testing for Lyme disease is highly specific but relatively insensitive, especially during the later stages of disease. Numerous studies have documented the failure of standard antibiotic therapy in patients with Lyme disease. Previous uncontrolled trials and recent placebo-controlled trials suggest that prolonged antibiotic therapy (duration, >4 weeks) may be beneficial for patients with persistent Lyme disease symptoms. Tickborne coinfections may increase the severity and duration of infection with *B. burgdorferi.*

Conclusions. Prolonged antibiotic therapy may be useful and justifiable in patients with persistent symptoms of Lyme disease and coinfection with tickborne agents.

Lyme disease is a controversial illness [1–6]. The classic features of the disease include receipt of a tick bite followed by the so-called erythema migrans or "bullseye" rash and significant joint swelling typical of arthritis. Unfortunately, the classic features of this tickborne disease are not always present. For example, only 50%–60% of patients with Lyme disease recall having received a tick bite, and often the erythema migrans rash is absent or not in the shape of a bullseye [5, 6]. According to health departments around the United States, the typical bullseye rash is only reported in 35%–60% of patients with Lyme disease [7, 8]. Furthermore, frank arthritis is only seen in 20%–30% of patients with Lyme disease [1, 2]. Thus, the classic features of the disease may be absent, and the diagnosis may be easily missed [1–4].

In the absence of typical features of Lyme disease, patients may go on to develop a syndrome with multiple nonspecific symptoms that affect various organ systems, including the joints, muscles, nerves, brain, and heart. The myriad symptoms prompt the question whether this is "post–Lyme disease syndrome," a poorly defined entity triggered by Lyme disease, or whether these symptoms are caused by persistent infection with the Lyme spirochete, *Borrelia burgdorferi.* To address this question, we must first examine the pathophysiology of the disease.

PATHOPHYSIOLOGY OF LYME DISEASE

B. burgdorferi is a fascinating bacterium [9, 10]. It has >1500 gene sequences with at least 132 functioning

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Reprints or correspondence: Dr. Raphael B. Stricker, 450 Sutter St., Ste. 1504, San Francisco, CA 94108 (rstricker@usmamed.com).

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genes. In contrast, *Treponema pallidum,* the spirochetal agent of syphilis, has only 22 functioning genes. The genetic makeup of *B. burgdorferi* is quite unusual. It has a linear chromosome and 21 plasmids, which are extrachromosomal strands of DNA. This is 3 times more plasmids than any other known bacteria (*Chlamydia* comes in a distant second, with 7 plasmids). Plasmids are thought to give bacteria a kind of "rapid response" system that allows them to adapt very rapidly to changes in the environment, and the complex genetic structure of *B. burgdorferi* suggests that this is a highly adaptable organism [9, 10].

In addition to its complex genetic makeup, *B. burgdorferi* engages in so-called "stealth pathology" to evade the human immune response [11–50]. Stealth pathology involves 4 basic strategies: immunosuppression; genetic, phase, and antigenic variation; physical seclusion; and secreted factors (table 1). These strategies are outlined below.

IMMUNOSUPPRESSION

During a tick bite and before transmission of the Lyme spirochete, tick saliva containing analgesic, anticoagulant, and immunosuppressive factors is expressed into the wound, allowing the spirochete to penetrate the skin and evade the local immune response [11–13]. *B. burgdorferi* also induces immunosuppression by complement inhibition and induction of inhibitory cytokines, such as IL-10. In addition, the bacterium induces monocyte and lymphocyte tolerization and antibody sequestration in immune complexes—all mechanisms of evading the immune response [14–19].

GENETIC, PHASE, AND ANTIGENIC VARIATION

B. burgdorferi engages in genetic, phase, and antigenic variation that shares various features with other organisms [20–23]. For example, gene switching is similar to what is seen with trypanosomes, mutation and recombination are typical of HIV, variable antigen expression is seen with *Neisseria* species, autoinduction of dormant organisms occurs in mycobacterial infection, and fibronectin binding occurs with staphylococcal and streptococcal infection.

B. burgdorferi may assume a dormant state with cyst formation [24–29]. Although spirochetal persistence in the cyst form is a controversial issue, it has recently been shown that neutrophil calprotectin can induce a dormant state in the spirochete, allowing it to persist in tissue without replicating and providing the means to avoid antibiotics [30].

Although antibiotic resistance associated with gene mutation was previously thought to be rare in *B. burgdorferi* infection [31], recent studies have demonstrated gene mutations in the Lyme spirochete that confer in vitro resistance to various antibiotics [32, 33]. The clinical implication of these gene mutations is uncertain at present.

PHYSICAL SECLUSION

The Lyme spirochete uses physical seclusion at intracellular sites as a means of evading the immune response in multiple cell types, including synovial cells, endothelial cells, fibroblasts, macrophages, Kupffer cells, and neuronal cells [34–43]. In culture, *B. burgdorferi* can be grown in fibroblasts for >8 weeks, suggesting that the organism can thrive over long periods of time in the right place and under the right conditions.

Physical seclusion at extracellular sites, including the joints, eyes, and CNS, may also promote survival of the Lyme spirochete. In addition, *B. burgdorferi* engages in "cloaking" mechanisms by binding to proteoglycan, collagen, plasminogen, integrin, and fibronectin. These substances can mask the bacterium and make it invisible to the immune system [38–42].

SECRETED FACTORS

There are a number of factors that are secreted either by *B. burgdorferi* itself or in response to infection with the spirochete [44–51]. For a number of years, it has been known that *B. burgdorferi* secretes a hemolysin, although its function is uncertain [44]. More recently, the spirochete has been shown to elaborate porin and adhesin, 2 proteins that allow bacteria to adhere to cells and pierce the cell wall to gain entry [45].

Even more recently, *B. burgdorferi* was found to secrete pheromones, including AI-2, which is also secreted by mycobacteria [46–50]. This is the first time that a spirochete has been shown to secrete an autoinducer and suggests that the Lyme spirochete engages in autoresuscitation like other dormant organisms, such as the tubercle bacillus [46–50]. In addition, *B. burgdorferi* can induce secretion of aggrecanase, an enzyme that damages cartilage [51]. This may be a mechanism by which the bacterium induces damage and inflammation in joints. Armed with these weapons of "stealth pathology," the Lyme spirochete is a formidable infectious agent.

LABORATORY TESTING

Let's turn briefly to laboratory testing in Lyme disease. A major problem is that current commercial Lyme serologic tests are not sensitive enough for diagnosis, especially during the later stages of disease [52–64]. The Centers for Disease Control and Prevention (CDC) advocates a "2-tier" testing system using an ELISA or immunofluorescence assay as a screening test, followed by a Western blot for confirmation if the result of the ELISA or immunofluorescence assay is positive. The CDC cautions, however, that the 2-tier system should only be used for surveillance purposes and not for diagnosis, and the reason for this warning is clear: although the 2-tier system has a very high specificity (99%–100%), thus avoiding the false-positive results that are the bane of surveillance statistics, it has relatively poor

Table 1. "Stealth" pathology of *Borrelia burgdorferi.*

Immunosuppression
Tick saliva components
Complement inhibition
Inhibitory cytokine induction (IL-10)
Lymphocyte/monocyte tolerization
Antibody sequestration in immune complexes
Genetic, phase, and antigenic variation
Gene switching (trypanosomes)
Mutation/recombination (HIV)
Variable antigen expression (*Neisseria* species)
Dormant state, autoinduction (*Mycobacterium* species)
Fibronectin binding (*Staphylococcus* and *Streptococcus* species)
Physical seclusion
Intracellular sites
Multiple cell types (synovial cells, endothelial cells, fibroblasts, macrophages, Kupffer cells, and nerve cells)
Persistent infection in vitro (8 weeks)
Extracellular sites
Privileged sites (joints, eyes, and CNS)
Cloaking mechanisms (binding to proteoglycan, collagen, plasminogen, integrin, and fibronectin)
Secreted factors
Hemolysin (BlyB)
Porin (Oms 28)
Adhesin (Bgp)
Pheromones (DPD/AI-2)
Aggrecanase (ADAMTS-4)

NOTE. See text for explanation and references.

sensitivity (50%–75%), which limits its use as a diagnostic test for individual patients.

Other problems with current Lyme disease testing include omission of highly specific bands from the commercial Western blot, sex differences in test reactivity, and limitations of molecular testing, and these issues have been discussed in detail elsewhere [1, 56, 60–63]. Thus, the diagnosis of Lyme disease remains problematic, with as many as one-half of patients experiencing failure with the current 2-tier testing approach [52–64].

TREATMENT OF LYME DISEASE

With this background concerning the clinical diagnostic problems, complex pathophysiology, and testing difficulties related to *B. burgdorferi,* we arrive at the topic of this debate, which is treatment failure in Lyme disease. Documented treatment failure with culture-confirmed *B. burgdorferi* infection was first reported >17 years ago by Preac-Mursic et al. [65], so it was surprising to see a quotation in the *New York Times* by 2 members of the Infectious Diseases Society of America (IDSA) Lyme disease guidelines committee stating that "[there] is no credible scientific evidence for the persistence of symptomatic *B. burgdorferi* infection after antibiotic treatment" [66]. Let's review the "credible scientific evidence" for persistence of this infection taken from articles published over the past 17 years.

ANIMAL MODELS

We can start with animal models of Lyme disease [67–75]. In the mouse, one study found that "persistence of spirochetes within macrophages provides a possible pathogenetic mechanism for chronic or recurring Lyme disease" [67, p. 909]. In another study, "nine months after treatment, low levels of spirochete DNA could be detected by real time PCR in a subset of antibiotic treated mice" [68, p. 1430]. So at least in the mouse model, spirochetes may persist after appropriate treatment.

Next is the dog model—a particularly convincing model, because Straubinger et al. [69] revealed that, in dogs that had been experimentally infected with *B. burgdorferi* by tick exposure, treatment with high doses of amoxicillin or doxycycline for 30 days diminished persistent infection but failed to eliminate it. Furthermore, when dogs were observed for a 500-day postinfection period (the equivalent of 3–4 human years), *B. burgdorferi* DNA was detectable at low levels in multiple tissue samples obtained from the dogs, despite the administration of "adequate" antibiotic treatment [70].

Finally, in a model using our closest relative, the nonhuman primate macaque monkey, Pachner and colleagues [71–75] found that neurologic and cardiac disease were associated with persistent infection in these monkeys, and cytokine and gene expression related to persistent *B. burgdorferi* infection could be demonstrated >3 months after infection. In summary, these animal models provide "credible scientific evidence" for persistent infection in Lyme disease.

HUMAN STUDIES

Turning to human studies, there are a number of reports that show persistent symptoms of Lyme disease after short-term antibiotic therapy [76–96]. Persistent symptoms have been noted in 25%–80% of patients with Lyme disease after 2–4 weeks of antibiotic therapy [76–87]. Furthermore, infection that was determined to be persistent on the basis of either culture or PCR evidence has been documented in up to 40% of patients following receipt of the "adequate" antibiotic treatment recommended by the IDSA [88–96]. For example, positive culture and PCR results were found in synovium and synovial fluid specimens obtained from a patient 7 years after treatment [92], and a positive result was reported for a culture of an iris biopsy specimen obtained from a treated patient [93]. These reports suggest that short-term antibiotic therapy may suppress the Lyme spirochete but not eradicate it.

In another case, the patient's condition deteriorated despite receipt of repeated courses of antibiotic treatment over a 2-

Table 2. Results of placebo-controlled trials of antibiotic treatment in chronic Lyme disease.

Study	Year	Treatment	Results	Comments
Klempner et al. [101]	2001	IV Ctri for 4 weeks followed by oral doxycycline for 2 months vs. placebo	No improvement in fatigue or quality of life	Study was criticized because subjects had been sick an average of 4.7 years, and similar treatment had already failed; the treatment regimen was inadequate for degree of functional impairment [104]
Krupp et al. [102]	2003	IV Ctri for 4 weeks vs. placebo	SI in fatigue noted in 64% of treatment group, compared with 19% of control group; no improvement in cognition	The exact duration of illness was not stated (at least 6 months), and the treatment duration was relatively short; previously untreated patients fared significantly better than control subjects in terms of fatigue improvement (69% vs. 0%; $P<.01$)
Fallon [105]	2005	IV Ctri for 10 weeks vs. placebo	SI in cognitive and physical functioning at 12 weeks in treatment group, compared with control group	Improvement in physical functioning but not cognitive functioning was sustained in the treatment group at 24 weeks
Cameron [106]	2005	Oral amoxicillin for 3 months vs. placebo	SI in cognitive and physical functioning in treatment group, compared with control group	Treatment was successful in two-thirds of the patients who had the best initial quality of life, but it failed in one-third of the patients who had the worst initial quality of life

NOTE. IV Ctri, intravenous ceftriaxone; SI, significant improvement.

Table 3. Precedents for prolonged antibiotic therapy.

Disease	Organism	Treatment	Duration of treatment, months
Drug-susceptible tuberculosis	*Mycobacterium tuberculosis*	2–4 antibiotics	6–9
Multidrug-resistant tuberculosis	*M. tuberculosis*	3–5 antibiotics	18–24
Leprosy	*Mycobacterium leprae*	3–4 antibiotics	24
Atypical tuberculosis	*Mycobacterium chelonae*	Oral and intravenous antibiotics	6–12
Q fever endocarditis	*Coxiella burnetii*	2 antibiotics	36

NOTE. Data are based on [143–147].

year period. She received 12 months of intravenous antibiotic treatment, followed by 11 months of oral antibiotics, and her condition improved significantly [95]. Thus, this case report suggests that longer treatment may be beneficial in some patients with Lyme disease. Taken as a whole, these studies provide "credible scientific evidence" for persistence of *B. burgdorferi* infection after "adequate" short-term antibiotic treatment in humans.

That brings up the next question: does longer antibiotic treatment help in persistent Lyme disease? There have been a number of uncontrolled trials that support longer treatment of persistent disease symptoms [97–100]. The largest study included 277 patients who were treated with tetracycline for 1–11 months (mean duration, 4 months). The study showed that, after 2 months of therapy, 33% of patients had improvement in symptoms, but after 3 months of treatment, 61% of patients had decreased symptoms [97]. So this study suggests that longer treatment may result in better symptom outcome in Lyme disease. There have been other small, uncontrolled trials showing that longer treatment may have better symptom outcomes in patients with Lyme disease, including one trial that showed that patients who were re-treated with intravenous therapy had the greatest improvement in their symptoms [98–100].

In contrast to these uncontrolled trials, 2 randomized, placebo-controlled trials examined re-treatment of patients with persistent symptoms of Lyme disease (table 2) [101, 102]. Krupp et al. [102] studied 1 month of intravenous ceftriaxone, whereas Klempner et al. [101] studied 1 month of intravenous ceftriaxone followed by 2 months of oral doxycycline. The Krupp study showed improvement in fatigue with its 30-day treatment regimen, whereas the Klempner study showed no improvement in quality of life following re-treatment for 90 days. The main problem with these studies is that they included patients who had been symptomatic for an average of 4–5 years, and treatment with 1 month of intravenous antibiotics, with or without low-dose doxycycline, is insufficient for patients who have been sick this long [103, 104]. Thus, the generalizability of results in these highly selected patients with persistent Lyme disease is questionable [104].

In contrast to these studies, 2 placebo-controlled trials were presented in 2005 at the Columbia/Lyme Disease Association's annual meeting (table 2) [105, 106]. One study involved oral amoxicillin for 3 months versus placebo for previously treated patients, and re-treatment was successful for the two-thirds of patients with the best initial quality of life. A second study administered intravenous ceftriaxone for 10 weeks to patients with persistent neurologic symptoms of Lyme disease, and these patients had significant cognitive improvement with this treatment. We look forward to publication of these 2 placebo-controlled trials, which show that longer courses of antibiotic therapy are useful in patients with persistent Lyme disease.

COINFECTION WITH TICKBORNE AGENTS

In addition to infection with *B. burgdorferi,* tickborne coinfections are being recognized more frequently. If a patient is treated for Lyme disease and has symptoms that have persisted or worsened, the lack of improvement may be due to the presence of *Babesia, Anaplasma, Ehrlichia,* or *Bartonella* coinfection [107–126]. Coinfection with *Babesia* and *Ehrlichia* has been shown to exacerbate Lyme disease in mouse models [108–110] and also in humans [111–118]. Traditionally, *Babesia*, *Anaplasma*, *Ehrlichia* and *Bartonella* are thought to produce acute fulminant infections, but in fact these pathogens may cause low-grade infections that can increase the severity and duration of Lyme disease [119–125].

A disturbing study from New Jersey examined the prevalence of coinfections in *Ixodes* ticks that transmit Lyme disease [126]. In that study, the prevalence of *B. burgdorferi* infection was 33.6%, but the prevalence of *Bartonella* infection was 34.5%. Thus, *Bartonella* species were found more often than the Lyme spirochete in these ticks. This observation presages a greater problem with *Bartonella* infection associated with tick exposure in the near future.

TREATMENT APPROACH TO CHRONIC LYME DISEASE

What is the approach for a patient who presents with persistent symptoms of Lyme disease [127–140]? First, the Lyme Western blot should be repeated, and coinfection testing should be performed by a laboratory that is proficient in tickborne disease analysis. At the same time, other medical problems that could

cause persistent symptoms should be ruled out. Measurement of the CD57 natural killer cell level, which is an immunologic marker that can be used to monitor treatment in chronic Lyme disease, should be performed [129–131]. If neurologic symptoms are severe, a single-photon emission CT SPECT brain scan should be obtained, to see how much inflammation is present in the brain. Neuropsychiatric evaluation may also be helpful [132].

On the basis of these results, coinfections should be treated first, if any are present, and then oral or parenteral antibiotics should be used to treat symptoms of persistent Lyme disease. Antibiotic therapy should be administered in a rotating and open-ended manner, in conjunction with probiotics, to minimize adverse effects [133–136]. Monitoring of clinical symptoms, CD57 natural killer cell levels, and markers of inflammation should be performed in conjunction with treatment [137–140].

This approach differs from the recommendations of the current IDSA guidelines, which do not recognize persistent infection in chronic Lyme disease [141]. However, the treatment approach is consistent with the guidelines of the International Lyme and Associated Diseases Society, which mandates treatment for persistent infection in patients with chronic Lyme disease symptoms [142]. It is helpful to recall that *B. burgdorferi* shares certain pathophysiological features with mycobacterial infection and other chronic infections (table 1), that these infections may require prolonged antibiotic therapy (6–36 months), and that the risks of long-term treatment are considered justifiable in those situations (table 3) [143–147]. On the basis of the foregoing discussion, prolonged antibiotic therapy appears to be useful and justifiable in chronic Lyme disease.

In summary, >18,000 scientific articles have been written about Lyme disease. Some of these articles focus on the complex pathophysiology of *B. burgdorferi,* whereas others highlight the clinical uncertainty surrounding tickborne disease. Because the optimal therapy for this complicated illness is still in doubt, we must keep an open mind about the treatment of patients who present with persistent symptoms of Lyme and associated tickborne diseases.

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