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

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(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...
was previously thought to be rare in *B. burgdorferi*

tations is uncertain at present.

*Lyme* spirochete that confer in vitro resistance to various an-

rochete, allowing it to persist in tissue without replicating and

form is a controversial issue, it has recently been shown that

mation [24–29]. Although spirochetal persistence in the cyst

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 spi-

rochete, tick saliva containing analgesic, anticoagulant, and im-

munosuppressive factors is expressed into the wound, allowing

the spirochete to penetrate the skin and evade the local immune

response [11–50]. Stealth pathology involves 4 basic strategies: immunosuppression; genetic, phase, and antigenic

variation; physical seclusion; and secreted factors (table 1).

**GENETIC, PHASE, AND ANTIGENIC VARIATION**

*B. burgdorferi* engages in genetic, phase, and antigenic variation

that shares various features with other organisms [20–23]. For

eexample, gene switching is similar to what is seen with try-

panosomes, mutation and recombination are typical of HIV,

variable antigen expression is seen with *Neisseria* species, au-

toinsduction of dormant organisms occurs in mycobacterial in-

fection, and fibronectin binding occurs with staphylococcal and streptococcal infection.

*B. burgdorferi* may assume a dormant state with cyst for-

mation [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 spi-

rochete, 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 an-

titibiotics [32, 33]. The clinical implication of these gene mu-

tations 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 cul-
ture, *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 spi-

rochete. In addition, *B. burgdorferi* engages in “cloaking” mech-

anisms by binding to proteoglycan, collagen, plasminogen, in-
tegrin, and fibronectin. These substances can mask the bac-

terium 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 un-
certain [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 pher-

omones, 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 aggregacase, an enzyme that damages
cartilage [51]. This may be a mechanism by which the bacte-

rium 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, fol-

lowed by a Western blot for confirmation if the result of the

ELISA or immunofluorescence assay is positive. The CDC cau-

tions, 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*.**

<table>
<thead>
<tr>
<th>Immunosuppression</th>
<th>Tick saliva components</th>
<th>Complement inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitory cytokine induction (IL-10)</td>
<td>Lymphocyte/monocyte tolerization</td>
<td>Antibody sequestration in immune complexes</td>
</tr>
<tr>
<td>Genetic, phase, and antigenic variation</td>
<td>Gene switching (trypanosomes)</td>
<td>Mutation/recombination (HIV)</td>
</tr>
<tr>
<td>Variable antigen expression (<em>Neisseria species</em>)</td>
<td>Dormant state, autoinduction (<em>Mycobacterium species</em>)</td>
<td>Fibronectin binding (<em>Staphylococcus</em> and <em>Streptococcus</em> species)</td>
</tr>
<tr>
<td>Physical seclusion</td>
<td>Intracellular sites</td>
<td>Persistent infection in vitro (8 weeks)</td>
</tr>
<tr>
<td></td>
<td>Multiple cell types (synovial cells, endothelial cells, fibroblasts, macrophages, Kupffer cells, and nerve cells)</td>
<td>Persistent infection in vitro (8 weeks)</td>
</tr>
<tr>
<td></td>
<td>Privileged sites (joints, eyes, and CNS)</td>
<td>Persistent infection in vitro (8 weeks)</td>
</tr>
<tr>
<td>Cloaking mechanisms (binding to proteoglycan, collagen, plasminogen, integrin, and fibronectin)</td>
<td>Cloaking mechanisms (binding to proteoglycan, collagen, plasminogen, integrin, and fibronectin)</td>
<td></td>
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</tbody>
</table>

**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 “[t]here is no credible scientific evidence for the persistence of symptomatic *B. burg-
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Treatment</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klempner et al.</td>
<td>2001</td>
<td>IV Ctri for 4 weeks followed by oral doxycycline for 2 months vs. placebo</td>
<td>No improvement in fatigue or quality of life</td>
<td>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]</td>
</tr>
<tr>
<td>Krupp et al.</td>
<td>2003</td>
<td>IV Ctri for 4 weeks vs. placebo</td>
<td>SI in fatigue noted in 64% of treatment group, compared with 19% of control group; no improvement in cognition</td>
<td>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&lt;.01)</td>
</tr>
<tr>
<td>Fallon [105]</td>
<td>2005</td>
<td>IV Ctri for 10 weeks vs. placebo</td>
<td>SI in cognitive and physical functioning at 12 weeks in treatment group, compared with control group</td>
<td>Improvement in physical functioning but not cognitive functioning was sustained in the treatment group at 24 weeks</td>
</tr>
<tr>
<td>Cameron [106]</td>
<td>2005</td>
<td>Oral amoxicillin for 3 months vs. placebo</td>
<td>SI in cognitive and physical functioning in treatment group, compared with control group</td>
<td>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</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Organism</th>
<th>Treatment</th>
<th>Duration of treatment, months</th>
</tr>
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<tbody>
<tr>
<td>Drug-susceptible tuberculosis</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>2–4 antibiotics</td>
<td>6–9</td>
</tr>
<tr>
<td>Multidrug-resistant tuberculosis</td>
<td><em>M. tuberculosis</em></td>
<td>3–5 antibiotics</td>
<td>18–24</td>
</tr>
<tr>
<td>Leprosy</td>
<td><em>Mycobacterium leprae</em></td>
<td>3–4 antibiotics</td>
<td>24</td>
</tr>
<tr>
<td>Atypical tuberculosis</td>
<td><em>Mycobacterium chelonae</em></td>
<td>Oral and intravenous antibiotics</td>
<td>6–12</td>
</tr>
<tr>
<td>Q fever endocarditis</td>
<td><em>Coxiella burnetii</em></td>
<td>2 antibiotics</td>
<td>36</td>
</tr>
</tbody>
</table>

**NOTE.** Data are based on [143–147].

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**Table 3.** Precedents for prolonged antibiotic therapy.
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.

Acknowledgments

This article is dedicated to the memory of Dr. Paul Lavoie and Billi Goldberg.


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References


