

Lyme Disease: The Quest for Magic Bullets

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Key Words

Anaplasma · *Babesia* · *Bartonella* · *Borrelia* · Coinfections · *Ehrlichia* · Lyme disease

Abstract

Lyme disease represents a growing public health threat. Recent molecular and genetic studies have confirmed that *Borrelia burgdorferi*, the spirochetal agent of Lyme disease, is one of the most complex bacteria known to man. Affinity for multiple cell types and the presence of non-replicating forms of *B. burgdorferi* have contributed to persistent infection and failure of simple antibiotic regimens. The controversial clinical science of Lyme disease has impeded reliable diagnosis and effective treatment of this protean illness. Two major clinical hurdles are the absence of a therapeutic endpoint in treating Lyme disease and the presence of tick-borne coinfections that may complicate the course of the illness. New strategies for the diagnosis, treatment and prevention of Lyme disease are urgently needed.

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Introduction

Virtually from the moment of its discovery in 1975, Lyme disease has been a controversial illness [1, 2]. The controversy is grounded in the murky nature of the disease, from its protean manifestations to its inconsistent diagnostic parameters to its uncertain treatment. As a result of these scientific inconsistencies, Lyme disease has become one of the most politically charged diseases in history, rivalling syphilis (always the ‘other country’s venereal disease’) and AIDS (the ‘scourge of alternative lifestyles’). The political battle over Lyme disease features two polarized medical camps: the dominant camp adheres to the philosophy that the disease is ‘hard to catch and easy to cure’, and that chronic infection with *Borrelia burgdorferi*, the spirochetal agent of Lyme disease, is extremely rare or nonexistent. The opposing camp views Lyme disease as an underreported and growing menace that often fails to respond to standard antibiotic therapy, resulting in a chronic debilitating infection that requires prolonged antibiotic treatment [3, 4]. This festering controversy has resulted in systematic denial of treatment for patients with chronic Lyme disease and prosecution of healthcare providers who treat these patients, and over the past decade the ‘Lyme Wars’ have become progressively more acrimonious.

What sustains this controversy? It is important to recognize that the science of Lyme disease suffers from two major problems. First, there is no test currently available that proves the eradication of *B. burgdorferi* from the human body [5, 6]. Conversely, there is growing evidence for long-term persistence of the Lyme disease spirochete in animal models [7–11] and humans [12–14] despite ‘adequate’ treatment for the disease. The second problem is that Lyme disease likes company, and over the past 20 years we have seen compelling evidence for coinfections transmitted by ticks (which have been called ‘sewers of infectious disease’) along with the Lyme disease spirochete [15–23]. Thus the term ‘Lyme disease’ often connotes a poorly characterized polymicrobial infection with no fixed endpoint [15]. This nebulous infectious disease presents a nightmare scenario for both the victim of Lyme disease and any rational healthcare provider who must deal with the complications of tick-borne illness. A corollary to this nightmare is the growing recognition of possible spread of the Lyme disease spirochete by a variety of tick species, including the American dog tick and Pacific coast tick [23]. Furthermore, studies in mice have demonstrated direct transmission of *B. burgdorferi* without a tick vector [24, 25], and recent epidemiologic and immunologic evidence suggests that transmission of the Lyme disease spirochete may occur by direct human contact [26, 27].

Despite the complexity of tick-borne diseases, numerous articles that address Lyme disease diagnosis and treatment provide a banal assessment of the Lyme disease nightmare [1, 4, 28, 29]. These articles generally present the gamut of half-truths about the disease, from misinformation about diagnosis to simplistic concepts of disease pathogenesis and politically charged views about the treatment of Lyme disease and its coinfections. Sadly, the banality of the articles reflects an entrenched and growing ignorance and neglect of the severity of Lyme disease, while its victims continue to suffer.

Drawing from Lyme disease articles published over the past decade [1, 4, 28, 29], we have selected representative excerpts that illustrate many misconceptions about tick-borne diseases, accompanied by appropriate commentary:

Fiction: ‘About 70–80%’ of Lyme disease patients present with a characteristic ‘bullseye’ erythema migrans (EM) rash.

Fact: According to recent health department statistics from Texas, Connecticut and California, only 35–59% of Lyme disease patients present with an EM rash, and the rate may be even lower depending on the location of the

tick bite and the awareness of the person who was bitten [29, 30]. The published incidence of the EM rash also reflects a type of circular reasoning that pervades Lyme disease research: since the presence of an EM rash is the best evidence for Lyme disease, it has become the most common criterion for admission into Lyme disease studies. Since most patients in these studies have an EM rash, the incidence of the rash becomes inflated in the medical literature. The literature then perpetuates the myth that the vast majority of Lyme disease patients have an EM rash [4, 26].

Fiction: ‘Early Lyme disease is readily treatable with a 2- to 3-week course of antibiotics.’

Fact: This statement is misleading for several reasons. First, ‘early Lyme disease’ often goes undetected due to lack of awareness of a tick bite and absence of an EM rash [30]. Second, recent studies have shown that tick saliva carries immunosuppressive substances that allow tick-borne agents to invade tissues while paralyzing the local immune response [31, 32]. Thus the Lyme disease spirochete may rapidly disseminate and become entrenched and resistant early in the disease (see below) [33–35]. Third, coinfections may alter the course of ‘early Lyme disease’, and these coinfections may make the Lyme disease patient more difficult to treat (see below).

Fiction: The Lyme enzyme-linked immunosorbent assay (ELISA) is the ‘preferred method’ to diagnose Lyme disease due to its ‘sensitivity, adaptability to automation and ease of quantitation’.

Fact: The Lyme ELISA consistently misses at least 50% of Lyme disease cases due to the insensitivity of the assay and variability with antibiotic treatment [5, 6, 29, 36]. It follows that the ‘two-tiered’ testing system endorsed by the Centers for Disease Control and Prevention (CDC), which includes an ELISA screening test followed by a confirmatory Western blot, will also miss 50% of Lyme disease cases because a positive ELISA result is required to proceed to the ‘confirmatory’ Western blot test [29, 30]. Parenthetically, the CDC criteria were developed for surveillance of Lyme disease, not for diagnostic purposes. This is an important distinction because it is inappropriate to apply surveillance criteria to symptomatic patients whose clinical picture already suggests the presence of Lyme disease. In fact, the clinical case rate for Lyme disease may be as much as 40 times greater than the CDC surveillance case rate [37]. Thus, in contrast to standardized blood testing for human immunodeficiency virus, there is currently no sanctioned, standardized, consistent serologic test for Lyme disease in the United States [5, 6, 29, 30].

Fiction: *B. burgdorferi* can be ‘readily cultivated in vitro’ using special culture medium.

Fact: This statement is also misleading. Although *B. burgdorferi* is easy to grow in vitro using laboratory strains, the organism is extremely difficult to culture from human blood or tissues, and virtually no clinical laboratory can perform this basic infectious disease test [38, 39]. This clinical drawback has severely limited the diagnosis of Lyme disease. A similar problem is seen with syphilis, an illness caused by the spirochete *Treponema pallidum*. Because this organism cannot be grown in vitro, the diagnosis of syphilis (like Lyme disease) is supported by serologic testing, prompting the observation that ‘any infection for which diagnosis and assessment of treatment response depend on serologic testing is one in which clinical certainty is elusive’ [40].

Fiction: Only motile forms of *B. burgdorferi* are ‘considered to be viable and capable of replicating’.

Fact: *B. burgdorferi* assumes different forms in different hosts [41–47]. The most troublesome is the so-called cyst form that may lie dormant in the human host, thus evading antibiotic therapy that targets replicating bacteria [41–45]. The non-replicating cyst form is undoubtedly the key to persistence of infection with the Lyme disease spirochete, and any antibiotic approach to Lyme disease that fails to recognize this pathogenic entity may fail to eradicate the infection, leading to chronic disease [46, 47].

Fiction: ‘To date, there is no evidence for the existence of any antibiotic-resistant strains of *B. burgdorferi*.’

Fact: Another misleading statement. *B. burgdorferi* is an extremely complex organism. With more than 1,500 gene sequences, the Lyme disease spirochete contains at least 132 functioning genes, in contrast to *T. pallidum*, the spirochete that causes syphilis, which contains only 22 such genes [48, 49]. Furthermore, the Lyme disease spirochete contains 21 plasmids (9 circular and 12 linear) [49]. This is by far the largest number of plasmids found in any known bacterium, and one of the plasmids is known to produce a functional complement resistance protein [49, 50]. Recent studies have shown that *B. burgdorferi* adapts to diverse environments in the tick and mammalian host by selective gene expression, and that several plasmid genes play a ‘critical role’ in immune evasion [50–52]. The combination of intracellular localization, genetic complexity, immune evasion and autoregulation makes the Lyme disease spirochete a formidable infectious agent [53].

Fiction: ‘It is unclear whether a concurrent *Anaplasma* or *Babesia* infection can influence the outcome of a standard course of treatment for Lyme disease.’

Fact: Animal models of coinfection with *B. burgdorferi* and either *Babesia microti* or *Anaplasma phagocytophilum* (the agent of human granulocytic ehrlichiosis) have demonstrated an altered immune response and clinically worse disease in these animals [54–56]. Similar exacerbation of clinical symptoms and resistance to treatment has been observed in humans [17, 57, 58]. Although *Babesia*, *Anaplasma* and *Bartonella* species were originally thought to produce only acute infection in their hosts, recent studies have demonstrated chronic infection with these organisms in both animals and humans [59–63]. It follows that persistent coinfection with tick-borne agents may enhance the chronicity of *B. burgdorferi* infection.

Fiction: A single dose of doxycycline given within 72 h after a recognizable tick bite was ‘highly effective in preventing early Lyme disease’.

Fact: The study that showed the alleged benefit of prophylactic single-dose doxycycline had inadequate follow-up (6 weeks) to prove the absence of clinical infection following this simple treatment [64]. Furthermore, the authors used development of an EM rash as an endpoint in the study. Since 41–65% of Lyme disease patients do not develop an EM rash, the study may have missed more than half the patients who eventually came down with Lyme disease after receiving single-dose prophylaxis. The use of single-dose doxycycline also raises concern about antibiotic resistance following this microbiologically unsound therapy. A more recent study of ultrashort course doxycycline therapy (10 days) for early Lyme disease had significant design flaws and showed efficacy in less than 50% of patients [65, 66].

Fiction: A ‘highly significant’ study by Klempner et al. [67] examined retreatment of Lyme disease patients who had persistent symptoms of the disease. The study concluded that ‘it is unlikely that prolonged antibiotic treatment will offer any major benefit to symptomatic patients who are no longer infectious’.

Fact: The highly flawed study by Klempner et al. [67] has been analyzed in detail elsewhere [68, 69]. At the beginning of this article, we noted that one of the main problems with Lyme disease is the lack of a test that proves the eradication of spirochetal infection. Thus the design of the study by Klempner et al. was basically flawed because the culture and molecular techniques used in the study were insufficient to prove that patients were ‘no longer infectious’ [69]. Furthermore, the choice of ‘prolonged’ antibiotic therapy for patients with neurologic disease (1 month of intravenous ceftriaxone followed by 2 months of low-dose oral doxycycline) was irrational and doomed to failure [68, 69]. Consequently, the study sim-

ply showed that inadequate retreatment of chronic Lyme disease leads to inadequate results [69]. Unfortunately, because of the widespread publicity given to this article and its prestigious publisher, the flawed data have been widely used to deny care for symptomatic patients with chronic Lyme disease. As mentioned previously, numerous studies have found evidence of persistent spirochetal infection in animals and humans with chronic Lyme disease [7–14, 70, 71].

Fiction: Healthcare providers who deal with Lyme disease can be divided into two groups: ‘specialists’ who are often affiliated with ‘large academic institutions’, versus ‘community-based’ providers in ‘private (family) practice’. The former group tends to adhere to the guidelines of the CDC and the Infectious Disease Society of America (IDSA) in diagnosing and treating Lyme disease. In contrast, the latter group tends to rely on ‘anecdotal reports citing an alarming number of Lyme disease patients who are supposedly coinfecting with one or more of the following: *Anaplasma*, *Bartonella* or *Babesia*. Such an unlikely scenario of multiple infections arouses suspicion on the authenticity of these cases and those willing to make such diagnoses’.

Fact: This politically charged statement features two issues that define the ‘Lyme Wars’. The first issue concerns the ‘academic specialists’ who follow the CDC and IDSA guidelines in diagnosing and treating Lyme disease. We have seen that the CDC guidelines give a poor diagnostic yield for Lyme disease, since they were meant for surveillance purposes and not for diagnosis [26, 29]. Many of the IDSA recommendations for diagnosis and treatment of Lyme disease are contingent on the weakest Category III evidence, which derives ‘from opinions of respected authorities that is based on clinical experience, descriptive studies, or reports of expert committees’ [72]. These guidelines do not conform to minimal standards of evidence-based medicine, and they have doomed thousands of suffering Lyme disease patients to lack of therapy based on the opinions of a handful of ‘academic specialists’. With this background, it is logical that ‘community-based’ providers who deal with the clinical nightmare of Lyme disease have rejected the CDC/IDSA guidelines and formulated their own diagnostic and therapeutic parameters [69, 73–75].

The second politically charged issue is reflected in the statement that Lyme disease treatment outside the CDC/IDSA guidelines represents a provider-driven policy that impugns the integrity of the provider. The reality is that suffering patients seek out ‘Lyme-literate’ providers because the ‘academic’ researchers have abandoned them.

These researchers and their followers offer nothing in the way of treatment for suffering Lyme disease patients other than pseudopsychiatric semantics [4, 26] or meaningless labels such as ‘chronic fatigue syndrome’ or ‘fibromyalgia’, which are often manifestations of chronic, poorly treated Lyme disease [76, 77]. As for the ‘alarming’ number of Lyme disease patients who are ‘supposedly’ coinfecting with other tick-borne organisms, studies have shown coinfection in 20% or more of Lyme disease cases [19, 21, 29, 30], confirming the risk of polymicrobial infection in chronic Lyme disease.

Fiction: The Lyme disease vaccine was withdrawn due to ‘lack of public interest’.

Fact: The GlaxoSmithKline Lyme vaccine (Lymrix®) was withdrawn in the face of a class action lawsuit involving over 300 patients who claim that they developed a ‘Lyme-like’ illness after receiving the parenteral vaccine [78]. A more attractive immunization strategy is based on a mucosal vaccine that targets *B. burgdorferi* antigens or associated tick salivary proteins [78, 79]. This form of prophylactic therapy has yet to be tested in clinical trials.

Fiction: ‘Future treatment options’ for Lyme disease include hyperbaric oxygen therapy (HBOT), shorter course treatment with antibiotics, and evernimicin therapy [28].

Fact: HBOT is currently being used as adjunctive treatment for chronic Lyme disease [29]. Although in theory it is effective in creating a more hostile environment for the Lyme disease spirochete, HBOT is a cumbersome procedure that probably will never be available to the majority of patients with chronic infection. The cost of multiple treatments is also prohibitive. The hepatic toxicity of evernimicin makes it doubtful that this risky antibiotic will ever be marketed for Lyme disease. Shorter course antibiotic therapy was the subject of a recent study [65], and this minimalist approach promises to yield more inadequately treated Lyme disease sufferers [66].

In contrast to these impractical or dangerous treatment options, current and future Lyme disease therapy should focus on combinations of antibiotics that are effective against spirochetes, readily available and administered in a rational manner, with monitoring of clinical and immunologic parameters [69, 80–86]. In this regard, it is important to remember that the current World Health Organization (WHO) recommendation for treating infection with *Mycobacterium tuberculosis* is a combination of two antimicrobial agents administered for 18 months, while the WHO-sanctioned treatment for leprosy is a combination of three antimicrobial agents administered

for 2 years [87–89]. For disseminated infection with nontuberculous mycobacteria such as *M. chelonae*, treatment may involve a combination of oral and intravenous antibiotics administered for 6–12 months [90]. In the case of Q fever endocarditis caused by another tick-borne infectious agent, *Coxiella burnetii*, the recommended treatment is a combination of two antibiotics administered for 3 years; even with prolonged antimicrobial therapy, the relapse rate in this disease is approximately 15% [91]. For a spirochete as complex and crafty as *B. burgdorferi*, these therapeutic guidelines are probably closer to what is needed for the eradication of chronic spirochetal infection in Lyme disease [75, 92]. As stated previously, recognition and evaluation of human transmission of Lyme disease will also play a role in developing effective treatment strategies for the disease [26, 27].

In conclusion, Lyme disease remains a public health threat of major proportions. The trivialization of spirochetal illness by various authors only serves to augment this threat by legitimizing ignorance of Lyme disease and neglect of Lyme disease patients. Until this trend is reversed, we will continue to see thousands of patients suffering at the hands of the medical establishment and des-

perately seeking care from the few providers who will listen. As modern medicine rockets into the 21st century, this ostracism of suffering patients and persecution of dissenting healthcare providers can no longer be tolerated from a medicolegal standpoint [92]. For their part, Lyme disease patients and their providers must learn from the AIDS experience, where activism brought change when it was perceived that nobody was listening. And as more people listen, the ‘Lyme Wars’ may finally reach an end.

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