Lyme disease: point/counterpoint

Raphael B Stricker†, Andrew Lautin and Joseph J Burrascano

Lyme disease represents a growing public health threat. The controversial science and politics of Lyme disease have created barriers to reliable diagnosis and effective treatment of this protean illness. Two major clinical hurdles are the absence of a therapeutic end point in treating *Borrelia burgdorferi*, the spirochetal agent of Lyme disease, and the presence of tickborne coinfections with organisms such as *Babesia*, *Anaplasma*, *Ehrlichia* and *Bartonella* that may complicate the course of the disease. From a pathophysiologic standpoint, the affinity of *Borrelia burgdorferi* for multiple cell types and the presence of nonreplicating forms of the Lyme disease spirochete have contributed to persistent infection and failure of simple antibiotic regimens. Newer approaches to the treatment of Lyme disease should take into account its clinical complexity in coinfected patients and the possible need for prolonged combination therapy in patients with persistent symptoms of this potentially debilitating illness. The optimal antibiotic regimen for chronic Lyme disease remains to be determined.

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†Author for correspondence
California Pacific Medical Center,
450 Sutter Street, Suite 1504, San
Francisco, CA 94108, USA
Tel.: +1 415 399 1035
Fax: +1 415 399 1057
rstricker@usmamed.com

Virtually from the moment of its discovery in 1975, Lyme disease has been a controversial illness [1,2]. The controversy is grounded in the complex nature of the disease, with its protean manifestations, inconsistent diagnostic parameters and uncertain treatment. As a result of these scientific inconsistencies, Lyme disease has become a politically-charged illness similar to syphilis (always the 'other country's venereal disease') and AIDS (the 'scourge of alternative lifestyles') [3,4]. 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' [5], 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 [6,7]. This difference of opinion has resulted in frequent 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 [8,9]. Conversely, there is growing evidence for long-term persistence of the Lyme disease spirochete in animal models [10–14] and humans [15–17], despite supposedly adequate treatment for the disease with 2 to 4 weeks of antibiotics. Persistent infection appears to be a more plausible mechanism of chronic Lyme disease than 'postinfectious autoimmunity' induced by molecular mimicry, which remains an unproven hypothesis that is discussed in detail elsewhere [18–20]. The second problem is that Lyme disease encompasses more than one infection, and over the past 20 years we have seen compelling evidence for coinfections transmitted by ticks along with the Lyme disease spirochete [21–29]. Thus the term 'Lyme disease' often connotes a poorly

characterized polymicrobial infection with no fixed end point [21]. This protean infectious disease presents a nightmare scenario for both the victim of Lyme disease and the healthcare provider who must deal with the complications of tickborne 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 [29]. Furthermore, studies in mice have demonstrated direct transmission of *B. burgdorferi* without a tick vector [30,21], and recent epidemiologic and immunologic evidence suggests that transmission of the Lyme disease spirochete may occur by direct human contact [32,33].

Despite the complexity of tickborne diseases, numerous articles that address Lyme disease diagnosis and treatment provide a one-sided assessment of the Lyme disease nightmare [1,7,34,35]. These articles generally focus on acute infection with *B. burgdorferi*, and their narrow point of view is embodied in the clinical guidelines of the Infectious Diseases Society of America (IDSA) [36]. In contrast, the clinical guidelines of the International Lyme and Associated Diseases Society (ILADS) encompass more recent evidence-based information about the diagnosis, pathogenesis and treatment of chronic Lyme disease and its coinfections [37]. Thus the medical community is now faced with two standards of care in dealing with the diagnosis and treatment of Lyme disease [38]. This dichotomy has created difficulties for physicians and patients who must judge the accuracy of the Lyme disease literature.

Drawing from Lyme disease articles published over the past 10 years [1,7,34,35], the authors have selected representative excerpts that illustrate many misconceptions about tickborne diseases, accompanied by appropriate commentary.

Points & counterpoints
Point
'About 70 to 80%' of Lyme disease patients present with a characteristic 'bullseye' erythema migrans (EM) rash [34,35].

Counterpoint
According to recent health department statistics from Texas, Connecticut and California, only 35 to 59% of Lyme disease patients present with an EM rash, and the rate may be even lower depending on the location of the tickbite and the awareness of the person who was bitten [38,39]. Furthermore, the EM rash often assumes an atypical form rather than the classic 'bullseye' pattern, making the rash more difficult to diagnose [38,40]. 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 false perception that the vast majority of Lyme disease patients have an EM rash [7,32].

Point
'Early Lyme disease is readily treatable with a 2- to 4-week course of antibiotics' [34,35].

Counterpoint
This statement is misleading for several reasons. First, 'early Lyme disease' often goes undetected due to lack of awareness of a tickbite and absence of an EM rash [39]. Second, recent studies have shown that tick saliva carries immunosuppressive substances that allow tickborne agents to invade tissues while paralyzing the local immune response [41,42]. Thus the Lyme disease spirochete may rapidly disseminate and become entrenched and resistant early in the disease (see below) [43–45]. 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).

Point
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' [34,35].

Counterpoint
The Lyme ELISA consistently misses at least 50% of Lyme disease cases due to the assay's insensitivity and variability with antibiotic treatment [8,9,37,38,46]. 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 [38,39]. 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 [47]. Thus the 'two-tiered' testing system is inappropriate for Lyme disease diagnosis.

Interpretation of the Lyme Western blot has also been problematic [9,38,48,49]. For historic reasons, several of the most important bands on the Lyme Western blot are not reported, while some of the reported bands are not specific for *B. burgdorferi* [38,48]. Furthermore, men and women with chronic Lyme disease appear to react differently on the Lyme Western blot, with women having a lower number of positive bands than men [49]. This observation suggests that gender bias may influence the interpretation of the Western blot. Currently there is no standardized version of the Lyme Western blot, and manufacturers are free to use different spirochetal strains that produce variable reactivity on the blot [8,9]. Thus in contrast to government-regulated standardized blood testing for HIV, there is currently no sanctioned, standardized, consistent serologic test for Lyme disease in the USA [8,9,38,39].

An additional problem is the reporting system for Lyme disease, which depends on physician reporting to the local health department in most areas. A previous study indicated that Lyme disease was under-reported by a factor of twelve in Connecticut [6]. When the surveillance system was changed from physician reporting to mandatory laboratory reporting of positive Lyme disease tests, the reporting rate for the disease increased as much as 27-fold in Connecticut [38,201]. Even considering possible false-positive results, this finding indicates that Lyme disease is seriously under-reported in high-risk areas.

A recent study from California may also change our way of thinking about the risk of tick exposure for humans. Traditionally it was thought that the greatest exposure to ticks carrying *B. burgdorferi* was from leaf litter and grass. However, Lane and colleagues found that the risk of nymphal tick exposure from human contact with wood was almost seven-times greater than the risk of exposure from leaves and grass [50]. Since nymphal ticks are more likely to transmit *Borrelia burgdorferi* because of their small size and relatively high infection rate, traditional analysis of ticks in leaf litter and grass may significantly underestimate the infection risk in a given location. Conversely, the greatest risk of acquiring Lyme disease may involve human contact with wood [50].

Point

B. burgdorferi can be 'readily cultivated *in vitro*' using special culture medium [34].

Counterpoint

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 [51,52]. 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' [53].

Point

Only motile forms of *B. burgdorferi* are 'considered to be viable and capable of replicating' [34].

Counterpoint

B. burgdorferi assumes different forms in different hosts [54–60]. The most troublesome is the so-called cyst form, or 'stress-starvation' form, that may lie dormant in the human host, thus evading antibiotic therapy that targets replicating bacteria [54–58]. The nonreplicating 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 [59,60].

Point

'To date, there is no evidence for the existence of any antibiotic-resistant strains of *B. burgdorferi*' [34].

Counterpoint

Another misleading statement. *B. burgdorferi* is an extremely complex organism (BOX 1). With more than 1500 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 [61,62]. Furthermore, the Lyme disease spirochete contains 21 plasmids (nine circular and 12 linear) [62]. This is by far the largest number of plasmids found in any known bacteria, and it is thought that the large number of plasmid genes provides a 'rapid response' system that allows the spirochete to cycle efficiently between ticks and mammals [62–64].

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 [63–66]. Gene exchange and plasmid transfers among *Borrelia* strains may also increase the pathogenicity of the organism [67], and newer mutagenic techniques have confirmed the genetic uniqueness and complexity of the Lyme disease spirochete [68,69]. A recent study demonstrated for the first time that the Lyme disease spirochete contains a secretory mechanism for porin and adhesin proteins, and these secreted products may contribute to the invasive properties of the organism [70]. Furthermore, *B. burgdorferi* appears to utilize the host fibrinolytic system to penetrate the blood–brain barrier and thus gain access to the CNS [71].

Box 1. Pathophysiologic mechanisms utilized by *Borrelia burgdorferi**

Immune suppression
- Complement inhibition
- Inhibitory cytokine induction (IL-10)
- Lymphocyte/monocyte tolerization
- Antibody sequestration in immune complexes

Phase and antigenic variation[‡]
- Gene switching (trypanosomes)
- Mutation/recombination (HIV)
- Variable antigen expression (neisseria)
- Autoinduction (mycobacteria)

Physical seclusion
- Intracellular sites: synovial cells, endothelial cells, fibroblasts, macrophages, Kupffer cells
- Extracellular sites: joints, eyes, CNS

Secreted factors
- Porin (Oms28)
- Adhesin (Bgp)

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* Based on [43,70,78,111].
[‡]Organisms in parentheses share this mechanism.
IL: Interleukin.

Based on its genetic complexity, *B. burgdorferi* has recently been shown to be resistant to certain antibiotics [72]. In addition, the spirochete can enter cells such as fibroblasts, synovial cells, endothelial cells and macrophages [73–79]. In these cells, *B. burgdorferi* becomes functionally resistant to treatment, partly due to 'camouflage' proteins produced by the organism or adsorbed from the cell, and partly due to the altered morphology and replication of the spirochetal cyst form (see above) [45,59,74,79]. This functional resistance leads to persistent infection despite 'adequate' treatment for Lyme disease. The immune evasion strategy of *B. burgdorferi* is reminiscent of chronic mycobacterial infections such as tuberculosis or leprosy [43–45]. The agents of these intracellular mycobacterial diseases also exist as nonreplicating cyst forms that can be 'resuscitated' by autocrine cytokine-like factors after lying dormant for months [80,81]. A recent study suggests that *B. burgdorferi* utilizes *luxS*, an autoinducer gene that regulates replication in other bacteria [82]. It is the first time that a spirochete has been shown to possess this autoinducer gene. Thus, the combination of intracellular localization, genetic complexity, immune evasion and autoregulation makes the Lyme disease spirochete a formidable infectious agent [79].

Point

'It is unclear whether a concurrent anaplasma or babesia infection can influence the outcome of a standard course of treatment for Lyme disease' [34].

Counterpoint

Animal models of coinfection with *B. burgdorferi* and either *Babesia microti* or *Anaplasma phagocytophila* (the agent of human granulocytic ehrlichiosis) have demonstrated an altered immune response and clinically worse disease in these animals [83–85]. Similar exacerbation of clinical symptoms and resistance to treatment has been observed in humans [23,86,87]. Although *Babesia*, *Anaplasma* and *Bartonella* spp. 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 [88–92]. It follows that persistent coinfection with tick-borne agents may enhance the chronicity of *B. burgdorferi* infection.

Point

A single dose of doxycycline given within 72 h after a recognizable tick bite was 'highly effective in preventing early Lyme disease' [34,35].

Counterpoint

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 [93]. Furthermore, the authors used the development of an EM rash as an end point in the study. Since 41 to 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 ultra-short course doxycycline therapy (10 days) for early Lyme disease had significant design flaws and showed efficacy in less than 50% of patients [94,95].

Point

A 'highly significant' study by Klempner and colleagues [96] examined the 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' [34,35].

Counterpoint

The highly flawed study by Klempner and colleagues [96] has been analyzed in detail elsewhere [97,202]. The study had at least three fundamental flaws:

- First and foremost, 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 neither long enough nor sufficiently bactericidal for patients with neurologic symptoms [97,202]. Consequently, the study simply showed that inadequate retreatment of chronic Lyme disease leads to inadequate results [202].

- Second, as stated previously, 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 and colleagues was basically flawed, since the culture and molecular techniques used as the study end points were insufficient to prove that patients were 'no longer infectious' [202].

- Third, the study failed to consider the role of untreated coinfections in patients with persistent Lyme disease symptoms.

Unfortunately, this single flawed study alleging the failure of 'long-term' antibiotic therapy has been widely used to deny care for symptomatic patients with chronic Lyme disease. A recently completed randomized controlled trial by Fallon and colleagues demonstrated that when Lyme disease patients suffering from persistent neurologic symptoms were retreated with 10 weeks of intravenous ceftriaxone, they had significant improvement in clinical and neuroradiologic parameters. The improvement was lost when treatment was discontinued, however [98]. Further controlled trials are needed to determine the optimal dose and duration of antibiotic therapy for chronic Lyme disease.

As mentioned previously, numerous studies have found evidence of persistent spirochetal infection in animals and humans with chronic Lyme disease [10–17,38,99–102]. Persistence of *B. burgdorferi* in joint fluid and cerebrospinal fluid has been examined in two large clinical trials [99,100]. In these studies using the polymerase chain reaction (PCR) to detect spirochetal DNA, evidence of persistent infection was found in 30 to 37% of joint fluids and in 25% of cerebrospinal fluid

despite 'adequate' antibiotic therapy [99,100]. Furthermore, the sensitivity of PCR testing in these studies was felt to be 'limited' [99]. Thus persistent spirochetal infection occurs in patients with chronic Lyme disease, and reliable testing for chronic infection is unavailable at present [38,98,202].

Point

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 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 coinfected 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' [34].

Counterpoint

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. As noted previuosly, the CDC guidelines give a poor diagnostic yield for Lyme disease, since they were meant for surveillance purposes and not for diagnosis [32,33]. The IDSA guidelines were written by a panel of 12 Lyme disease researchers and clinicians, and dissenting opinion was ignored in formulating the guidelines [DONTA S, PERS. COMMUN., 2004]. Many of the IDSA recommendations for diagnosis and treatment of Lyme disease were 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' [36]. Thus these guidelines do not conform to current standards of evidence-based medicine. 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 [37,38,103,104].

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 failed them. These researchers and their followers offer nothing in the way of treatment for suffering Lyme disease patients other than pseudopsychiatric semantics [7,32] or pejorative labels such as 'chronic fatigue syndrome' or 'fibromyalgia', which are often manifestations of chronic, poorly treated Lyme disease [37,38]. As for the 'alarming' number of Lyme disease patients who are 'supposedly' coinfected with other tickborne organisms, studies have shown coinfection in 20% or more of these patients, confirming the risk of polymicrobial infection in chronic Lyme disease [25,27,38,39].

Point

The Lyme disease vaccine was withdrawn due to 'lack of public interest' [34].

Counterpoint

The GlaxoSmithKline Lyme vaccine (Lymerix®) 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 [105]. A more attractive immunization strategy is based on a mucosal vaccine that targets *B. burgdorferi* antigens or associated tick salivary proteins [105–107]. This form of prophylactic therapy has yet to be tested in clinical trials. Vaccination of wild-mouse reservoirs against *B. burgdorferi* appears to have limited influence on transmission of the Lyme disease spirochete to ticks [108].

Point

'Future treatment options' for Lyme disease include hyperbaric oxygen therapy (HBOT), shorter-course treatment with antibiotics, and evernimicin therapy [34,35].

Counterpoint

HBOT is currently being used as adjunctive treatment for chronic Lyme disease [37]. Although in theory it is effective in creating a more hostile environment for the Lyme disease spirochete, HBOT is a cumbersome procedure that will probably never be available to most 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 [94], and this minimalist approach promises to yield more inadequately treated Lyme disease sufferers [95].

In contrast to these impractical or dangerous treatment options, current and future Lyme disease therapy should focus on combinations of antibiotics that are readily available and administered in a rational manner, with monitoring of clinical and immunologic parameters [37,38,103,109–114]. In particular, monitoring of cytokine changes would be extremely useful [115,116], but cytokine testing is not reliable with currently available routine laboratory technology. Treatment of Lyme disease and tickborne coinfections involves decisions about the choice of antibiotics (BOX 2) and the duration of therapy. For recent uncomplicated infection with *B. burgdorferi* (within 1 month), treatment with single oral antibiotics, such as doxycycline or amoxicillin is often adequate [36,37,103]. In contrast, patients with predominantly musculoskeletal symptoms of chronic *B. burgdorferi* infection (greater than 3 months) generally require treatment with combination antibiotic regimens in a rotating manner (BOX 2). Therapy should be monitored with standardized clinical assessment and immunologic testing [37,103,109–111].

For patients with predominantly neuropsychiatric symptoms of Lyme disease, intravenous or intramuscular antibiotic therapy is usually required to control the infection [37,103]. Monitoring

Box 2: Antibiotic regimens for Lyme disease*

Borrelia burgdorferi
    Oral monotherapy
- Tetracycline
- Doxycycline, minocycline
- Amoxicillin ± sulbactam
    Oral combination therapy
- Macrolide (clarithromycin and azithromycin) plus third-generation cephalosporin (cefdinir, cefuroxime, ceftibuten, cefixime)
- Macrolide plus nitroimidazole (metronidazole, tinidazole)
- Macrolide plus amoxicillin ± sulbactam
- Ketolide plus third-generation cephalosporin or nitroimidazole
- Clarithromycin plus hydroxychloroquine
    Intravenous therapy
- Ceftriaxone
- Cefotaxime
- Azithromycin
- Imipenem/cilastatin
- Meropenem
- Doxycycline
    Intramuscular therapy
- Benzathine penicillin G
Coinfections
    Babesia
- Clindamycin plus quinine, macrolide plus atovaquone, macrolide plus nitroimidazole, doxycycline/minocycline plus mefloquine, ?artemesia plus trimethoprim/sulfamethoxazole
    Anaplasma/Ehrlichia
- Doxycycline/minocycline, macrolide, rifampin
    Bartonella
- Fluoroquinolone (ciprofloxacin, levofloxacin), macrolide

*Based on [37,38,104,113–115].

of neuropsychiatric deficits with single-photon emission computerized tomographic brain imaging and neuropsychological testing is helpful to assess the efficacy of treatment in these cases [117]. In contrast, cerebrospinal fluid analysis and brain magnetic resonance imaging is often unrevealing, despite the presence of significant neuropsychiatric symptoms [37,103,118]. As a general rule, patients with tickborne coinfections such as *Babesia*, *Anaplasma*, *Ehrlichia* and *Bartonella* should have treatment for these organisms prior to treating the Lyme disease spirochete (BOX 2). If coinfections are not eradicated, the infection with *B. burgdorferi* becomes more difficult to treat, as discussed previously [37,83–87,103].

In terms of the duration of therapy for chronic Lyme disease, 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 [119–121].

For disseminated infection with nontuberculous mycobacteria such as *Mycobacterium chelonae*, treatment may involve a combination of oral and intravenous antibiotics administered for 6 to 12 months [122]. In the case of Q fever endocarditis, caused by another tickborne 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% [123]. 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 [37,38,103]. 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 [32,33].

Conclusions

In conclusion, Lyme disease is a growing public health threat, and the trend toward trivialization of spirochetal illness only serves to augment this threat. Until the trend is reversed, we will continue to see thousands of patients suffering at the hands of the medical establishment and desperately seeking care from the few providers who will listen. As modern medicine rockets into the 21st Century, the ostracism of suffering patients and persecution of dissenting healthcare providers can no longer be tolerated from a medico–legal standpoint [38]. 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. As more people listen, the 'Lyme Wars' may finally reach an end.

Expert opinion

Two standards of care have emerged in the treatment of Lyme disease. One is based on short-term treatment regardless of symptoms, while the other is based on open-ended therapy that is pegged to the patient's clinical response. Given the clinical variability of Lyme disease, the genetic complexity of the inciting agent *B. burgdorferi* and the recognition of coinfections that may complicate the disease, a more aggressive approach to treatment of Lyme disease is warranted; specifically, the use of combination oral and/or parenteral antibiotic therapy over longer periods of time appears to be effective in controlling or eradicating the disease. In the absence of a safe and effective Lyme disease vaccine, greater awareness and avoidance of the disease by patients and earlier recognition and treatment by physicians is essential. In this regard, improvement and standardization of laboratory testing for Lyme disease is highly desirable. The potential spread of Lyme disease by direct human contact has major health implications and merits further study.

Five-year view

Based on the points outlined above, a compromise between the two standards of care will be reached over the next 5 years. As more data emerges on the complexity of tickborne diseases in conjunction with better testing procedures, the scope of antibiotic therapy for Lyme disease will be

expanded. Newer antimicrobial agents that target tickborne diseases will be developed and tested in controlled clinical trials, and optimal antibiotic regimens incorporating both older and newer medications will be identified and implemented. Complementary treatment strategies based on immune modulation will also be developed.

Laboratory testing will be expanded to include bacterial load analysis, antibiotic resistance testing and strain typing of *B. burgdorferi* – similar to the existing tests for HIV disease. With effective strain typing, transmission patterns of Lyme disease will be analyzed and the risk of direct human transmission will be delineated. Appropriate prophylaxis and treatment for this type of transmission can then be implemented.

A Lyme disease vaccine will be developed based on tick saliva protein recognition. This vaccine will protect against all tickborne infections, including Lyme disease, and it will avoid potential crossreactivity between spirochetal and human cellular components.

Finally, government agencies will modify their diagnostic criteria for Lyme disease, and a standardized format for tickborne disease recognition will allow patients expanded access to care for Lyme and associated tickborne diseases. The 'Lyme Wars' will then reach an end.

Key issues

- Two standards of care currently exist for the treatment of Lyme disease: one standard is based on short-term treatment, while the other is based on open-ended therapy.
- The clinical manifestations of Lyme disease are highly variable, and diagnosis may be complicated by the presence of tickborne coinfections and the unreliability of laboratory testing for Lyme disease. Diagnostic guidelines for chronic Lyme disease need to be revised.
- Currently there is no definitive test for the eradication of Lyme disease. The genetic complexity of *Borrelia burgdorferi*, the spirochetal agent of Lyme disease, implies that this organism may be difficult to eradicate.
- Treatment of Lyme disease should be pegged to the patient's clinical symptoms in conjunction with immunologic, radiologic and/or neuropsychiatric testing.
- Further controlled clinical trials are needed to define the optimal treatment regimens for chronic Lyme disease and associated tickborne coinfections.
- Development of a safe and effective Lyme disease vaccine is desirable, and the vaccine should protect against all tickborne diseases. Targeting tick saliva proteins may be an effective strategy for this vaccine.
- Transmission of Lyme disease by direct human contact merits further study.

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Affiliations

- *Raphael B Stricker, MD*
  California Pacific Medical Center, 450 Sutter Street, Suite 1504, San Francisco, CA 94108, USA
  Tel.: +1 415 399 1035
  Fax: +1 415 399 1057
  rstricker@usmamed.com
- *Andrew Lautin, MD*
  New York University School of Medicine, New York, NY, USA
- *Joseph J Burrascano, MD*
  East End Medical Associates,, East Hampton, NY, USA