Treatment of Lyme disease: a medicolegal assessment

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Lyme disease is the most common tick-borne disease in the world today. Despite extensive research into the complex nature of Borrelia burgdorferi, the spirochetal agent of Lyme disease, controversy continues over the diagnosis and treatment of this protean illness. This report will focus on two aspects of the treatment of Lyme disease: first, the medical basis for diagnosis; and second, therapeutic uncertainty in Lyme disease, including variability in clinical presentation, shortcomings in laboratory testing procedures, and design defects in therapeutic trials. Second, the standard of care and legal issues that have resulted from the clinical uncertainty of Lyme disease diagnosis and treatment.

Specifically, the divergent therapeutic standards for Lyme disease are addressed, and the difficult process of creating treatment guidelines for this complex infection is explored. Consideration by healthcare providers of the medicolegal issues outlined in this review will support a more rational approach to the diagnosis and treatment of Lyme disease and related tick-borne illnesses.

Lyme disease & diagnosis

Characteristics of Lyme disease

Ticks have been called "vector of infectious disease. Hard-shelled (linden) ticks are capable of transmitting Borrelia burgdorferi, the agent of Lyme disease, and other pathogens such as Babesia, Ehrlichia and Rickettsia. Thus, the term Lyme disease often signifies a poorly defined polymicrobial infection. Coinfections may alter the course of Lyme disease and may make the infected patients more difficult to treat [1,2]. Recent studies have shown that tick saliva carries immunosuppressive substances that enable tick-borne agents to invade tissues while paralyzing the local immune response [14]. This may allow the Lyme disease spirochete to disseminate rapidly and become established and persistently in the disease 15-7. Although scientists believe that Lyme disease is transmitted primarily by ticks, some studies suggest gonads of transplacental transmission and transmission by other insects, blood transfusion and intimate human contact [15-17].

In 2004, the number of Lyme disease cases reported to the US Centers for Disease Control and Prevention (CDC) increased by 40%, to 23,763 cases (18). Since only 10 to 15% of Lyme disease cases are actually reported (18), it is estimated that the true number of cases throughout the USA may exceed 257,600 annually. The highest reported incidence of Lyme disease occurs in children under 15 years of age (16). Morbidity associated with persistent Lyme disease is significant, with patients suffering a degree of physical health deterioration equal to that of patients with congestive heart failure (19). Although it is commonly believed that Lyme disease does not result in death, at least 21 research studies have documented deaths associated with Lyme disease (19,20). However, epidemiological studies are needed to document the fatality rates or proportionate mortality.

Stages of disease

Lyme disease may have devastating effects if not promptly diagnosed and adequately treated. A multisystemic illness, Lyme disease can manifest with:

- Neurological symptoms, such as Bell's palsy (causing paralysis of facial nerves)
- Meningitis (causing headache, fever and stiff neck)

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Nerve inflammation (causing numbness and tingling in the arms and legs).

- Encephalitis (causing learning difficulties, confusion and dementia).
- Musculoskeletal symptoms such as myalgias and arthralgias.
- Heart involvement (causing irregularities in heart rhythm and congestive heart failure).

Lyme disease mimics many other conditions, including psychiatric syndromes, progressive dementia, stroke, disorders, atypical arthralgias, disorders, myocarditis, peripheral neuritis, Guillain-Barre syndrome and progressive demyelinating diseases such as multiple sclerosis [9]. B. burgdorferi genotypic changes should be kept in mind when reviewing studies from other countries.

Like syphilis, Lyme disease has been described as having three stages: early localized, early disseminated and late stage or chronic Lyme disease. Early disease may involve an erythema migrans (EM) (bulls-eye or target-like rash) as the flu-like illness. While the EM rash alone is generally considered diagnostic of Lyme disease, only 65% of reported cases observed an EM rash [10].

Disseminated Lyme disease involves one or more organ systems (most commonly musculoskeletal, neurologic or cardiac) as spirochetes spread to distant sites. Late-stage or persistent Lyme disease occurs months to years after infection, and typically involves the musculoskeletal and neurologic systems (both central and peripheral). In late-stage or persistent Lyme disease, the infection is more entrenched and difficult to treat. In practice, infection forms a continuum along which early and late features overlap. For instance, the spirochete and its DNA have been isolated from the cerebrospinal fluid (CSF) early in the course of the disease when the EM rash is still present, and spirochetes have been cultured from the skin years after primary infection [11].

Diagnostic difficulties

Failure to recognize and treat Lyme disease early on can allow the infection to progress, permitting a treatable acute infection to become a relapsing chronic disease that is ultimately less responsive to antibiotics [12]. There is a general consensus among the physicians who are most familiar with treating this disorder that the earlier that Lyme disease is treated, the greater the chance for a complete cure. Late disease presents the greatest treatment challenge and may be refractory to various treatment modalities.

Prempt diagnosis of Lyme disease is hampered by many factors. The symptoms can persist for years without causing symptoms and some patient present initially with neurologic or dermatologic complaints since EM rash is either not present or is unrecognized or misdiagnosed [13]. Misdiagnosis is also made more likely by the fact that Lyme disease mimics many other syndromes. A central diagnostic difficulty in Lyme disease is the lack of a definitive and readily available laboratory test for the diagnosis of active infection [14].

The most definitive diagnostic procedure for Lyme disease is biopsy and isolation of B. burgdorferi in culture [15]. However, B. burgdorferi spirochetes are scarce, tissue bound, and divide slowly [16], making it extremely difficult to culture the organism using routine methods [17]. Diagnosis of Lyme disease is most commonly supported by serologic techniques that detect antibodies in the patient’s blood, and laboratory techniques that detect antibody changes in the patient's blood over time. The most commonly used methods for detecting antibodies against the spirochetal agents of Lyme disease are the enzyme-linked immunosorbent assay (ELISA) and the western blot. Recent studies by the group responsible for the Lyme disease proficiency testing for the College of American Pathologists (CAP) came to the conclusion that the currently available ELISA test do not have adequate sensitivity to meet the two-tiered approach recommended by the CDC for surveillance [18].

The western blot is recognized by the National Institute of Allergy and Infectious Diseases (NIAID), a division of the National Institutes of Health (NIH), as the most useful method for detecting borrelia antibodies currently available [19]. The western blot may be used to measure both immunoglobulin (IgM and G antibodies). Commonly, IgM antibodies appear first, wane after the first few weeks and do not recur.
followed by IgG antibodies, which are regarded as the major enduring antibody response in chronic infectious disease. However, in Lyme disease, IgM antibodies may persist for years, suggesting persistent infection or a reaction to latent infection (as it is, for example, in leptospirosis, Leishmaniasis, and syphilis) (96). A number of studies point to the importance of the IgM response in recurrence or persistence of Lyme disease (92-94).

Physicians treating Lyme disease should consider the particular band that test positive for an individual patient and the specificity of the bands to the disease (95). Western blot bands have been shown to be important in the definitive staging of the illness. A study by Enright and colleagues found that two of five bands gave them a specificity of 63% to 56% and a sensitivity of 100% in the 70% of the patients who manifested antibodies (96). Another study that included 186 defined patients and 320 negative controls showed excellent sensitivity and specificity for IgM and a good sensitivity and specificity for IgG using two of five bands (97).

The issue of sensitivity with antibody detection techniques is significant. One researcher found that only three of 14 patients who were culture positive for B. burgdorferi had positive antibody tests (98). Another group of researchers showed that only 76% of documented Lyme disease patients in their study had a significant antibody response (99). Another group found that approximately 20% of patients with Lyme disease were seronegative (100). Clinically, seronegative patients may be the least able to mount an effective defense to the infection and, hence, may be the worst affected (101).

Other tests can help corroborate a diagnosis of Lyme disease. Polymerase chain reaction (PCR) tests detect the presence of B. burgdorferi DNA in body fluids (102). PCR is considered to be highly specific, but has low yield, particularly in body fluids (103). Signs of CNS involvement include abnormal CSF protein or pleocytosis, abnormal brain single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI) or electroencephalogram (EEG), intravascular antibody production or a positive PCR for B. burgdorferi, or a positive culture. Lyme disease is a chronic illness.

Lyme disease is a chronic illness. Diagnostic testing of active infection is not feasible as a matter of exclusion, given the transitory nature of the PCR test, the insensitivity of culture tests, and the difficulties of antibody detection methods. Conversely, the current state of disease testing cannot demonstrate the eradication of B. burgdorferi (because negative test results do not mean an absence of infection). Due to the weeks to months in laboratory tests, the diagnosis of Lyme disease remains primarily clinical, with the focus on treatment response and symptoms that reflect the manifestations of the disease, with laboratory tests playing a supporting role (104).

The CDC, US Food and Drug Administration (FDA), and NIAID have all expressed concerns regarding the over-reliance on laboratory tests for diagnosing Lyme disease (105,106), with the FDA stating that tests should never be the primary basis for making diagnostic or treatment decisions. Diagnosis should be based on a patient history, including symptoms and exposure to the tick vector and physical findings (107). In addition, studies recommend treatment for confirmed cases (108,109). Although some advocates maintain that diagnosis should be supported by positive serology (110), use of the CDC surveillance criteria for diagnosis (111) also occurs because of the minute of the strict CDC surveillance case definition and testing standards for diagnosis. The CDC surveillance definition does not take into account neurological Lyme disease or chronic Lyme disease, and therefore misses many confounded Lyme cases. For surveillance purposes, the CDC requires five of ten IgM bands and two of three IgG bands for a positive result. Although a majority (80%) of patients with EM confirmed Lyme disease develop an IgM response at some time during the disease, only 22% are positive by CDC criteria (112,113). In addition, for surveillance definition, the CDC recommends a monitored testing approach. However, this approach is problematic because it requires the first test, the ELISA test, to be sufficient sensitivity. The CDC has cautioned that this surveillance case definition was developed for national reporting of Lyme disease and that it is not appropriate for clinical diagnosis (114).

As a CDC official explained, the distinction between diagnostic tests and surveillance goals is crucial. Surveillance case definitions are created for the purpose of standardization, new patient cases, whereas physicians appropriately are on the side of over-diagnosis, merely counting them does not cases, surveillance case definitions appropriately are on the side of specificity, thereby ensuring that they do not disproportionately require ill-treatment in other conditions (115).

The CDC further notes that it is inappropriate to use surveillance case definitions for making clinical diagnosis, determining the standard of care necessary for a particular patient, setting guidelines for quality assurance, or providing standards for reimbursement (116).

Factor that may complicate treatment B. burgdorferi, the spirochete bacterium that causes Lyme disease, is at extremely complex organism. The genetic structure of B. burgdorferi is the most complex identified in a prokaryote (117). Experimentally, B. burgdorferi has been shown to penetrate human fibroblasts and live insatiably even when the extracellular milieu contains bioavailable levels of nutrients (118,119,120). This mechanism may permit the spirochete to evade normal host defense mechanisms (120). Their findings are critically important, since chronic infections are highly dependent on an immunosuppressed patient as a mode of persistence (121). Intracellular pathogens are notoriously difficult to treat and cure (122).
Divergent treatment options

Antibiotic treatment

The ideal antibiotic, route of administration, and duration of treatment for persistent Lyme disease are not established. No single antibiotic or combination of antibiotics appears to be capable of completely eradicating the infection, and treatment failures or relapses are reported with all regimens, although they are less common with early aggressive treatment.

There appear to be discrepancies in antibiotic choices. Pre-Muric and colleagues found substantial variation in the kill rate of given antibiotics within different strains of B. burgdorferi and even within the same species. They described other antibiotics that may be more effective than penicillin in the bactericidal and eradication phases of the infection. These antibiotics may be more effective than penicillin in the treatment of Lyme borreliosis.

No fixed treatment and point creates divergent treatment options

There are no reliable microbiologic or immunologic criteria to document active infection in Lyme disease. Without reliable biological markers, the risk of determining who has the disease, the effectiveness of a course of treatment, or the end point of treatment is problematic. The lack of definitive diagnostic tests for Lyme disease, not only means that diagnosis is a clinical determination, but also that treatment and point must be determined by other means, becoming, by definition, essentially clinical determination.

Neither the Western blot nor the ELISA tests are sufficiently quantitative to enable one to monitor and evaluate the efficacy of antibiotic therapy during the course of treatment. The Western blot is not a test that is both sensitive and diagnostic of acute infections with B. burgdorferi and would not be able to identify those patients who would benefit from antibiotic therapy, nor would it occur in the treatment of infections (1:256).

Two Lyme camps

Given the current lack of a test that can document the presence of B. burgdorferi and the lack of studies demonstrating the optimum length of antibiotic treatment or even the optimum choice of antibiotic in patients, two different schools of practice have emerged. Some physicians treat for 30 days regardless of patient response unless relapse is shown by relevant objective measures.

Other physicians reason that if a diagnosis cannot be made clinically because the current diagnostic tests are inadequate, then the determination of the treatment end point must also be made clinically (1:256). The different approaches are equally valid, and time will reveal the difference between the two Lyme camps.

A number of conflicting guidelines reflecting the views of the two Lyme camps have been promulgated over the years. Most recently, a set of guidelines was published under the auspices of the Infectious Disease Society of America (IDSA) in 2000; while another set was published by the International Lyme and Associated Diseases Society (ILADS) in 1998. Both guidelines are evidence-based and peer-reviewed, with the IDSA generally recommending short-term treatment and ILADS recommending individualized treatment based on the clinical course of the patient.

Short-term treatment approach

The short-term treatment approach is reflected in the IDSA guidelines. Although the IDSA itself is a large specialty organization, the panel that drafted the guidelines was heavily drawn from and combined mostly exclusively of academic rheumatists with well-known institutional views, representing one of the two Lyme camps.

The guidelines advise that response to treatment is usually slow and may be incomplete but nevertheless after a 30-day course of antibiotics, is not recommended in the avoidance of reliable objective measures. The guidelines also state that there are no convincing published data showing that repeated or prolonged courses of oral or intravenous antimicrobial therapy are effective for this purpose.

Physicians advocating the short-term treatment approach note the overlap of symptoms of persistent Lyme disease and other autoimmune diseases and hypothesize that any persistent
Symptoms after treatment reflect an autoimmune process triggered by the infection. Basically, three physicians assume that the infection has been eradicated once the patient has received the presumptively adequate antibiotic treatment. They provide the patient with palliative treatment for the remaining symptoms. The assumption that the infection has been adequately treated is presumptively because:

- There have been no trials demonstrating the efficacy of the 30-day antibiotic treatment duration
- There is currently no diagnostic test that can establish the eradication of B. burgdorferi
- There is no evidence to support the hypothesis that the late-stage syndromes that persisting symptoms is the precursor of immune complexes

Terminating treatment despite persistent symptoms is a high-stakes risk for patients with progressive disease. In addition, steroids, which may be used to crud autoimmune conditions, increase the propensity of active infection and are contraindicated for active Lyme disease (76). Some physicians have characterized the termination of treatment despite persistent symptoms as medically sanctioned negligence (76), because termination of treatment may result in advanced neurological injury, debilitation, and death (71).

The IDSA guidelines have drawn sharp criticism from treating physicians (71,87) and patients (88) because they make strong influential treatment recommendations based on weak evidence, place undue weights on flawed laboratory tests, discount the diagnostic value of patient symptoms, and fail to consider individual treatment response variability, coinfections, patient preferences, or treatment options. Moreover, they do not contain any data of note regarding the treatment of patients with late and chronic Lyme disease. The focus on reliable objective measures as a determinant for the continued treatment of symptomatic patients is particularly disturbing in light of the current state of diagnostic testing. Straubinger's animal studies proved persistent infection after antibiotic treatment only by harvesting 25 tissue samples from each dog at necropsy (76). Animal studies indicate that considerable infection with B. burgdorferi in the CNS can be present without overt clinical signs (76). As the CDC, NIAMD, and FDA all have acknowledged (71,2016), the commercially available tests today simply cannot carry the weight of this food, which is why each of these agencies call for clinical diagnosis and discourage over reliance on laboratory tests.

Long-term treatment

The longer-term treatment approach is reflected in the IDSA guidelines. IDSA is an interdisciplinary group of physicians and researchers dedicated to improving the diagnosis and treatment of tick-borne diseases. Members include virologists, immunologists, internists, family practitioners, pediatricians, immunologists, infinologists, and psychiatrists. The IDSA guidelines stipulate that a laboratory test should play a supportive role in the clinical diagnosis and treatment determinations for Lyme disease. Similarly, the duration of therapy should be guided by clinical response to treatment, and treatment should continue until resolution of laboratory abnormalities and symptoms. The treatment guidelines discuss persistent, recurrent and refractory Lyme disease, treatment failure, and coinfection.

Physicians who advocate long-term antibiotic treatment use empirically recommended courses of antibiotics on the clinical evidence of active infection that is demonstrated at treatment duration. Evidence of ongoing infection is determined by examining clinical data, including persistence of symptoms, serologic testing, and other forms of corroborating tests such as MRI scans, SPECT imaging, autoantibodies, or other neurological indications. Ultimately, the determination of efficacy is dependent on the clinical response. Once a physician determines the treatment approach as follows:

- Currently, no definitive tests are available for assessing the complete absence of borreliae in patients. Only through a careful evaluation of individual clinical data can the ongoing duration of treatment be established. Our observations indicate that if antibiotic therapy is terminated before the major active symptoms have cleared, a relapse is likely (74).

Physicians who advocate a long-term treatment approach point to:

- High rate of treatment failures using short-term antibiotics
- Studies showing persistent infection despite antibiotic treatment
- Clinical evidence that antibiotic treatment may suppress but not eradicate infection in some patients
- Clinical evidence of the benefit of longer treatment regimens
- Favorable clinical response of patients who are reviewed

These physicians believe that it is likely that standardization of treatment regimens, and that these regimens should be individualized based on the patient's symptoms and clinical course. From experience, they have seen that prolonged courses of therapy similar to those used in other chronic diseases such as tuberculosis and lupus are more in keeping with the treatment needs of patients with persisting symptoms of Lyme disease. Although they acknowledge that immunosuppression may contribute to symptoms in chronic Lyme disease, they regard it as unlikely that this activity accounts for the majority of symptoms in Lyme disease patients, particularly given that many of the symptoms are not inflammatory, improve in response to antibiotic treatment (75). Moreover, some macrolide antibiotics have recently been shown to possess not only bactericidal effects but also immunomodulatory effects (87).

Validation of guidelines

The IDSA guidelines provide for validation using a single-center, prospective, surveillance database and encourage additional treatment outcome studies, while no validation procedure is provided for the IDSA guidelines. IDSA notes that treatment following the IDSA guidelines has been successful and recommend that centers employing the IDSA guidelines perform formal validation.
The period of follow-up appears to be critical in determining relapse rates given the low recurrence of symptoms in initially recovered patients (Table 1). Short-term studies that do not last 2 to 4 years, even in patients with negative serological testing, tend to show lower relapse rates than longer-term studies. A few studies have shown that relapse rates remain constant even after 2 years of follow-up, suggesting that the immune system may have reached a state of equilibrium. However, these studies have been limited by sample size and the use of less sensitive testing methods.

**Table 1. Treatment failures and relapses of short-term therapy for *Borrelia burgdorferi* infection.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Rx Duration</th>
<th>Rx Failure</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td>37%</td>
<td>69 out of 184</td>
<td>Overall, 69 case patients (37%) relapsed a previous relapse of Lyme disease</td>
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<td></td>
<td>&gt;50%</td>
<td>(44 total)</td>
<td>4.2 ± 1.2 years after 2-3 weeks of intravenous ceftriaxone 2 g daily, more than half of the 44 patients with clinical signs of neuroborreliosis and specific intrathecal antibody production had hospital complaints resembling acute clinical fatigue syndrome and showed persisting positive immunoglobulin M tests for <em>Borrelia burgdorferi</em> in western blot analysis</td>
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<td></td>
<td>30%</td>
<td>(40 out of 126)</td>
<td>3 years after treatment of 26 patients, 10 showed progressive improvement of relapse occurred in 21 patients and new manifestations in 4 of the cases</td>
</tr>
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<td></td>
<td>25%</td>
<td>(10 out of 36)</td>
<td>Within 1 year of treatment, 10 of 36 patients reported relapse and had repeated antibiotic treatment (five patients with intravenous ceftriaxone)</td>
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<td></td>
<td>20%</td>
<td>(60 out of 314)</td>
<td>A mean of 12 years after treatment, 20% had relapsed with major organ involvement; 18% relapsed. <em>Borrelia burgdorferi</em> also was reisolated in 29% (43/150) patients were symptomatic. Clinically definite Lyme disease had been found in 19 (9%) patients. Persistent symptoms in 110 (53%)</td>
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<td>20%</td>
<td>(10 out of 51)</td>
<td>A mean of 8.1 months after a 3-week course of intravenous ceftriaxone or cefuroxime, 10 of 12 patients were symptomatic and <em>Borrelia burgdorferi</em> was isolated from the cerebrospinal fluid of one patient</td>
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<td></td>
<td>17%</td>
<td>(10 out of 51)</td>
<td>6 months after a 2-week course of intravenous ceftriaxone (2 g daily) of 17 patients (69%) showed improvement, but 50% showed no improvement and four (18%) showed no change in their condition</td>
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**Persistence of infection despite antibiotic treatment**

The persistence of *B. burgdorferi* despite presumptive adequate antibiotic treatment has been repeatedly demonstrated by persistent infection of the bloodstream. In fact, *B. burgdorferi* has been cultured from patients who have been given intensive antibiotic therapy. A patient with antibiotic-resistant *B. burgdorferi* infection, 23 days after a 10 day course, from the bloodstream, was found to have a large number of *B. burgdorferi* in the bloodstream, which was not detectable in the treated patients. The exact cause of this persistence is unknown, but it has been suggested that the persistence of *B. burgdorferi* may be due to the inability of the body to eliminate the bacteria from the bloodstream. Further investigation is needed to determine the exact cause of this persistence.

**References**

The reason for this persistence is not known. Researchers have proposed various factors, including the presence of the B. burgdorferi bacterium, the immune system, and the potential for the infection to spread to other organs.

Long application time, as well as genetic variability may also contribute to the organism's resistance to standard treatments. B. burgdorferi infection in Lyme disease and other diseases is believed to contribute to resistance to standard immunologic functions and evasion of immune system attacks.

In chronic Lyme disease, the symptoms persist even after treatment with antibiotics. The duration of symptoms can vary from months to years, and the treatment may be ineffective.

Unfortunately, there is evidence that in some cases, antibiotic treatment of late Lyme disease, as in late syphilis and chronic tuberculosis, may merely suppress the infection and not cure it.

A urinary tract infection may be treated with different antibiotics, depending on the severity and duration of symptoms, and the type of organism involved.
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-recommended regimen for leprosy is a combination of three antimicrobial agents administered for 2 years (199-219). Cope and colleagues have observed the similarities between Lyme disease and other spirochetal infections such as syphilis and leptospirosis, both of which may also require long-term treatment regimens (61).

The immune-evasion strategy of B. burgdorferi is analogous to mycobacterial infections such as tuberculosis or leprosy (5-7), and many physicians find the treatment guidelines for these conditions in keeping with their clinical observations of what is needed for the eradication of chronic spirochetal infection in Lyme disease (202,203,204,205). A number of researchers have also found that long-term treatment provides a better treatment response (Table 4).

Conflicting long-term treatment studies

Studies of long-term treatment outcomes have yielded conflicting results. One study by Wilsbach and colleagues of 100 patients with late Lyme disease in the Aland Islands compared the length of treatment with therapeutic efficacy and found that longer treatment periods were significantly more successful (45). Successful treatment outcomes occurred in only four out of 12 patients (33%) treated with 14 days of ceftriaxone. In contrast, successful outcomes were seen in 50 out of 59 patients (84%) treated with ceftriaxone followed by 100 days of amoxicillin (Amoxil®, GlaxoSmithKline) plus probenecid, and in 19 out of 23 patients (83%) treated with ceftriaxone followed by 100 days of doxycycline (Vibramycin®, Bristol-Myers Squibb). Chai observed a 90% excellent or good response in his study of 30 European patients with disseminated Lyme disease treated for 100 days (46). Despite study of 277 patients it is of particular interest because it showed that the longer the course of antibiotic treatment, the more improvement was seen. Following 2 months of treatment, 23% of patients had significantly improved (degree of improvement: 75-100%). In contrast, after 3 months of treatment, 61% of patients had significantly improved (97).

The NIH has funded their double-blind, placebo-controlled, treatment-outcome studies for persistent Lyme disease. One study is ongoing and is expected to be completed soon (98). The findings of the other two studies, one by Klesap and colleagues (99), and the other by Kapp and colleagues (100), are controversial. The Kapp study treated patients with persistent Lyme disease with 4 weeks of intravenous ceftriaxone. Following 6 months of treatment, 64% of patients showed an improvement in fatigue levels compared with 16.5% in the placebo group. The Klesap study that treated patients with 4 weeks of intravenous ceftriaxone followed by 2 months of oral doxycycline (Periostin®, CalBioChem), showed no improvement in those treated on the outcome measure, the SF-36 (a self-reported measure of ability to function).

The Klesap study has generated substantial controversy. ILADS has issued a detailed critique of the design flaws in the study (101). A subsequent commentator questioned the lead author's bias in the long-term treatment study, noting that halfway through the study Klesap commented to the press that it was irrelevant for any Lyme disease patient to take months of antibiotics for persisting symptoms of Lyme disease (102). The problem of bias in scientific studies and guidelines is well-known and is an issue of particular concern in Lyme disease because of the degree of controversy between the two Lyme camps (103).
Table 4. Benefit of longer treatment regimens for disseminated *Borreli a burgdorferi* infection.

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<th>Study</th>
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<td>Oksanen</td>
<td>Of 165 patients with disseminated Lyme disease treated for a median duration of 4 weeks, 72 had treatment failure.</td>
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|        | "We conclude that the treatment of Lyme borreliosis with appropriate antibiotic for more than 3 months may not always evaluate the specificity."
| Oksanen | 35 patients treated for 100 days. Consideration: the general overview of infection in patients with disseminated Lyme borreliosis, after 6 to 7 months of therapy indicates that prolonged course of antibiotics may be beneficial in this setting, since 59% of the patients showed excellent or good treatment response. |
| Rustad | Of 277 patients with chronic Lyme disease treated with penicillin for 1 to 11 months (mean 4.6 months), 30% were treated with penicillin for 4 weeks and 70% for 8 weeks. |
| Warming | Of 100 patients with late Lyme disease, the following success rates for treatment regimens were seen: 40% of 13 patients (61% treated with 14 days of ceftriaxone, 50% of 26 patients (81%) treated with cefuroxime followed by 600 mg/day plus probenicid, and 10 out of 23 patients (43%) treated with cefuroxime followed by 1000 mg of cefuroxime daily. |

This is a abiotic, and medical research is no exception. From the very outset, investigator bias can influence the general attitude toward a research project. Research is at its best when it is open, where previous ideas and is likely to approach a project with a point. In essence, a researcher who is convinced of a particular treatment or, worse, has a vested interest in it, could mimic science to demonstrate the efficacy of his therapy. Equally, an investigator with a preconceived negative attitude toward a particular intervention can at best to deprive its efficacy.

Although the Klempner study appears to contradict the findings of Oksanen and colleagues, Walford and colleagues and Denes and colleagues, the patients may design different treatments in different studies. Both the Klempner and Knupp studies were double-blind controlled studies, but they each used different antibiotic regimens (MP-36 vs. the fatigue-recovery cycle). The Oksanen, Walford and Denes studies were not controlled. Despite the present focus on controlled studies, it is important to remember that non-controlled studies often provide more clinically relevant treatment information (Tables). In addition, variations in study samples, treatment types and durations, and outcome measures make it difficult to compare these studies.

In a recent commentary, Stein reported that a central problem with Lyme disease studies in general, is that the patient group studied may be heterogeneous, as might be expected in the absence of accepted diagnostic criteria or biological markers. Positive therapeutic findings may therefore have been masked by biological noise (137). The lack of a homogeneous population in persistent Lyme disease studies is also suggested in the treatment guidelines (120). Animal studies do not suffer from the same flaws as those that plague human studies. Advantages of animal studies generally include the ability to have a study population that is initially homogeneous and pathogen-free, immune inoculation with B. burgdorferi, and quarantine against reinfection risk. In addition, after the treatment protocol, the animal may be sacrificed and extensive PCR testing of tissue samples may be performed to determine the effectiveness of the treatment. This cannot be done in human, in particular in human, in particular, a dog study that examined 25 tissue samples per dog demonstrated that while only 30 days of antibiotic therapy may reduce the bacterial load, it does not eradicate the organism (197). Thus, despite blindness and randomization, outcomes in human studies suffer from more uncertainty than those in animal investigations.

Steiner reported that all human studies focusing on Lyme disease face three fundamental issues:

- Which patients should be included - who is the definition of the condition, and what are the diagnostic criteria?
- Which treatment should be tried - what are the characteristics of chronic Lyme disease - if it is caused by persistent infection, how long should antimicrobial treatment be continued?
- What end point should be established - how should the response of objective complaints to treatment be assessed?

He concludes: "(Without an objective surrogate preferably biological marker to evaluate remission of homogeneous study groups, every attempt to add clinical questions in the realm of persistent Lyme disease) is doomed, almost by definition, to leave these questions (whether treatment protocols are appropriate and whether an ongoing infection occurred)."

The existence of a heterogeneous patient group suggests that individualization makes the standardization of treatment approach may be more effective. Until reliable biological markers for the disease are developed, there may be no substitute for observing the patient's actual response to treatment as determined by the appropriate diagnostic of antibiotic therapy.

The ongoing Lyme disease treatment study headed by Fallon at Columbia University is expected to be completed in 2005. However, if Stein's concern that valid study results require a strong biological marker is correct, the debate regarding the appropriate length of treatment for persistent Lyme disease is not likely be settled soon.

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As persistent Lyme disease symptoms respond to treatment with antibiotics, investigators have argued that three symptoms syndromes cannot only be caused by ongoing infection. Test post-infectious syndromes do not respond to multiple antibiotics. When symptoms persist, antibiotic treatment is generally followed by clinical improvement (7, 8). Relapsing disease is obvious in the teaching physicians and patients and generally responds to continuation of therapy (20). The trial and error approach in medicine is a constant. For instance, physician may institute medication doses to find a level that would best for a patient and may try a variety of different treatments approaches before finding the one that is the most effective test. If a patient presents with an infection, responds favorably to antibiotic treatment, relapses when the treatment is withdrawn and responds favorably when the treatment is reinstated, there is empirical evidence of an infectious process. This is one experimental treatment – it is the way infection has been tested for years (11).

Standard of care for treating Lyme disease
Role of evidence & consensus in the standard of care

Historically, the physician's judgment has taken the leading role in medical decisions. This is reflected in the legal standard for determining standard of care that is determined by the consensus of professional judgment in the community. Since the 1990s, however, radical forces of change have swept the medical field, including the introduction and increased use of controlled studies in medical research and the increased influence of the managed care industry on the practice of medicine. In this context, it is important to understand the relative roles of evidence and consensus in medicine, the risks and benefits of treatment guidelines, and the effect that each of these has on the legal standard of care.

Table 5. Favorable response to Borrelia burgdorferi treatment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Comments</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knapp</td>
<td>28 patients with persistent Lyme disease in a double-blind placebo-controlled study treated with intravenous etanercept for 4 weeks showed a 61% improvement rate on self-reported fatigue scale versus 15.8% of the placebo group</td>
<td>[120]</td>
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<tr>
<td>Fallen</td>
<td>16 patients treated with either interferon, intramuscular or oral antibiotics scored better on overall and individual measures of cognition. Those treated with intravenous antibiotics showed the greatest improvement.</td>
<td>[174]</td>
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<tr>
<td>Gil et al.</td>
<td>13 patients with clinical relapse and Borrelia burgdorferi culture or polymerase chain reaction positivity were retreated for an additional 4 to 6 weeks with intravenous antibiotics with a good response in 10 of 13 (78%)</td>
<td>[173]</td>
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<tr>
<td>Jintins</td>
<td>91 patients treated with either tetracycline, a combination of macrolide and hydroxychloroquine, or intravenous etanercept showed a cure rate of significant improvement of 18.4% or 85%, respectively</td>
<td>[144]</td>
</tr>
<tr>
<td>Lawrentz et al.</td>
<td>Despite appropriate and adequate antibiotics, the patient experienced repeated progressive neurocognitive relapses. Patient now on oral clonazepam for 22 months with no new symptoms or deficits</td>
<td>[175]</td>
</tr>
<tr>
<td>Masters</td>
<td>Patient treated with high dose of prednisolone for 6 months; he relapsed and spirochetes were subsequently cultured from his blood. The patient was placed back on antibiotics and responded to therapy</td>
<td>[170]</td>
</tr>
<tr>
<td>Cimino et al.</td>
<td>Two patients with chronic Lyme arthritis resistant to the recommended antibiotic regimens were cured by long-term treatment with tetracycline</td>
<td>[197]</td>
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Evidence attempting to document the actual effects of ordinary clinical care are relatively new phenomenon (196). Moreover, the actual situations calling for controlled studies may be far limited.

Diagnosis for appropriate make controlled should, therefore, only be in the absence of any well-established standard treatment. (if the response has substantial mean for use in the clinical wider of an investigational treatment, then may be considerable is with a randomized controlled study) that should deny the intervention to some subjects in the natural course of the study(195).

There is also a tendency in developing certain types of qualitative evidence as anecdotal, discrediting the fact that historically most medical research was of this nature (196). The cumulative weight of anecdotal evidence can be substantial. Toler, for instance, the information gleaned from aggregating isolated adverse drug event reports or outcomes research, which accesses the effectiveness of various medical practices in the real world by pooling large numbers of comparable patients (197). Many believe this type of outcomes research may be more meaningful than controlled trials because the effectiveness of the medical practice is assessed in actual practice settings (198). The cumulative value of anecdotal evidence is also presumably the reason why physician proficiency in an area may be predicted based on the volume of similar cases treated (199).

Similarly, evidence immediately available from the patient's history, clinical examination, presentation of symptoms, course of disease, and response to treatment may also be documented both by guidelines and on a broad basis (200). The evidence that comes from human experience is not likely to be included in studies (200). The cumulative value of anecdotal evidence is also presumably the reason why physician proficiency in an area may be predicted based on the volume of similar cases treated (199).

In practice, evidence-based medicine is essential to enhance the practice of medicine by integrating the medical professional's experience and the patient's right to choose between diagnostic and treatment options based on the best available clinical evidence (200). The best available evidence may vary from the known range of treatment options to the best available evidence. It may come from a wide range of sources in different well-designed randomized trials or expert opinions (200).

If a well-conducted randomized trial does not resolve the issue, the next best available evidence may be longitudinal or observational studies. If these do not provide the answers, expert opinions or clinical experience may provide the best available evidence. In the treatment of complex multi-variables, when treatment outcomes studies are limited and misleading, the most valuable evidence in fact may be the clinical course of an individual patient (200). For instance, patient response to treatment is considered an important diagnostic feature suggestive of Parkinson's disease. Similarly, in the context of the individual patient's clinical presentation, antibiotic responsiveness may be suggestive of Lyme disease.
While the IDSA guidelines would leave patient symptoms — except as reflected in quantifiable tests — completely out of the equation, it is important to recall the phrase, 'all that can be measured may not have value, and all that has value may not be measured.' The recommendation in the IDSA guidelines that patients' symptoms of relapse be disregarded in the absence of 'objective measures' is tantamount to asking a surgeon to operate with one hand tied behind their back.

Many conditions (such as Alzheimer's disease, Parkinson's disease, multiple sclerosis and psychological disorders) lack biological markers and therefore rely heavily on presenting symptoms for diagnosis. Evidence is scarce, and none of it should be ignored.

Role of evidence-based guidelines

Unlike Lyme disease, which was not discovered until the late 1970s, the treatment protocols of many diseases, such as tuberculosis, were established long ago and have been better able to weather the onslaught of cost-containment measures unhindered by managed care. With newly discovered diseases like Lyme disease, burgeoning treatment approaches do not have the luxury of unfolding over time unimpeded by outside economic influences. Physicians treating these newer maladies may have a hard time holding out for the goal of improving long-term health outcomes. Deeply entrenched viewpoint develop quickly in this environment, and economic battles may be fought by experts wearing white coats.

Certainly, the treatment controversy in Lyme disease has been framed by cost-containment issues, with some of the research appearing to be little more than deemed unactual tables [10]. Early on, guidelines for the treatment of Lyme disease were being written by actuarial firms, such as Milliman and Robertson, whose entire revenue stream is tied to help insurers manage costs [11]. It has been observed that if money were not an issue, there would be no treatment controversy in Lyme disease [6].

Recent reviews of practice guidelines have shown that most fall to meet quality standards [12], and that guidelines produced by specialty societies are generally of poor quality [13]. At their best, evidence-based guidelines represent an unbiased summary of the relevant research for the physician who is too busy to sift and review the research personally. At their worst, such guidelines represent attempts of third parties to influence the medical decision-making process. With the recent controversy surrounding the Centers for Medicare and Medicaid Services' denial of reimbursement for Lyme disease treatment, physicians may be faced with the dilemma of following guidelines that may not be in the best interest of their patients [14].

The problem of bias can result from a number of other factors, including entrenched ideological beliefs and professional territorial considerations [15]. Guideline developers necessarily make choices: whose views are represented on the drafting committee, which studies are included and how the studies are interpreted [16]. When guidelines conclude that evidence is or is not convincing or compelling, theppropriateness question is, to whom? When, as is more often than not, the case, the science is narrow, limited and conflicting, there can be a major leap between what the evidence lays out and what the guidelines suggest [17].

Evidence-based protocols reflect value judgments about the relative importance of health and economic outcomes in specific clinical situations. The question is whether these issues are being examined from the perspective of the insurer, the patient, the healthcare provider, or society as a whole — in other words, whose interests dominated the drafting panel? Not surprisingly, conflicting guidelines are common [18]. To overcome the tendency toward bias and to ensure that a broad body of evidence is reviewed by the drafting panel, the IOM recommends that panels include a diverse group of stakeholders that may be affected by the guidelines — treating physicians, patients, and researchers [17].

The panel drafting the ILAD's guidelines included primary care clinicians, researchers, community healthcare providers, and patients. In contrast, the IDSA did not solicit input from patient groups, nor from the physicians who treat the majority of patients with persistent Lyme disease — even those who are members of the IDSA [19]. When faced with divergent opinions regarding the treatment of persistent Lyme disease, the ILAD panel purged its sole dissenting member [20]. Moreover, 11 of the 12 authors of the guidelines were primarily infectious disease specialists with little or no experience treating patients with persistent Lyme disease [20]. Panel members who do not spend their days treating patients may fail to grasp either the complexity of the illness or the fact that 3,000 referred in randomized studies or the seriousness of failing to treat a patient with a progressive systemic illness.

Significantly, the goals of research and treatment are very different. Like surveillance, the goal of research is to see on the side of evolution to insus a homogeneous study population. The emphasis on measuring results based on reliable objective criteria also makes sense in this context. The fact that these criteria may exclude a single portion of patients who have the illness is not an issue for research purposes. Treatment goals, on the other hand, revolve around the issue of inclusion and overdiagnosis to ensure that serious conditions are not left untreated. When research criteria such as reliable objective measures are applied to treatment protocols, treatment goals are not met and patients are left untreated.
The IDSA guidelines recommend that symptomatic patients not be treated because 'there are no convincing published data' evidencing the efficacy of prolonged treatment or re-treatment. In making this assertion, the IDSA EPC cited studies evidencing persistent infection, including those listed in Table 2. Not surprisingly, failure to control all relevant evidence is one of the pitfalls the IOM warned against when guidelines are drafted by narrowly drawn panels. Similarly, the narrowness of the panel precludes the consensus that 'there is insufficient evidence to regard chronic Lyme disease as a separate diagnostic entity.'

Seen in this light, what the IDSA guidelines are really suggesting is that physicians refrain from treating patients until better science comes along—a view that undoubtedly holds greater appeal to insurers and researchers than patients. Yet even the strongest proponents of evidence-based medicine would not require that patients go untreated pending stronger evidence [942,97]. This notion has been soundly rejected by the IOM because 'scientific evidence is not likely to exist for a great many of the combinations of clinical problems and characteristics that patients bring to clinicians in the real world' [97].

The appropriate role of guidelines is to 'ensure that patients and practitioners are well informed about the risks and benefits of alternative courses of care' [17]. Guidelines that attempt to supplant, rather than inform, overstep their role in the decision-making process. When guidelines become pathfinders for the viewpoints of those on the drafting committee, they no longer serve as information tools that assist physicians and patients in their decision-making process [97], and instead fall prey to the criticism that they 'constitute the exercise of power without responsibility,' and only 'generate systematic and perennialistic pressure for the many to conform to the views of the few' [946].

Legal standard of care

The legal standard of care is defined as 'the care and skill ordinarily exercised in like cases by reputable members of the profession practicing in the same or similar locality under similar circumstances' [1012]. It is defined by the actual practice of physicians in the community, not by guidelines. The legal emphasis on consensus provides a suitable filter for the interest of stake-holders in guidelines. Consensus is, after all, not only a crude measure of the cumulative anecdotal evidence of practicing physicians; it also reflects the extent to which varying types of evidence (including controlled studies) have been critically reviewed and have demonstrated efficacy in actual medical practice.

As a legal matter, the relevance of evidence-based medical protocols in determining the standard of care depends upon the extent to which the practice recommended has been adopted within the medical community [1012]. In courts, the standard of care is determined by expert testimony [1016]. Although an expert may introduce evidence-based protocols in support of testimony, the protocols themselves do not establish a standard of care [1016].

Notwithstanding the rise in evidence-based medicine, the emphasis on a community-based standard of care is not likely to change. A survey of legal actions found that guidelines played a relevant or pivotal role in determining negligence in less than 7% of malpractice actions [1016]. Guidelines also appear to be understated in clinical practice, suggesting that their role in shaping consensus may be limited [1016]. In fact, as does the realization that, like expert testimony, the seemingly objective quantitative approach of guidelines is vulnerable to a 'subjectivity of objectivity' [1014], or thinly disputed (frequently even unintentional) bias clouded in science, with 'lured good' all around. Of course guidelines are not created on the eve of a trial to support one party over the other, but the risk of their misuse at instrument of cost control rather than as impartial guides for treatment decision is widely recognized.
The treatment issue seems to have created a split within the medical community in terms of practice, and all jurisdictions that have considered the matter have found that two standards of care exist in the treatment of persistent Lyme disease (Title 17, U.S. Code and Rev. Act 1942, 2004).

Role of clinical judgment when different treatment options exist

There is a controversy between scientific research and clinical judgment. Professional judgment must be applied to the scientific base, and science must inform professional judgment, not vice versa. The degree of individualization of treatment varies with the complexity of the illness and the amount of confounding variables involved, such as coinfactions. The greater the need for individualization, the greater the role of the clinical judgment of the treating physician plays.

In Lyme disease, treatment response is highly variable. The confounding variables affecting the course of treatment are extensive, and the amount of discretion required in treatment is considerable. Variables include:

- Length of time between tick bite, symptom onset, diagnosis, and treatment
- Presence of untreated (identified or not yet identified) coinfections
- Whether the patient's immune system is compromised
- Severity of the patient's presenting symptoms
- Presence of neurological symptoms
- Whether the course of the illness is progressive
- Whether the illness significantly affects the patient's quality of life or functional level of achievement
- Patient's response to treatment
- Whether the patient is antibiotic responsive
- Which medications the patient can tolerate
- Whether prior treatment was sufficient in terms of antibiotic dose and duration
- Whether the patient relapses when treatment is withdrawn
- Whether diagnostic tests, symptoms or treatment response suggest ongoing infection
- Risks/benefits of the treatment approach under consideration
- Alternative treatment approaches available
- Risks associated with failing to treat

Needless to say, separate scientific studies do not exist isolating each of these variables.

Even those who follow the treatment approach advocated by the IDSA are not at liberty to ignore the clinical presentation of their patients. In the absence of a clear alternative exists, progressive neurological symptoms in patients with a prior diagnosis of Lyme disease should raise a high degree of suspicion that the infection is ongoing. Similarly, if a patient responds to treatment and then relapses when treatment is discontinued, a physician who elects to withhold treatment of this patient's antibiotic responsive condition does so at substantial risk. The variability in patient response to treatment has critical implications in the treatment of Lyme disease.

When faced with uncertainty, physicians must make an election (and accept the accompanying risk) to over- or under-treat a condition. While insurers implement cost-containment measures to guard against wasteful defensive medicine, the goal of the medical malpractice system is to deter... healthcare providers from putting patients at excessive risk of bad outcomes (166). Medication that improves outcomes contributes to the deterrence goal. The Office of Technology Assessment suggests weighing the following factors (166):

- Whether the disease under consideration is life-threatening or disabling
- Whether timely decision change therapy
- Whether the change in therapy can be expected to make a real difference to the patient's ultimate state of health
- Whether the treatment option is readily available and low risk

When the medical implications of being wrong are serious, as in the case of a life-threatening or debilitating condition such as Lyme disease for which early diagnosis or treatment may have substantial consequences for the patient while the risks of treatment are relatively low, electing to treat the patient may be the more prudent course.

Approximately 25 to 50% of medical malpractice lawsuits alleged missed or delayed diagnosis (and treatment) (295). When the medical consequences of being wrong are severe, to wit are the consequences of malpractice. Failure to diagnose and treat Aaron Murray, a 14-year-old boy who then suffered a significant decline in cognitive function, resulted in an original judgment of US$5.2 million (subsequently reduced to US$4.8 million) against his medical provider (923).

Role of patient preference when different treatment options exist

Good medical care requires that decision-making be shared to varying degrees between practitioners and patients (117). Respect for the basic autonomy of the patient is a fundamental principle of medical ethics (296). Without adequate information about treatment options, their probable outcomes, and the risks and benefits associated with each, patients cannot act autonomously. The American Medical Association requires that the physician disclose and discuss with the patient, not only the risks and benefits of the proposed treatment, but also those of available treatment options (regardless of their cost) to the extent to which the treatment options are covered by health insurance.

The physician's role in this process is to provide information to the patient along with any treatment recommendations that the physician may have based on previous clinical experience and a review of relevant research. Regardless of the physician's personal or professional views on the matter, the final decision among treatment options should be the patient's (347).

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The reason patient preference matters is that a large role in the decision-making process is clear because patients ultimately reap the benefits and burdens of medical decisions. We must end by respecting patient autonomy unless there is a very compelling reason not to do so (110). When a patient has a serious illness, like Lyme disease, where different treatment options exist with different risk-benefit profiles, the stakes are high, and there is no correct treatment. The treatment choice involves trade-offs between the risks and benefits of the different treatment options that only patients—who know the kinds of risks they are willing to take and the kinds of quality of life trade-offs that matter to them—are uniquely suited to make (144).

Respect for autonomy is the primary moral justification underlying the legal obligation to obtain informed consent. Excess in emergency situations, a healthcare provider must obtain consent from a patient for a course of treatment. The scope of this duty is measured by the amount of information necessary for a patient to make an informed choice in the selection of treatment. California has adopted the patient's point of view on informed consent:

The patient's right to self-determination is the measure of the physician's duty to reveal. That right can be effectively exercised only if the patient possesses adequate information to enable an intelligent choice. The scope of the physician's communication to the patient, then, must be measured by the patient's need, and that is whatever information is material to the decision (151).

The physician must choose to a patient material treatment options. In Melito v. Murray, the California Court of Appeal discussed this issue:

"The (physician) . . . would have a duty . . . to disclose the two recognized schools of treatment so that the patient could be sufficiently informed to make the final, general decision. As the Cobb court explained, (a) medical doctor, being the expert, appreciates the risks inherent in the procedure he is prescribing, the risks of a decision not to undergo the treatment, and the probability of a successful outcome of the treatment. But once that information has been disclosed, that aspect of the doctor's expertise function has been performed. The weighing of these risks against the individual subjective facts and hopes of the patient is not an expert skill. Such evaluation and decision is a nonmedical judgment reserved to the patient alone (155)."

In the case of mặtito v. Macromotions, the New Jersey Supreme Court also upheld the patient's right to make an informed decision among medically reasonable treatment options, and did not deem informed consent to have been given when the physician discussed only the physician's treatment (or non-treatment) of choice. The court stated that 'physicians may neither impose their values on their patients nor substitute their level of risk aversion for that of their Patients' (151)."
Role of insurance when treatment options exist

When managed care tools began to be used in the healthcare marketplace, the economic incentives to deny payers or access to care began to impact the medical decisions made by physicians. The reason in which the policies of managed care companies can interfere with Lyman disease treatment decisions is illustrated by a patient who died within 1 month of being denied further insurance coverage for incurable antibiotic treatment (195).

To deal with the influence that managed care can have on medical decision making, courts began applying the state standard of care applicable to health professionals to other entities participating in managed care. Today, the same clinical standard of care applies to all parties involved in medical decision making, including physicians, hospitals, and utilization reviewers (196-199).

The legal standard of care is controversial and reflects the pressures of today's physicians (200). Unfortunately, there is evidence to suggest that many managed care organizations rely heavily on summary procedures to deny patients the treatments reimbursed by their physicians (201). This coupled with the fact that managed care organizations are incentivized to increase profits by reducing costs at the expense of expected treatment outcomes (202), creates a significant potential for abuse.

Many, if not most, medical care, even that which is generally accepted in the medical community, would be denied under an insurer-based standard because of the lack of cost-saving measures available to providers. The lack of treatment approval by managed care organizations is not incidental to the goal of containing costs but is instead intended to control costs (203).

Even worse, some commentators suggest that the use of summary procedures as trip wires for treatment denotes a wide variety of scenarios involving potential fraud, waste, and abuse (204). The Utilization Review Accreditation Commission (URAC) and the National Committee for Quality Assurance, both insurance accreditation organizations, provide that only licensed physicians can make medical necessity decisions or deny treatment. In fact, Standards 22 and 33 of URAC's Health Utilization Management Standards require that organizations provide the patient or his physician with the clinical rationale for the denial, which must be reviewed specifically by the patient's physician (205).

This is because a physician's clinical judgment, taken into account the patient's unique clinical presentation and course of treatments, is key to determining the standard of care. When an insurance company physician merely renders and communications treatments guidelines to the treating physician, there is no excuse for independent clinical judgment. Such attempts to devise a rate structure fail short of the mark.

Beyond this, medical necessity is the legal standard of care that applies to all medical decisions. The standard of care is the specific analytical process, which produces a clinical yardstick (reflecting both the art and science of medicine) and holds providers and managed care systems accountable in determining exposure to liability. It is based on national and
elated physician practices, as opposed to the medical practices or paper review practices of the managed care organization or insurer. Allowing each provider to define medical necessity individually would essentially allow insurers to define their own standard of care—a notion that has been soundly rejected by the courts (1995). Guidelines do not constitute the standard of care, which must be based on the clinical judgment of practicing physicians taking into account the unique clinical presentation and course of treatments for the particular patient. There relying on guidelines or other cost-containment mechanisms for any part of the medical decision-making process are not required of their obligation to follow the clinical standard of care. However impressive the organization that sponsored the guidelines, or its peers, for developing them, the fact that a protocol exists is a particular condition does not mean that what it proposes is true. Nor does it guarantee that the protocol accurately represents ordinary practice—questioning may address the scope of the guidelines, how it was developed and adopted, the existence of known exceptions to its application, and whether any school of medical thought rejects it and offers a different approach to treatment. (1995)

Courts have held that certain guideline developers can be held liable for faulty guidelines, and that doctors (and other medical decision makers, including insurers) cannot pass off their liability by claiming that adherence to guidelines has corrected clinical judgment (1995). Third-party payers may be liable for injuries caused by negligent utilization review decisions (1995). The courts in the case of Wachter v. State of California stated that third-party payers can be held liable when medically inappropriate decisions result from, or implementation of cost containment mechanisms (1995). Although the patient had not sued the treating physician, the case further noted that the physician who compiles without protest—when his medical judgment dictates otherwise—cannot avoid his ultimate responsibility for his patient's care. Specifically, cost containment mechanisms were one of the key factors in Murray v. Cheeseboro, in which the court held the findings in the US3.2 million verdict (1995). This principle is also recognized by the Department of Quality Assurance of the American Medical Association, the American College of Medical Quality, and the US Agency for Healthcare Research and Quality.

In cases focusing on whether a treatment provided is medically necessary, a treating physician's judgment, while not dispositive, is entitled to great deference by the courts. In Saborh v. Blue Shield of California, the court stated that 'with doubt respecting coverage resolved in favor of the subscribers, there will be few cases in which the physician's judgment is in plain unassailable or counter to good medical practice, that the coverage must be refused' (1995). Furthermore, all utilization review decisions must be consistent with community medical standards. In Hughes v. Blue Cross of Northern California, the court found that the insurer breached the covenant of good faith by employing a standard of medical necessity that was significantly at variance with community standards. Consistent with the doctrine that policy language be construed literally in favor of the insured, the court also made it clear that the 'medical necessity' will be defined literally (1995).

The obligation of insurance companies is either to render services in conformity with the standard of care applicable to the medical community at large or to reimburse the insured for medical services provided within that standard of care, subject to any existing exclusions of benefits restated in the insurance contracts. When two standards of care exist, the obligation is to provide reimbursement or reimbursement for treatment conforming to either standard of care. Under the medical ethics doctrine of autonomy and the legal principle of informed consent, the choice between different treatment approaches must remain with the patient after consultation with the treating physician. The absence of malpractice does not imply the presence of informed consent (1995).

Employee Retirement Income Security Act

In many instances, state law may be preempted by the federal Employee Retirement Income Security Act (ERISA) for insurance plans offered by employers to their employees. ERISA imposes on the insurer the same substantial and capacious standard that applies to fiduciaries generally and limits extracontractual and punitive damages. ERISA was initially enacted to protect against breaches of fiduciary duty by those administering pension plans, and its application to health insurance medical malpractice situations has been a constant exercise leading to lawsuits without any adequate remedy when insurers favor reducing short-term costs over improving long-term patient outcomes. Due to the inequities that arise when ERISA is applied to malpractice situations, there has been a trend toward narrowing the ERISA preemption, through:

Case law imposing state malpractice law standards in cases involving mixed benefits and treatment decisions.

State statutory law explicitly imposing state common law to cases that might otherwise have been pre-empted by ERISA.

Recently, the Supreme Court ruled that state statutory law could not survive an ERISA preemption claim and refused to permit a malpractice claim against insurers under a mixed benefit and treatment standard in the case of Aetna Health Inc. v. Davila, 513 U.S. 681, 251 J. 2004. It is noteworthy, however, that the Supreme Court pointedly differentiated the present cases from previous mixed benefit and treatment cases involving the decisions of treating physicians or treating physicians' employers. In making the ruling, Justice Ginsburg and Breyer issued a concurring opinion, but joined the 'striking judicial chorus urging the Congress and the courts revisit what is an injustice and increasingly tangled ERISA regime'. The decision resulted in renewed calls for Congress to either amend ERISA or pass patients' rights legislation. Due to the fact that the analysis of law is currently under significant flux, the import of ERISA on the state law obligations applicable to insurers is beyond the scope of this article.
Expert opinion

Knowledgeable and respected professionals can, and often do, come down on opposite sides of a particular treatment issue. When this occurs, the standards of care embrace the practices of each of the different schools of thought. Regardless of the standard of care preferred by a physician, the physicist is required to exercise the best clinical judgment, and to present to the patient and the patient's unique clinical presentation.

The existence of treatment options with different risks and benefits shifts the focus to patient preferences. Patients cannot make informed, autonomous choices among options unless the physician discloses the patient's options information about different treatment approaches to enable the patient to make a meaningful choice. Once this information has been disclosed to the patient, the decision about treatment shifts to the patient.

In the treatment of persistent Lyman disease, two schools of thought have emerged, and patients are faced with a choice of treatment options. The obligation of insurance companies is to render services in conformity with either community-based standard of care, or to reimburse the insured for medical services provided within either standard of care, subject to any exclusion of benefits contained in the insurance contract. However, in the absence of a provision to the contrary in the insurance contract, the determination of treatment choice ultimately remains with the patient, not the insurer.

Allowing a serious multisystemic infection to progress unabated can result in irreparable physical damage, deterioration, and death. Untreated Lyman disease may mimic other conditions such as varicella, depolarizing disorders, von Recklinghausen disease and dementia (50). While it can be expensive to treat persistent Lyman disease, this cost pales in comparison with the cost of untreated Lyman disease manifesting as progressive neurologic and cardiac disorders.

The central difficulties in the diagnosis and treatment of Lyman disease stem from the lack of sufficiently sensitive and reliable biological markers of the disease. Without such markers, it is difficult to determine which has the disease, the effectiveness of a course of treatment, and the end point of treatment. Under these circumstancess, the best evidence to guide treatment decisions may be the patient's unique clinical course. Medical decision-making in the gray zone exists on a continuum, framed by the competing goals of avoiding unnecessary costs on the one hand, and avoiding suboptimal exposure on the other hand. Here, too, rules can make a legal, medical, and moral purpose by promoting medical accountability (51). The treating physician should keep in mind that the factors against which those frequently competing goals must be balanced is the patient's individual clinical presentation and preferences.

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A key concern with Lyman disease outcomes studies to date has been the suggestion that the conflicting results of these trials may reflect a heterogeneous patient population (52). The need to provide more flexibility in standardized treatment regimen represents an important area of development. For instance, recent study of chronic hepatitis C suggested a novel approach to treating heterogeneous patient groups. In that study, the length of treatment given was individualized, based on whether the patient was deemed to be a rapid responder, slow partial responder, flat partial responder, or a null responder (53). Similar novel treatment strategies based on patient individualization may be required to solve the treatment issues in chronic Lyman disease. Those with persistent Lyman disease may be recognized as a heterogeneous group, consisting of patients who respond rapidly, slowly, partially, or not at all to anticoagulant treatment.

Another issue that may contribute to heterogeneity among persistent Lyman disease patients is the number of pathogens creating the illness. Since the identification of B. burgdorferi as the agent of Lyman disease in 1982, 15 tick-borne bacterial pathogens have been described throughout the world, including three species of Ehrlichia, and four species (possibly five) of B. burgdorferi (54). Scientists have yet not identified all of the pathogens that ticks carry (55). Until we can able to identify all of the infectious agents contributing to a patient's illness, difficulties may be expected in determining the appropriate course of treatment. Moreover, the diversity of species of bacteria among the tick-borne pathogens also complicates diagnosis because current antibiotic tests are species-specific (56). Improvement in genotyping techniques holds promise for not only detecting and identifying other pathogenic bacteria carried by ticks in the future, but also improving the diagnostic tests used to determine who should be treated, whether a course of treatment is being effective, and when treatment has been successful.

The increasing understanding of human genetics may also influence the treatment of persistent Lyman disease. While it is known that host genes (human leukocyte antigen HLA-H) may be associated with chronic Lyman arthritis and lack of response to antibiotic treatment (57), other genes may eventually be associated with persistence of neurologic Lyman disease in the future. Those advances, in turn, could affect the determination of the best course of treatment for an individual patient.

Recently, the focus of a large pharmaceutical company disclosed high failure rates of commonly prescribed medications due to the genetic variation of patients (more than 90% of medications work only 90-90% of patients), and the executive proposed targeting drugs to genetically determined responsive patients (58). Genetic testing that would enable a physician to target drug treatment to persistent Lyman disease patients would fundamentally alter the landscape of Lyman disease diagnosis and treatment.

The 5-year view in terms of the medical assessment depends on a large degree on the extent to which the Lyman continuum can be disrupted. Scientific uncertainty is not settled by opinion — even the opinion of researchers. Moreover, when researchers start to hold entrenched viewpoints, science itself is in trouble. In the present palaeolithic environment, even the ability to design appropriate research studies.

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Unfortunately, researchers who adhere to short-term treatment protocols have rebuffed past proposals by members of IADS for convening a dialogue between the two camps. When invited by legislative bodies to participate in an open forum, these same researchers, by and large, refuse to partici- pate. This is clearly unacceptable conduct for those who receive public funding to conduct research. There can be no progress in bridging the gap between the two camps without dialogue. The government, which holds the purse strings for the research grants, has the power and the obligation to ensure that researchers who receive grants engage in the type of open dialogue and free exchange of ideas vital to the perform- ance of research that addresses the needs of all stakeholders in this controversy.

In summary, although this 5-year mediolocial perspective is not particularly optimistic, more enlightened funding of Lyme disease research by government agencies and initiation of meaningful dialogue between the Lyme camps should ultimately lead to resolution of the "Lyme war".

Acknowledgements
The authors thank Beverafield, R. Dickson, K. Duvall, P. Fallon, B. Gallo, A. Gerberding, J. Harris, N. Harris, S. Harvey, W. Haggard M. Johannes B. Kremers A. Lane B. Luger K. Lull R. Moore D. Macnow S. Phillips F. Prevo W. Silva S. Smith H. Sugerman G. and Winger E. for the helpful discussion. The authors are grateful to Graves L. Maxon L. and Shepard L. for mediolocial commentary, and to Haggard M. for technical assistance. The authors would also like to thank Smith P. of the Lyme Disease Association, Moore B. L. Sullivan L. L. Leonard P. and Banter Andi B. of the California Lyme Disease Association, and Forscher K. of the Lyme Disease Foundation for continuing support. This article is dedicated to the memory of Paul Lavelle.

Key Issues
• The lack of sufficiently sensitive and reliable biological markers of Lyme disease makes it difficult to determine who has the disease, the effectiveness of a course of treatment and the end point of treatment.
• The bulk of medicine today is practiced in the gray zone, where evidence is unclear. Evidence-based medicine requires only that medicine be practiced in accordance with the evidence that currently exists, not that treatment be withheld pending research.
• Opinion is deeply divided regarding the best approach for treating persistent Lyme disease. This split has resulted in two standards of care, each of which is reflected in peer-reviewed, evidence-based guidelines.
• While each standard of care is supported by a strong underlying hypothesis, each research is limited and conflicting.
• The legal standard of care is determined by the practices of physicians who actually treat patients, not by treatment guidelines.
• All healthcare providers and insurers are held to the same legal standard of care. Medical necessity is determined by the legal standard of care.

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28. Para 11.2.1: Consider the diagnosis of Lyme disease in patients with symptoms consistent with those of Lyme disease, even if there is no history of exposure to tick bite.