Treatment of Lyme disease: a medicolegal assessment

Lorraine Johnson and Raphael B Stricker[†]

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 disase. First, the medical basis for diagnostic and 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.

Expert Rev. Anti-infect. Ther. 2(4), 533–557 (2004)

Lyme disease & diagnosis

Characteristics of Lyme disease

Ticks have been called 'sewers of infectious disease'. Hard-shelled (*Ixodes*) ticks are capable of transmitting *Borrelia burgdorferi*, the agent of Lyme disease, and other pathogens such as *Babesia*, *Ehrlichia* and *Bartonella*. 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 patient 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 [3,4]. This may allow the Lyme disease spirochete to disseminate rapidly and become entrenched and resistant early in the disease [5–7]. Although scientists believe that Lyme disease is transmitted primarily by ticks, some studies suggest gestational transmission and transmission by other insects, blood transfusion and intimate human contact [8–12].

In 2002, the number of Lyme disease cases reported to the US Centers for Disease Control and Prevention (CDC) increased by 40%, to 23,763 cases [13]. Since only 10 to 15% of Lyme disease cases are actually reported [12], it is estimated that the true number of cases throughout the USA may exceed 237,630 annually. The highest reported incidence of Lyme disease occurs in children under 15 years of age [12]. 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 [14]. 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 [15,16,201]. 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 disorder, Lyme disease can manifest with:

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

- 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, with or without arthritis
- Heart involvement (causing irregularities in heart rhythm and congestive heart failure)

Lyme disease mimics many other conditions, including psychiatric syndromes, progressive dementias, seizure disorders, strokes, extrapyramidal disorders, amyotrophic lateral sclerosis, Guillain–Barre syndrome and progressive demyelinating diseases such as multiple sclerosis [17]. *B. burgdorferi* genospecies are believed to exhibit strain-dependent organotropism, with the two European species *Borrelia afzelii* and *Borrelia garinii* observed to produce a predominance of skin and neurologic symptoms, respectively [18]. The potential strain-dependent organotropism of *B. burgdorferi* genospecies 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 atypical) rash or a flu-like illness. While the EM rash alone is generally considered diagnostic of Lyme disease, only 68% of reported cases observed an EM rash [13].

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 [202].

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 [19]. 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.

Prompt diagnosis of Lyme disease is hampered by many factors. The spirochete can persist for years without causing symptoms [202], and some patients present initially with neurologic or rheumatologic complaints, since EM rash is either not present or is unrecognized or misdiagnosed [202]. 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 [20].

Lack of definitive laboratory tests for active infection

The most definitive diagnostic procedure for Lyme disease is biopsy and isolation of *B. burgdorferi* in culture [21]. However, *B. burgdorferi* spirochetes are scarce, tissue bound, and divide slowly [22], making it extremely difficult to culture the organism using routine methods [23,24]. Diagnosis of Lyme disease is most commonly supported by serological techniques that detect antibodies in the patient's blood [25]. Laboratory techniques that detect antibodies suffer from two primary drawbacks:

- A positive antibody response merely reflects past or present exposure to borrelia infection and, hence, is not truly diagnostic of on-going infection
- These techniques rely on the immune response following exposure and will necessarily fail if the patient is not producing detectable antibodies

There are many reasons why Lyme seronegativity might occur:

- Serologic tests may be given too early (before antibodies are formed); *B. burgdorferi* may not be present in the blood (it may be in tissues) or may have eluded the immune system by adopting a cell wall-deficient L-form
- Antibodies in the patient's blood may be bound into immune complexes
- Antibodies may not be present in the patient's blood for other reasons (e.g., the use of antibiotics early in the course of the disease or systemic steroid therapy may abrogate the immune response to *B. burgdorferi*, and late in the disease, antibody levels may fall to very low levels) [22,26–28]

The two most commonly used methods for detecting antibodies against the spirochetal agent 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 tests do not have adequate sensitivity to meet the two-tiered approach recommended by the CDC for surveillance [29]. Donta has observed that 52% of patients with chronic Lyme disease are found negative by ELISA but positive by western blot [30].

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 [203]. The western blot may be used to measure both immunoglobulin (Ig)M and G antibodies. Commonly, IgM antibodies appear first, wane after the first few weeks and do not recur. These are

followed by IgG antibodies, which are regarded as the major enduring antibody response in chronic infectious diseases. However, in Lyme disease, IgM antibodies may persist for years, suggesting persistent infection or a reactivation of latent infection (as is seen, for example, in toxoplasmosis, leishmaniasis and cytomegalovirus infection) [31]. A number of studies point to the importance of the IgM response in recurrent or persistent Lyme disease [32–36].

Physicians treating Lyme disease should consider the particular bands that test positive for an individual patient and the specificity of the bands to the disease [32,37]. Western blot bands have been shown to be important in the endemic setting of the region. A study by Engstrom and colleagues found that two of five bands gave them a specificity of 93 to 96% and a sensitivity of 100% in the 70% of the patients who manufactured antibodies [38]. 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 [39].

The issue of seronegativity 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 titers [40]. Another group of researchers showed that only 70% of documented Lyme disease patients in their study had a significant antibody response [41,42]. Another group found that approximately 20% of patients with Lyme disease were seronegative [32]. Ironically, seronegative patients may be the least able to mount an effective defense to the infection and, hence, may be the worst effected [204].

Other tests can help corroborate a diagnosis of Lyme disease. Polymerase chain reaction (PCR) that detects the presence of *B. burgdorferi* DNA in blood, CSF, urine, synovial fluid or tissues, is regarded as highly specific, but has a low yield, particularly in body fluids [43,44]. Signs of CNS involvement include elevated CSF protein or pleocytosis, abnormal brain single-photon emission computerized tomography (SPECT), magnetic resonance imaging (MRI) or electroencephalogram (EEG), intrathecal antibody production or a positive PCR for *B. burgdorferi*, or a positive culture.

Lyme disease is a clinical diagnosis

Demonstration of active infection is not feasible as a matter of routine, given the insensitivity of the PCR test, the impracticality of culture tests, and the drawbacks of antibody detection methods. Conversely, the current state of diagnostic testing cannot demonstrate the eradication of *B. burgdorferi* (because negative test results do not mean an absence of infection). Due to weaknesses in laboratory tests, the diagnosis of Lyme disease remains primarily clinical, with the focus on vector exposure and symptoms that reflect the multisystemic nature of the disease, with laboratory tests playing a supporting role [205].

The CDC, US Food and Drug Administration (FDA), and NIAID have all expressed concern regarding the over-reliance on laboratory tests for diagnosing Lyme disease [21,47,205], 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' [21]. In accordance with these recommendations, most practitioners use a clinical definition of Lyme disease that includes a combination of symptoms and clinical signs with or without positive serological support [45], although some clinicians maintain that diagnosis should be supported by positive serology [46].

Misuse of the CDC surveillance criteria for diagnosis

Misdiagnosis also occurs because of misuse of the strict CDC surveillance case definition and testing standards for diagnosis. The CDC surveillance definition does not take into account neurological Lyme disease nor chronic Lyme disease, and therefore misses many confirmed Lyme cases. For surveillance purposes, the CDC requires five of ten IgG bands and two of three IgM bands for a positive result. Although a majority (89%) of patients with EM-confirmed Lyme disease develop an IgG response at some time during the disease, only 22% are positive by CDC criteria [41,42]. In addition, for its surveillance definition, the CDC recommends a two-tiered testing approach. However, this approach is problematic because the first tier test, the ELISA test, lacks 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 [47].

As a CDC official explained, the distinction between diagnostic goals and surveillance goals is critical:

> *'Surveillance case definitions are created for the purpose of standardization, not patient care...whereas physicians appropriately err on the side of over-diagnosis, thereby assuring they don't miss a case, surveillance case definitions appropriately err on the side of specificity, thereby assuring that they do not inadvertently capture illnesses due to other conditions'* [206].

The CDC further notes that it is inappropriate to use surveillance case definitions 'for establishing clinical diagnoses, determining the standard of care necessary for a particular patient, setting guidelines for quality assurance, or providing standards for reimbursement' [47].

Factors that may complicate treatment

B. burgdorferi, the spiral-shaped bacteria that causes Lyme disease, is an extremely complex organism. The genetic structure of *B. burgdorferi* is the most complex identified in a prokaryote [48]. Experimentally, *B. burgdorferi* has been shown to penetrate human fibroblasts and live intracellularly, even when the extracellular milieu contains bacteriocidal levels of ceftriaxone (Rocephin®, Roche) [202]. This mechanism may permit the spirochete to evade normal host defense mechanisms [202]. These findings are critically important, since chronic infections are highly dependent on intracellular asylum as a mode of persistence [49–51]. Intracellular pathogens are notoriously difficult to treat and cure [52].

B. burgdorferi displays an altered morphology, referred to collectively as L-forms. L-forms of many bacteria have long been shown to be central in setting up chronic infection [53,54]; and the existence of cell wall-deficient L-forms of *B. burgdorferi* suggests that antibiotic treatment failures will arise. Some researchers hypothesize that the ability of *B. burgdorferi* to change to a cyst form and back to a helical form may be major factors in the relapsing and persistent nature of Lyme disease [55–58].

Other factors that may complicate treatment include the existence of untreated coinfections and the slow rate of *B. burgdorferi* reproduction (many antibiotics rely on actively dividing organisms), as well as its ability to either suppress or evade the immune system [59–62].

Divergent treatment options

Antibiotic treatment

The ideal antibiotics, 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 [63], and treatment failures or relapses are reported with all current regimens, although they are less common with early aggressive treatment [22,63].

There are frequent discrepancies between *in vitro* and *in vivo* antibiotic results [22]. Preac-Mursic 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 factors that make antibiotic treatment more difficult, including the increased virulence of the infecting borreliae, the long generation time of the spirochete, infection in immunologically privileged sites, the inability of the antibiotic to penetrate those sites, and insufficient antibiotic dosage [64]. Given these variations, it is unlikely that a 'one size fits all' approach to treatment will be successful in Lyme disease.

Combinations of medications featuring different modes of action (e.g., cell wall acting vs. replication dependent) are common [65]. Among the factors to consider are tissue and CNS penetration, intracellular site of action, cell wall versus other mechanisms of action, patient tolerance and the existence of coinfections [66]. Route of administration plays a substantial role, with intravenous being the most effective, followed by intramuscular and then oral therapy [66]. Parenteral antibiotics are generally recommended when there is neurological involvement, carditis, or complicated Lyme arthritis [12].

No fixed treatment end point creates divergent treatment options

There are no reliable microbiologic or immunologic criteria to document active infection in Lyme disease [22,67,68]. Without reliable biological markers, the task 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 the treatment end point must be determined by other means, becoming, by default an essentially clinical determination [30].

The NIAID notes the problem of false negatives and positives with the currently existing tests (the ELISA and western blot) and observes that:

> *'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 availability of a test that is both sensitive and indicative of active infection with* B. burgdorferi *would also enable one to identify those patients who would benefit from antibiotic therapy, as well as to judge the effectiveness of such therapy on the resolution of infection'* [205].

Two Lyme camps

Given the current lack of a test that can demonstrate the eradication of *B. burgdorferi*, and the lack of studies determining the optimum length of antibiotic treatment or even the optimum choice of antibiotic [63], two different schools of practice have emerged. Some physicians treat for 30 days regardless of patient response unless relapse is shown by reliable objective measures [69]. Other physicians reason that if a diagnosis can only be made clinically because the current diagnostic tests are inadequate, then the determination of the treatment end point must also be made clinically [37]. The different approaches have crystallized into a polemic, and at times rancorous debate between the two Lyme camps [70].

A number of conflicting guidelines reflecting the views of the two Lyme camps have been promulgated over the years. Most recently, one set of guidelines was published under the auspices of the Infectious Disease Society of America (IDSA) [69], while another set was published by the International Lyme and Associated Diseases Society (ILADS) [37]. Both guidelines are evidence-based and peer reviewed, with the IDSA generally recommending standardized 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 narrowly drawn and consisted almost exclusively of academic researchers with well-known ideological views, representing one of the two Lyme camps. The guidelines advise that response to treatment is usually slow and may be incomplete but retreatment, after a 30-day course of antibiotics, is not recommended in the absence 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 such patients.

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, these 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 presumptive 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 sole cause of the continuing symptoms is the presence of immune complexes

Terminating treatment despite persistent symptoms is a high-stakes risk for patients with progressive illness. In addition, steroids, which may be used to curb autoimmune conditions, increase the progression of active infection and are contraindicated for active Lyme disease [78]. Some physicians have characterized the termination of treatment despite persistent symptoms as medically sanctioned negligence [204], because termination of treatment may result in advanced neurological injury, debilitation and death [72].

The IDSA guidelines have drawn sharp criticism from treating physicians [204,207] and patients [208] because they make strong inflexible treatment recommendations based on weak evidence, place undue weight 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 [44]. Animal studies indicate that considerable infection with *B. burgdorferi* in the CNS can be present without overt clinical signs [73]. As the CDC, NIAID and FDA have all acknowledged [21,47,205], the commercially available tests today simply cannot carry the weight of this load, 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 ILADS guidelines. ILADS is an interdisciplinary group of physicians and researchers dedicated to improving the diagnosis and treatment of tick-borne diseases. Members include neurologists, rheumatologists, internists, family practitioners, pediatricians, immunologists, ophthalmologists, dentists, and psychiatrists. The ILADS guidelines stipulate that laboratory tests 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 longer-term antibiotic treatment use an empirical approach based on the clinical evidence of active infection to determine treatment duration. Evidence of ongoing infection is determined by examining all clinical data, including persistence of symptoms, serologic testing, and other forms of corroborating tests such as MRI scans, SPECT imaging, neurocognitive testing, or other neurological indications. Ultimately, the determination of efficacy of therapy depends on the clinical response. One physician summarizes the treatment approach as follows:

> *'Currently, no definitive tests are available for assessing the complete absence of spirochetes in patients. Only through a careful evaluation of individual clinical data can the optimum 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 retreated

These physicians believe that it is too early for standardization of treatment regimens, and that these regimens should be individualized based upon the patient's symptoms and clinical course. From experience, they have seen that prolonged treatment regimens similar to those used in other chronic diseases such as tuberculosis and leprosy are more in keeping with the treatment needs of patients with persistent symptoms of Lyme disease. Although they acknowledge that immune reactivity may contribute to symptoms in chronic Lyme disease, they regard it as unlikely that this reactivity accounts for the majority of progressive symptoms in Lyme disease patients, particularly given that many of the symptoms characterized as inflammatory, improve in response to antibiotic treatment [19]. Moreover, some macrolide antibiotics have recently been shown to possess not only bacteriocidal effects, but also immunomodulatory effects [75].

Validation of guidelines

The ILADS 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. ILADS notes that treatment following the IDSA guidelines has not been successful and recommends that centers employing the IDSA guidelines perform formal evaluations

of the results of their own programs. Validation of the two treatment approaches through outcome studies could provide critical information regarding the treatment of Lyme disease. Two factors to bear in mind, however, are insuring sufficiently long-term follow-up to capture meaningful relapse rates and recording patient symptom data. Patients who report disability analogous to congestive heart failure should not be considered well by any measure.

Failure rates of short-term antibiotic treatment

The IDSA guidelines recommend intravenous antibiotics for 2 to 4 weeks or oral antibiotics for 4 weeks for the treatment of persistent Lyme disease [69]. There have been no human trials proving the effectiveness of 30-day antibiotic regimens [32]. However, animal studies demonstrate that, while this duration of treatment may reduce the bacterial load, it does not eradicate the organism [71]. A number of studies have found treatment failures ranging from 24 to 50% using short-term protocols (TABLE 1). The IDSA conclusion, that their protocols result in 'eventual recovery in most patients', only serves to highlight the issue – namely what level of success is necessary to support an inflexible treatment protocol. The question with persistent Lyme disease has never been what to do with the 50 to 76% who find short-term treatment approaches successful. The issue is how to treat those 24 to 50% who fail under this treatment approach.

The period of follow-up appears to be critical in determining relapse rates given the late recurrence of symptoms in initially recovered patients (TABLE 1). Short-term studies that do not follow patients over a period of years are of questionable value, given that the longer patients are followed after receiving antibiotic treatment, the higher the relapse rates climb [79]. Recognizing that relapse may occur long after treatment is discontinued, Donta defined cure as an absence of symptoms for a year or more following therapy in his study of 277 patients treated with tetracycline [32].

Persistence of infection despite antibiotic treatment

The persistence of *B. burgdorferi* despite presumptively adequate antibiotic treatment has been repeatedly demonstrated by post-treatment isolations of the bacteria [65]. In fact, *B. burgdorferi* has been cultured from patients who have been given intensive antibiotic therapy with intravenous third-generation cephalosporins for 21 days to 1 year [80–84]. Due to the known limitations of the currently available tests, it is not practical to routinely obtain laboratory evidence of continuing *B. burgdorferi* infection in humans. However, the Straubinger canine studies, examining 25 tissue samples per dog, support the concept of elusive yet persistent *B. burgdorferi* infection [44], and isolation of the spirochete has been repeatedly demonstrated in patients with persistent symptoms of Lyme disease (TABLE 2). Thus, the weight of evidence favors persistent infection in chronic Lyme disease.

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

Study	Relapse or failure	Comments	Ref.
Shadick *et al.*	37% (69 out of 184)	Overall, 69 case patients (37%) reported a previous relapse of Lyme disease	[90]
Treib *et al.*	>50% (44 total)	4.2 ± 1.2 years after a 2-week course of intravenous ceftriaxone (2 g daily), more than half of the 44 patients with clinical signs of neuroborreliosis and specific intrathecal antibody production had nonspecific complaints resembling chronic fatigue syndrome and showed persisting positive immunoglobulin M serum titers for *Borrelia burgdorferi* on western blot analysis	[36]
Valesova *et al.*	38% (10 out of 26)	3 years after treatment of 26 patients, 19 showed complete response or marked improvement; relapse occurred in six and new manifestations in four of the cases	[162]
Shadick *et al.*	26% (10 out of 38)	Within 1 year of treatment, ten out of 38 patients reported relapse and had repeated antibiotic treatment (five patients with intravenous ceftriaxone)	[79]
Asch *et al.*	28% (60 out of 216)	A mean of 3.2 years after treatment, 28% had relapsed with major organ involvement; 18% reinfected. *Borrelia burgdorferi* antibodies remained positive in 32%. 82 (38%) patients were asymptomatic. Clinically active Lyme disease found in 19 (9%). Persistent symptoms in 114 (53%)	[163]
Pfister *et al.*	37% (10 out of 27)	A mean of 8.1 months after a 2-week course of intravenous cefotaxime or ceftriaxone, ten out of 27 patients were symptomatic, and *Borrelia burgdorferi* was isolated from the cerebrospinal fluid of one patient	[84]
Logigian *et al.*	37% (10 out of 27)	6 months after a 2-week course of intravenous ceftriaxone (2 g daily), 17 patients (63%) showed improvement, six (22%) showed improvement but then relapsed, and four (15%) showed no change in their condition	[164]

Table 2. Laboratory evidence of persistent *Borrelia burgdorferi* infection despite antibiotic treatment.

Study	Comments	Ref.
Breier *et al.*	Following treatment with four courses of ceftriaxone with or without methylprednisolone for up to 20 days, *Borrelia burgdorferi* was isolated from cultures obtained from enlarging skin lesions	[165]
Horowitz	80 patients treated with multiple courses of antibiotics for an average of 13 months who continued to have persistent symptoms were PCR-positive	[166]
Oksi *et al.*	40% (13 out of 32 clinical relapses) were confirmed by PCR or culture	[102]
Bayer *et al.*	97 patients with symptoms of chronic Lyme disease were PCR-positive despite having been treated with antibiotics for extended periods of time	[167]
Preac Mursic *et al.*	Isolation of *Borrelia burgdorferi* by culture in five patients, four of whom had tested antibody-negative on previous occasions	[64]
Burrascano	Patient treated with amoxicillin for 7 months, intravenous cefotaxime for 26 weeks, then cefuroxime for 5 months. Became pregnant at start of cefotaxime. At birth, the placenta tested positive for *Borrelia burgdorferi*	[168]
Battafarano *et al.*	A patient had chronic septic Lyme arthritis of the knee for 7 years, despite multiple antibiotic trials and multiple arthroscopic and open synovectomies. *Borrelia burgdorferi* was documented in synovium and synovial fluid	[169]
Haupl *et al.*	After repeated antibiotic treatment, *Borrelia burgdorferi* was cultured from a ligament sample	[82]
Preac-Mursic *et al.*	Patient with blurred vision treated with two separate month-long cycles of tetracycline had symptoms that persisted for several years. *Borrelia burgdorferi* was cultured from iris biopsy	[88]
Liegner *et al.*	After treatment with cefotaxime and minocycline, T-cell stimulation test with *Borrelia burgdorferi* antigens were strongly positive. A year later, paired serum and CSF samples were also strongly positive	[80]
Pfister *et al.*	*Borrelia burgdorferi* cultured from the CSF of a patient 7.5 months after treatment	[84]
Preac-Mursic *et al.*	*Borrelia burgdorferi* cultured from the CSF of three patients and from the skin of three others after treatment	[27]

CSF: Cerebrospinal fluid; PCR: Polymerase chain reaction.

The reason for this persistence is not known. Researchers have proposed various different factors, including the virulence and organotropism of the bacterial strain, inoculum size, host immunity, coinfection with other tick-borne diseases, insufficient antibiotic therapy (tissue penetration, dose or duration), intracellular location of the bacteria, survival of *B. burgdorferi* in various human tissues (e.g., heart muscle, spleen, and brain) and certain types of cells, reinfection, and the ability of the bacteria to adopt different forms to ensure survival [86–88].

Long replication time, as well as genetic variability may also contribute to an organism's resistance to standard lengths of antibiotic treatment [19]. Antigen variation in Lyme disease and other diseases is believed to contribute to resistance to normal immunologic functions and evasion of routine laboratory detection [19,89]. Patients with persistent symptoms of Lyme disease report a longer duration of infection before receiving treatment than those without persistent symptoms [90]. In the chronic Lyme encephalopathy study currently being funded by the NIH, the mean number of years between symptom onset and treatment for over 3400 patients was 1.2 years [91].

Unfortunately, there is evidence that in some cases, antibiotic treatment of late Lyme disease, as in late syphilis and chronic tuberculosis [89], may merely suppress but not eradicate the infection. A number of researchers have compared Lyme disease to syphilis [17,22,92]. Chronic syphilitic infection may have periods of latency alternating with periods of active disease [48], and lack of syphilis eradication despite 'adequate' treatment is well known [93]. Similar observations have been made with respect to *B. burgdorferi* [85], and a number of studies support the view that, at least in some cases, antibiotics may suppress but not cure Lyme disease (TABLE 3).

Theory behind longer treatment regimens

Given the high failure and relapse rates of short treatment regimens and evidence of persistence of *B. burgdorferi*, many, if not most, physicians practising in this area, believe that longer durations of treatment may be needed to achieve significant improvement or cure [45,94]. Long-term antibiotics are used for a number of conditions, including tuberculosis, leprosy, recurrent acute otitis media, endocarditis, salmonella infections, prophylaxis of at-risk populations (asplenic children, young children with sickle cell disease, and patients with prior rheumatic fever) and Reiter's syndrome, as well as Lyme disease [95,96,209]. While there are no specific studies that directly assess the safety of long-term antibiotic use, the FDA Center for Drug Evaluation and Research reports that a significant amount of data support the safety of long-term antibiotic therapy [209].

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 [97–99]. Coyle 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 [22].

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 [30,32,37,100,210]. A number of researchers have also found that longer treatment periods provide a better treatment response (TABLE 4).

Conflicting long-term treatment studies

Studies of long-term treatment outcomes have yielded conflicting results. One study by Wahlberg 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 [101]. Successful treatment outcomes occurred in only four out of 13 patients (31%) treated with 14 days of ceftriaxone. In contrast, successful outcomes were seen in 50 out of 56 patients (89%) 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 cefadroxil (Baxan®, Bristol-Myers Squibb). Oksi observed a 90% excellent or good response in his study of 30 European patients with disseminated Lyme disease treated for 100 days [173]. Donta's study of 277 patients is of particular interest because it showed that the longer the course of antibiotics, the more improvement was seen. Following 2 months of treatment, 33% of patients had significantly improved (degree of improvement: 75–100%). In contrast, after 3 months of treatment, 61% of patients had significantly improved [32].

The NIAID has funded three double-blind, placebo-controlled, treatment-outcome studies for persistent Lyme disease. One study is ongoing and is expected to be completed soon [91]. The findings of the other two studies, one by Klempner and colleagues [14], and the other by Krupp and colleagues [103], are contradictory. The Krupp 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 fatique levels compared with 18.5% in the placebo group. The Klempner study that treated patients with 4 weeks of intravenous ceftriaxone followed by 2 months of oral doxycycline (Periostat®, CollaGenex), showed no improvement by those treated on the outcome measure, the SF-36 (a self-reported measure of ability to function).

The Klempner study has generated substantial controversy. ILADS has issued a detailed critique of the design flaws in the study [211]. Another commentator questioned the lead author's bias in the long-term treatment study, noting that halfway through the study Klempner commented to the press that it was irrational for any Lyme disease patient to take months of antibiotics for persisting symptoms of Lyme disease [212]. 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 contention between the two Lyme camps [104].

Table 3. Evidence that antibiotics may suppress but not eradicate *Borrelia burgdorferi* infection.

Study	Comments	Ref.
Breier *et al.*	Despite treatment with four courses of ceftriaxone with or without methylprednisolone for up to 20 days, a patient with lichen sclerosus et atrophicus had regression of skin lesions for up to 1 year. She repeatedly relapsed despite initially successful antibiotic treatment; these relapses were treated successfully with a course of the same antibiotics as previously used	[165]
Petrovic *et al.*	Despite repeated intravenous and oral treatment, symptoms improved only temporarily shortly after treatment, but re-emerged within weeks or months	[170]
Bayer *et al.*	97 patients with symptoms of chronic Lyme disease, confirmed by polymerase chain reaction. Most of the patients had been treated with antibiotics for extended periods of time: 'It seems to be characteristic for most of the patients in our study that, after antibiotic-free periods of a few months, they had again become increasingly ill with neurological and arthritic symptoms, so that treatment had to be resumed'	[167]
Ferris *et al.*	Despite seven short-term antibiotic treatments received during a 2-year period, the patient's condition greatly deteriorated. 12 months of intravenous followed by 11 months of oral antibiotics improved the quality of life greatly. Antibiotics expected to be continued in the long-term, until cure or to delay progression of the disease	[171]
Lopez *et al.*	With long-term antibiotics (intravenous and oral), patient's general condition improved, but each antibiotic course was followed by a relapse	[172]
Haupl *et al.*	The patient had relapsing Lyme borreliosis with choroiditis, arthritis, carditis, and tendonitis. Repeated antibiotic treatment stopped progression of disease but did not completely eliminate *Borrelia burgdorferi*. *Borrelia burgdorferi* cultured from ligament sample	[82]

Table 4. Benefit of longer treatment regimens for disseminated *Borrelia burgdorferi* infection.

Study	Comment	Ref.
Oksi *et al.*	Of 165 patients with disseminated Lyme disease treated for a median duration of 16 weeks, 32 had treatment failure. 'We conclude that the treatment of Lyme borreliosis with appropriate antibiotics for more than 3 months may not always eradicate the spirochete'	[102]
Oksi *et al.*	30 patients treated for 100 days. Conclusion: the general outcomes of infection in patients with disseminated Lyme borreliosis after 3 to 4 months of therapy indicate that prolonged courses of antibiotics may be beneficial in this setting, since 90% of the patients showed excellent or good treatment responses	[173]
Donta	Of 277 patients with chronic Lyme disease treated with tetracycline for 1 to 11 months (mean: 4 months), 20% were cured and 70% of the patients improved. 10% had treatment failures	[32]
Wahlberg *et al.*	Of 100 patients with late Lyme disease, the following success rates for treatment regimens were seen: four out of 13 patients (31%) treated with 14 days of ceftriaxone; 50 out of 56 patients (89%) treated with ceftriaxone followed by 100 days of amoxicillin plus probenecid; and 19 out of 23 patients (83%) treated with ceftriaxone followed by 100 days of cephadroxil	[101]

'Bias is ubiquitous, and medical research is no exception. From the very outset, investigator bias can influence the general attitude towards a research project. Research is at its best when it tests (or, more precisely, falsifies) hypotheses. The biased researcher, however, has preconceived ideas and is likely to approach a project to prove a point. For example, a researcher who is convinced of a particular treatment or, worse, has a vested interest in it, could misuse science to demonstrate the efficacy of his therapy. Equally, an investigator with a preconceived negative attitude towards a particular intervention can set out to disprove its efficacy' [105].

Although the Klempner study appears to contradict the findings of Oksi and colleagues, Wahlberg and colleagues and Donta and colleagues, this may reflect design differences in the studies. Both the Klempner and Krupp studies were double-blind controlled studies, but they each used different outcome measures (SF-36 vs. the fatigue-severity scale). The Oksi, Wahlberg and Donta studies were not controlled. Despite the current focus on controlled studies, it is important to remember that noncontrolled studies often provide more clinically relevant treatment information [104,106]. In addition, variations in study samples, treatment types and durations, and outcome measures make it difficult to compare these studies.

In a recent commentary, Steiner noted 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 [107]. The lack of a homogeneous population in persistent Lyme disease studies is also suggested in the treatment guidelines promulgated by the IDSA.

Animal studies do not suffer from the same flaws as those that plague human studies. Advantages of animal models generally include the ability to have a study population that is initially homogeneous and pathogen free, insure 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 is not feasible in humans. Straubinger's dog studies that examined 25 tissue samples per dog demonstrated that while 30 days of antibiotic therapy may reduce the bacterial load, it does not eradicate the organism [44]. Thus, despite blinding and randomization, outcomes in human studies suffer from more uncertainty than those in animal investigations.

Steiner reasons that all human studies focusing on Lyme disease face three threshold issues:

- Which patients should be included – what is the definition of the condition, and what are the diagnostic criteria?
- Which treatment should be tried – what is the pathogenesis of 'post-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 subjective complaints to treatment be assessed?

He concludes:

'Without an objective surrogate (preferably biological) marker to enable recruitment of homogenous study groups, every attempt to address 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 there is ongoing infection) unanswered.'

The existence of a heterogeneous patient group suggests that individualization rather than 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 to determine the appropriate duration of antibiotic therapy.

The other ongoing Lyme disease treatment study headed by Fallon at Columbia University is expected to be completed in 2005. However, if Steiner's conclusion 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 to be settled soon.

Favorable response to retreatment

As persistent Lyme disease symptoms respond to retreatment with antibiotics, investigators have argued that these symptoms can only be caused by ongoing infection. True post-infectious syndromes do not respond to repeated antibiotics [22]. When symptoms persist, antimicrobial treatment is generally followed by clinical improvement (TABLE 5). Relapsing disease is obvious to the treating physician and patient and generally responds to reinstitution of therapy [85]. The trial and error approach in medicine is a constant. For instance, physicians may titrate medication doses to find a level that works best for a patient and may try a variety of different treatment approaches before finding the one that is the most effective [109]. 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 reinstituted, there is empirical evidence of an infectious process. This is not experimental treatment – it is the way infection has been treated for years [110].

Standard of care for treating Lyme disease

Role of evidence & consensus in the standard of care

Historically, the physician's judgment has taken the laboring oar 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 1950s, 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.

The amount of attention evidence-based medicine has garnered is disproportionate to the relatively small role that it plays in medical practice. Most medicine, even that which is widely accepted, is not based on rigorous scientific studies. The Institute of Medicine (IOM), which has prepared national standards for guideline development, considers the hypothetical data set forth in FIGURE 1 indicative of how scientific evidence and consensus might be distributed across the entire range of healthcare services [117]. Medical services, for which there is strong scientific evidence, constitute only 4% of total medical services provided, yet 51% of services have poor supportive scientific evidence, or even lack it entirely. Clearly, the bulk of medical practice is about managing uncertainty in the absence of definitive research [213].

A recent article indicates that only 20% of medical practice is confirmed by rigorous scientific research [118]. Although some argue that this percentage is unduly pessimistic, it is agreed that medical practice is often not based on controlled studies [214]. For example, many well-accepted practices, like cardiopulmonary resuscitation, close observation of suicide risk patients, blood transfusion, surgical treatment of low back pain, and the treatment of meningitis with antibiotics, have no rigorous and little nonrigorous science to support their use [119,214]. Similarly, most advances in surgery result from clinical innovations on the part of the treating physician, and the off-label use of prescription medications is well accepted [109]. These practices show how dangerous the leap is from 'without substantial evidence' to 'without substantial value' [214].

There is a tendency to overvalue the quantitative approach of randomized controlled studies (that may be flawed or inadequate for complex multivariate illnesses) and to discount less quantitative (but frequently more appropriate) approaches, such as observational or longitudinal studies [214]. Controlled

Table 5. Favorable response to *Borrelia burgdorferi* retreatment.

Study	Comments	Ref.
Krupp	28 patients with persistent Lyme disease in a double-blind placebo-controlled study treated with intravenous ceftriaxone for 4 weeks showed a 64% improvement rate on self-reported fatigue scale versus 18.5% of the placebo group	[103]
Fallon	18 patients retreated with either intravenous, intramuscular or oral antibiotics scored better on overall and individual measures of cognition. Those retreated with intravenous antibiotics showed the greatest improvement	[174]
Oksi *et al.*	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 nine of 13 (69%)	[173]
Donta	98 patients retreated with either tetracycline, a combination of macrolide and hydroxychloroquine, or intravenous ceftriaxone showed a cure rate or significant improvement of 98, 74 or 85%, respectively	[32]
Lawrence *et al.*	Despite aggressive oral and intravenous antibiotic therapy, patient experienced repeated progressive neurologic relapses. Patient now on oral clarithromycin for 22 months with no new symptoms or deficits	[175]
Masters	Patient treated with high doses of penicillin for 6 months; he relapsed and spirochetes were subsequently cultured from his blood. The patient was placed back on antibiotics and responded to therapy	[176]
Cimmino *et al.*	Two patients with chronic Lyme arthritis resistant to the recommended antibiotic regimens were cured by long-term retreatment with benzathine penicillin	[177]

studies attempting to document the actual effects of ordinary clinical care are a relatively new phenomenon [106]. Moreover, the actual situations calling for controlled studies may be quite limited.

> *'Demands for equipoise make controlled trials appropriate only in the absence of any well-established standard treatment...(and) if researchers have substantial reason for confidence about the clinical utility of an investigational treatment, they may not corroborate it with [a randomized controlled study] that would deny the intervention to some subjects in the control arm of the study'* [109].

There is also a tendency to devalue certain types of qualitative evidence as anecdotal, notwithstanding the fact that historically most medical research was of this nature [109]. The cumulative weight of anecdotal evidence can be substantial. Take, for instance, the information gleaned from aggregating isolated adverse drug event reports or outcomes research, which assesses the effectiveness of particular medical practices in the real world by pooling large numbers of comparable patients [109]. Many believe this type of outcomes research may be more meaningful than controlled trials because the effectiveness of the medical practice is measured in actual practice settings [109]. 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 [109].

Similarly, evidence immediately available from the patient's history, clinical examination, presentation of symptoms, course of disease, and response to treatment may also be discounted both by guidelines that do not take these factors into consideration and by insurance review processes that determine the necessary level of medical intervention without examination of the patient. Yet these are all vital pieces of evidence upon which the practice of medicine depends. Guidelines (and insurance companies that rely on guidelines to determine treatment or treatment reimbursement decisions) have the necessary effect of suppressing physician expertise, which is further compounded by state independent external review board decisions to the extent that the reviewers, in turn, rely on practice guidelines to frame their decisions [120].

The truth is that there is no bright line separating evidence-based medicine from other medicine. All medicine is based on evidence, but only a small portion of it is based on controlled studies. Even proponents of the evidence-based medicine movement embrace 'compelling nonexperimental evidence' when trying to bolster the percentage of medicine claimed to be evidence-based [214]. When guidelines, like those from the IDSA, state that there is no compelling evidence, the question is, what type of evidence? If the answer is controlled studies, then this is hardly a surprise. Given the limited circumstances in which controlled studies are appropriate and the cost constraints of such studies, it is unlikely that a substantial portion of medicine will be supported by controlled studies in the foreseeable future.

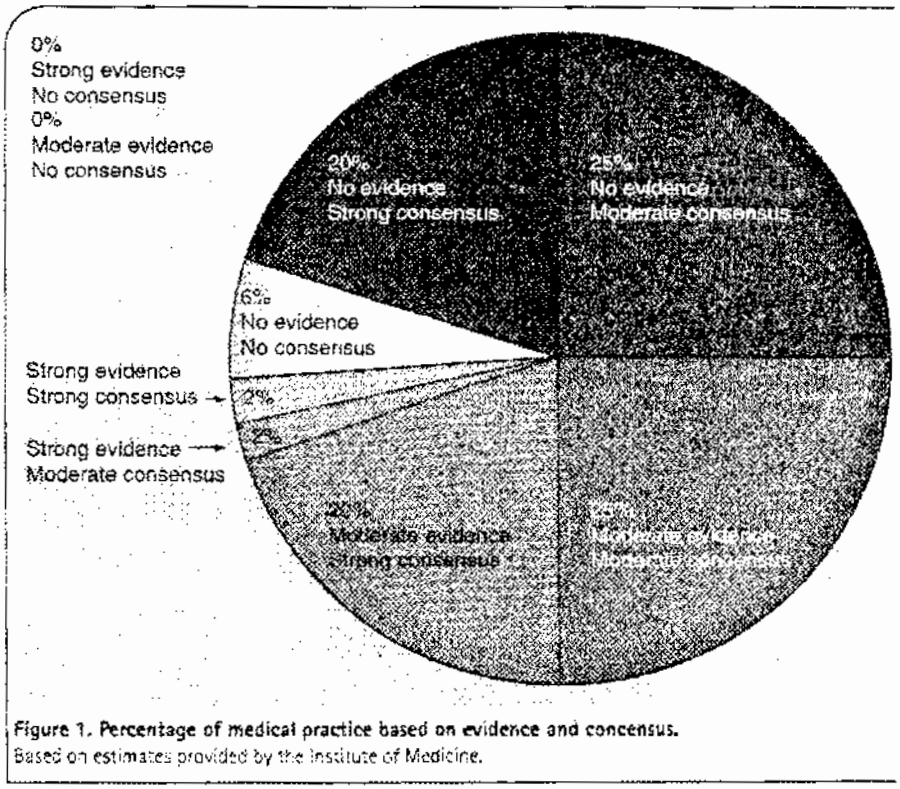

Figure 1. Percentage of medical practice based on evidence and concensus.
Based on estimates provided by the Institute of Medicine.

In practice, evidence-based medicine is intended to enhance the practice of medicine by integrating the medical professional's expertise and the patient's right to choose between diagnostic and treatment options with the best available external clinical evidence from systematic research [121,122]. The best available evidence means simply that – the best evidence available. It may come from a wide range of sources as diverse as well-conducted randomized trials or expert opinion [123].

If a relevant, 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 answer, expert opinion or clinical experience may provide the best available evidence. In the treatment of complex multivariate conditions, when treatment outcome studies are limited and conflicting, the most valuable evidence in fact may be the clinical course of an individual patient. For instance, patient response to levodopa is considered an important discriminative 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 sparse, 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 ushered in by managed care. With newly discovered diseases like Lyme disease, burgeoning treatment approaches do not have the luxury of unfolding over time unfettered 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 viewpoints 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 dressed up actuarial tables [124]. Early on, guidelines for the treatment of Lyme disease were being written by actuarial firms, such as Milliman and Roberts, whom critics assert are hired to help insurers manage costs, not care [125]. It has been observed that if money were not an issue, there would be no treatment controversy in Lyme disease [126].

Recent reviews of practice guidelines have shown that most fail to meet quality standards [127], and that guidelines produced by specialist societies are generally of poor quality [128]. At their best, evidence-based guidelines represent an unbiased summary of the relevant research for the physician who is too busy to select and review the research personally. At their worst, such guidelines represent attempts of third parties to influence the medical decision-making process. Indeed, some critics contend that guidelines are used primarily to ration care and limit the doctor's autonomy and judgment in providing for his or her patients what the patients actually need [129]. As the foregoing suggests, the key issues in treatment guidelines are conflict of interests and bias on the part of the panel members.

Between 72 and 90% of physicians writing clinical practice guidelines have undisclosed conflicts of interest [130,131]. While most of the focus has been on conflicts that arise as a result of pharmaceutical ties, conflicts resulting from ties with the insurance industry also pose a serious risk because of the insurance company's inherent conflict of interest, namely, making more money by denying further care. Because of this, payer guidelines, even those shrouded in the aura of science and objectivity as evidence-based medicine, are viewed as less authoritative [132].

The problem of bias can result from a number of other factors, including entrenched ideological beliefs and professional territorial considerations [135]. Guideline developers necessarily make choices: whose views are represented on the drafting committee, which studies are included and how the studies are interpreted [127]. When guidelines conclude that evidence is or is not convincing or compelling, the appropriate 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' [215].

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 at large – in other words, whose interests dominated the drafting panel? Not surprisingly, conflicting guidelines are common [134]. To overcome the tendency toward bias and to insure 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 [117].

The panel drafting the ILADS 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 [216]. When faced with divergent opinion regarding the treatment of persistent Lyme disease, the IDSA panel purged its sole dissenting member [208]. Moreover, 11 of the 12 authors of the guidelines were primarily research scientists with little or no experience treating patients with persistent Lyme disease [100]. Panel members who do not spend their days treating patients may fail to grasp either the complexity of the illness that is not reflected in controlled 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 err on the side of exclusion to insure 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 sizable portion of patients who have the illness is not an issue for research purposes. Treatment goals, on the other hand, err on the side of inclusion and overdiagnosis to insure 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 retreatment. In making this assertion, the IDSA fails to consider scores of studies evidencing persistent infection, including those listed in TABLES 4 & 5. Not surprisingly, failure to consider all relevant evidence is one of the pitfalls the IOM warns against when guidelines are drafted by narrowly drawn panels. Similarly, the narrowness of the panel predetermines 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 – an idea 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 research [136,217]. 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' [117].

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' [117]. Guidelines that attempt to supplant, rather than inform, overstep their role in the decision-making process. When guidelines become polemics 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 [137], and instead fall prey to the criticism that they 'constitute the exercise of power without responsibility', and only 'generate systematic and paternalistic pressure for the many to conform to the views of the few' [104].

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 practising in the same or similar locality under similar circumstances' [138]. It is defined by the actual practices of physician 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 practising 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 medicine protocols in determining the standard of care depends upon the extent to which the practice recommended has been adopted within the medical community [139]. In court, the standard of care is determined by expert testimony [140]. Although an expert may introduce evidence-based protocols in support of testimony, the protocols themselves do not establish a standard of care [141].

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 [141]. Guidelines also appear to be underused in clinical practice, suggesting that their role in shaping consensus may be limited [215]. In part, this reflects the realization that, like expert testimony, the seemingly objective quantitative approach of guidelines is vulnerable to a 'subjectivity of objectivity' [142], or thinly disguised (frequently even unintentional) bias cloaked in science, with 'hired guns' 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 as instruments of cost control rather than as impartial guides for treatment decisions is widely recognized.

Standard of care when different treatment options exist

The standard of care for treating a condition is determined by the manner in which clinically practising physicians actually treat patients. Most jurisdictions recognize that more than one standard of care may exist for treating a medical condition. For example, in California, a variation of the two schools of thought or respectable minority standard is codified in its jury instructions as follows:

> *'Where there is more than one recognized method of diagnosis or treatment, and no one of them is used exclusively and uniformly by all practitioners of good standing, a physician is not negligent if, in exercising their best judgment, they select one of the approved methods, which later turns out to be a wrong selection, or one not favored by certain other practitioners'* [143].

The establishment of a school of thought requires only that a group of respectable treating physicians adhere to a method of treatment. The size of the group following a particular approach need not be particularly large. One court in Arizona found 65 physicians sufficient [144]. The existence of different schools of practice is determined by expert testimony that, in addition to offering opinion on practices within the community, may also introduce guidelines evidencing a treatment approach, or consensus surveys suggesting the number of practitioners following that approach.

As was noted previously, both schools of thought about Lyme disease have introduced guidelines regarding their treatment approach. In addition, a number of consensus surveys illustrate the division within the medical community. One survey found that 57% of responding physicians treat persistent Lyme disease for 3 months or more [45]. Fallon notes that for over 3400 patients screened for the Columbia persistent Lyme disease study, the mean duration of intravenous treatment was 2.3 months and the mean duration of oral antibiotic therapy was 7.5 months [91]. In another survey, 50% of the responders considered using antibiotics for a time 'greater than 1 year in a symptomatic seropositive Lyme disease patient. Almost the same number would extend therapy to 18 months if needed' [94].

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 [145,218]. When more than one standard of care exists, practice in accordance with either of the acceptable standards of care is considered acceptable for malpractice purposes.

Role of clinical judgment when different treatment options exist

There is a necessary interplay between scientific research and clinical judgment. 'Professional judgment must be applied to the science base, and science must inform professional judgment' [117]. The degree of individualization of treatment varies with the complexity of the illness and the amount of confounding variables involved, such as coinfections. The greater the need for individualization, the greater the role 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 type, 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 cause, 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 undertreat 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' [146]. Medicine that improves outcomes contributes to the deterrence goal. The Office of Technology Assessment suggests weighing the following factors [146]:

- Whether the disease under consideration is life-threatening or disabling
- Whether timely detection changes 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 30% of medical malpractice lawsuits allege missed or delayed diagnosis (and treatment) [147]. When the medical consequences of being wrong are severe, so too 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$3.2 million (subsequently reduced to US$1.8 million) against his medical provider [160,219].

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 [220]. 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 or 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 belongs to the patient [147].

The reason patient preference assumes such 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' [147]. 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 types of quality of life outcomes that matter to them – are uniquely suited to make [148].

Respect for autonomy is the primary moral justification underlying the legal obligation to obtain informed consent. Except 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 exercise informed choice in the selection of treatments. California has adopted the patient's point of view on informed consent:

'The patient's right of self-decision 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 communications to the patient, then, must be measured by the patient's need, and that is whatever information is material to the decision' [149].

The physician must disclose to a patient material treatment options. In *Mathis v. Morrissey*, 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, personal decision. As the Cobbs 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 this information has been disclosed, that aspect of the doctor's expert function has been performed. The weighing of these risks against the individual subjective fears and hopes of the patient is not an expert skill. Such evaluation and decision is a nonmedical judgment reserved to the patient alone' [151].

In the case of *Matthies v. Mastromonaco*, 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 nontreatment) 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' [150].

Whether information of treatment options is material for the purposes of informed consent depends upon the circumstances of the case at hand. However, one commentator has noted that the duty of physician disclosure is often triggered by risks approximating a 1% probability if the severity of the risk is high [109]. Indeed, many physicians feel that the best safeguard against lawsuits is to give patients the full range of treatment options and withhold their personal recommendations [148]. In the case of Lyme disease, the magnitude of the risk of terminating treatment prematurely can be severe, permitting a serious systemic condition to progress with the risk of irreparable injury or even death [72]. Most, if not all, patients would consider these risks material and would want to be informed of the existence of another treatment option that reduced these risks.

Granted, the common law's bark is frequently worse than its bite when informed consent cases are adjudicated [182]. The law varies substantially between US states regarding whether the disclosure obligation is viewed from the patient's perspective or based on medical custom and on the extent and circumstances under which information must be disclosed. That said, it is clear that the willingness of courts to permit a certain degree of paternalism in the past has been rooted in the notion that physicians always act in the best interest of patients – a notion that no longer holds in the era of managed care.

Taking patient preferences into account not only increases patient satisfaction; it is also good healthcare policy. When Wennberg analyzed inefficiencies in the Medicare system by looking at small area variations in medical practice, he found that most variation in preference-sensitive care reflects physician opinion. Preference-sensitive care exists whenever different treatment approaches exist and may arise where treatment outcome studies supporting a treatment approach are weak (as in the choice between watchful waiting, radiation or surgery for prostate cancer) or where the quality of life implications of the alternate treatment approaches are significant (as in the choice between lumpectomy and mastectomy for breast cancer):

'Preference-sensitive decisions must sometimes be made in the face of scientific uncertainty about the effect of treatment on the main outcome. The choice of treatment for prostate cancer is a good example...because there have been few clinical trials to evaluate...treatments, the advantages of active treatments are not clear, and patients face a decision that can be characterized as a wager: those who choose active treatment make a bet that the treatment does in fact prolong life to a sufficient degree to be worth the known risks of the procedures' [152].

Wennberg observes that patient and provider values are often in conflict in patient preference situations and recommends reducing the medical practice variations in these situations by 'reducing scientific uncertainty through outcomes research....and establish(ing) shared decision making for preference-based treatments' [119]. Implementing patient choice in preference-based treatments may also lower overall medical costs. Costs incurred in connection with preference-sensitive

surgery, for instance, decline when shared decision-making is implemented [119,221]. Moreover, a significant portion of all healthcare costs are associated with end-of-life care, where giving a greater weight to patient preferences may reduce the amount and degree of medical intervention.

The patient preference issue clearly exists in the treatment of persistent Lyme disease. Patients should be provided with sufficient information to weigh and choose between the trade-offs implicit in the treatment choices available. Patients who suffer more serious forms of the illness or who have progressive illness could be expected to weigh the risk of side effects from antibiotics quite differently from those who suffer mild, nonprogressive symptoms. For some patients, the quality of life issues surrounding the wish to achieve sufficient functionality or symptom control to return to work may influence treatment decisions. Similarly, patients who have tried a number of antibiotic treatments without success may weigh their choices differently from relapsing patients who have been responsive to antibiotics in the past.

According to the IOM, respect for patient autonomy and patient preference should also be reflected in treatment guidelines [117]. The IDSA guidelines suggest that a failed conventional treatment is the only option, when in fact another viable treatment option, namely continued treatment, exists. By failing to acknowledge the treatment options that exist for persistent Lyme disease, the IDSA guidelines not only mislead treating physicians, they also usurp patient autonomy. Rigid guidelines that fail to consider patient preference or allow for the exercise of clinical discretion are inherently paternalistic [148].

While it is appropriate to consider treatment costs when drafting protocols, medicine is not an actuarial science. In this day of cost containment-driven healthcare, it is easy to lose sight of the fact that the ultimate goal of healthcare is the improvement of long-term healthcare outcomes. This issue can only be addressed by asking if the patient is well. The IDSA guidelines attempt to define wellness by excluding subjective symptoms, but such sleights of hand do not make patients well. Patients with persistent Lyme disease suffer disability comparable to those with congestive heart failure [14]. By any definition, they are not well. The cost-saving benefit to insurers under the IDSA guidelines from terminating treatment for symptomatic patients (at least over the short-term) is clear. Recently, commentators have noted that the 'single-minded pursuit of economic efficiency and emphasis on beneficent care' represents a resurgence of paternalism in the managed care environment that jeopardizes patient autonomy [153].

The view set forth in the IDSA guidelines, that treatment should be withheld from patients with ongoing symptoms who have been previously treated, results in a *de facto* naturalistic experiment reminiscent of the Tuskegee experiment for syphilis that has been so widely condemned for its essential failure to uphold medical ethics – namely the duty to help or cure, to protect the patient's health, to provide unbiased information to the patient and to respect the patient's autonomy. Not surprisingly, most patients with persistent Lyme disease opt out of this experiment.

Role of insurance when different treatment options exist

When managed care tools began to be used in the healthcare marketplace, the economic incentives to deny payment or access to care began to impact the medical decisions made by practitioners. The extent to which the policies of insurance companies can interfere with Lyme disease treatment decisions is illustrated by a patient who died within 1 month of being denied further insurance coverage for intravenous antibiotic treatment [154].

To deal with the influence that insurance plans can have on medical decision making, courts began applying the state legal 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, insurers, and utilization reviewers [155–157].

The legal standard of care is community based and reflects the practices of treating physicians [155]. Unfortunately, there is evidence to suggest that many managed care organizations rely unduly on summary protocols to deny patients the treatment recommended by their physicians [120]. This, coupled with the fact that managed care organizations are incentivized to increase profits by reducing costs at the expense of expected treatment outcomes [120], creates a significant potential for abuse:

> *'Much, if not most, medical care, even that which is generally accepted in the medical community, would be denied under an evidence-based standard because so few healthcare services have been subject to rigorous research. At particular risk for denial of needed services are disabled people, because of the lack of treatment proven effective through clinical trials'* [213].

Even worse, some commentators suspect that the use of summary protocols as trip wires for treatment denials may be part of a larger strategy by insurers to enhance profitability by intentionally encouraging chronically ill patients to disenroll [120].

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 denials. In fact, Standards 32 and 33 of URAC's Health Utilization Management Standards require that organizations provide the patient or physician with the clinical rationale for the denial, which must relate specifically to this patient's condition or treatment plan. This is because a physician's clinical judgment, taking into account the patient's unique clinical presentation and course of treatment, is key to determining the standard of care. When an insurance company physician merely reads and communicates treatment guidelines to the treating physician, there is no exercise of independent clinical judgment. Such attempts to elevate form over substance fall 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 case 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

clinical physician practices, as opposed to the medical practices or payor 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 [158].

Guidelines do not constitute the standard of care, which must be based on the clinical judgment of practising physicians taking into account the unique clinical presentation and course of treatment for the particular patient. Those relying on guidelines or other cost-containment mechanisms for any part of the medical decision-making process are not relieved of their obligation to follow the clinical standard of care:

> *'However impressive the organization that sponsored the guidelines, or its process for developing them, the fact that a protocol exists for a particular condition does not mean that what it proposes is true. Nor does it guarantee that the protocol accurately represents customary practice...questioning may address the scope of the guideline, how it was developed and adopted...the existence of known exceptions to its application, and whether any school of medical thought rejects it and adopts a different approach to treatment...'* [141].

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 corrupted clinical judgment [156]. Third-party payors may be liable for injuries caused by negligent utilization review decisions [157]. The court in the case of *Wickline v. State of California* stated that third party payors can be held responsible 'when medically inappropriate decisions result from...implementation of cost containment mechanisms' [156]. Although the patient had not sued the treating physician, the case further noted that 'the physician who complies without protest...when his medical judgment dictates otherwise, cannot avoid his ultimate responsibility for his patients' care.' Significantly, cost containment measures were one of the key factors in *Murray v. Chesepeake*, where the clinic as well as the physician were found liable in the US$3.2 million verdict [160]. 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 Policy and Research.

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 *Sarchett v. Blue Shield of California*, the court stated that 'with doubts respecting coverage resolved in favor of the subscriber, there will be few cases in which the physician's judgment is so plainly unreasonable or contrary to good medical practice, that the coverage must be refused' [161]. 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 liberally in favor of the insured, the court also made it clear that the term 'medical necessity' will be defined liberally [155].

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 express exclusions of benefits contained in the insurance contract. Where two standards of care exist, the obligation is to provide treatment or reimburse 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 [182].

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 arbitrary and capricious 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 contorted exercise leaving injured plaintiffs without an 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 pre-emption, through:

- Case law imposing state malpractice law standards in cases involving mixed benefit 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*, [US LEXIS 4571, (US 21 JUNE 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, Justices Ginsburg and Breyer issued a concurring opinion, but joined the 'rising judicial chorus urging that Congress and the court revisit what is an unjust 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 this area of law is currently under significant flux, the impact of ERISA on the state law obligations applicable to insurers is beyond the scope of this article.

Expert opinion

Knowledgeable and respected professional groups can, and often do, come down on opposite sides of a particular treatment issue. When this occurs, the standard of care embraces the practices of each of the different schools of thought. Regardless of the standard of care preferred by a physician, the physician is required to exercise the best clinical judgment, and tailor treatment to the individual 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 to the patient sufficient 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 Lyme 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 irreversible physical damage, debilitation, and death [72]. Untreated Lyme disease may mimic other conditions such as vasculitis, demyelinating disorders, motor neurone disease and dementia [19]. While it can be expensive to treat persistent Lyme disease, this cost pales in comparison with the cost of untreated Lyme disease manifesting as progressive rheumatologic, neurologic and cardiac disorders.

The central difficulties in the diagnosis and treatment of Lyme disease stem from the lack of sufficiently sensitive and reliable biological markers of the disease. Without such markers, it is difficult to determine who has the disease, the effectiveness of a course of treatment, and the end point of treatment. Under these circumstances, the best evidence to guide treatment decisions may be the patient's unique clinical course. Medical decision-making in the grey zone exists on a continuum, framed by the competing goals of avoiding unnecessary costs on the one hand, and avoiding malpractice exposure on the other hand. Here, tort rules can serve a legal, medical and moral purpose by promoting medical accountability [159]. The treating physician should keep in mind that the fulcrum against which these frequently competing goals must be balanced is the patient's individual clinical presentation and preferences.

Five-year view

A key concern with Lyme disease outcomes studies to date has been the suggestion that the conflicting results of these trials may reflect a heterogeneous patient population [107]. The need to provide more flexibility in standardized treatment regimens represents an important area of development. For instance, a 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 [111]. Similar novel treatment strategies based on patient individualization may be required to solve the treatment issues in chronic Lyme disease. Those with persistent Lyme disease may be recognized as a heterogenous group, consisting of patients who respond rapidly, slowly, partially, completely or not at all to antibiotic treatment.

Another issue that may contribute to heterogeneity among persistent Lyme disease patients is the number of pathogens creating the illness. Since the identification of *B. burgdorferi* as the agent of Lyme 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* [112]. Scientists have still not identified all of the pathogens that ticks may carry [113]. Until we are 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 antibody tests are species-specific [114,115]. Improvement in genotyping techniques holds promise for not only detecting and identifying other pathogenic bacteria carried by ticks in the future [113], 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 Lyme disease. While it is known that host genes (human leukocyte antigen class II alleles) may be associated with chronic Lyme arthritis and lack of response to antibiotic treatment [116], other genes may eventually be associated with persistence of neurologic Lyme disease in the future. These advances, in turn, could affect the determination of the best course of treatment for an individual patient. Recently, the head 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 in only 30–50% of patients), and the executive proposed targeting drugs to genetically determined responsive patients [178]. Genetic testing that would enable a physician to target drug treatment to persistent Lyme disease patients would fundamentally alter the landscape of Lyme disease diagnosis and treatment.

The 5-year view in terms of the medicolegal assessment depends to a large degree on the extent to which the Lyme controversy can be depolarized. 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 polemical environment, even the ability to design appropriate research studies

and interpret the results of studies in an unbiased manner has become compromised. There is a strong need for the two Lyme camps to begin a dialog, and it seems likely that a formal structured approach will be necessary.

Attempting to achieve an artificial consensus among contentious groups is not likely to be fruitful [179]. Although the NIH offers a consensus process using an independent panel that looks quite promising on paper, commentators point out that the reality falls short, suffering from a lack of impartiality, biased evidence selection, and exclusion of important stakeholders [180]. The concept of a science court, first advanced in the 1960s, addresses many of these issues by offering stakeholder input, impartial adjudication, managed selection of evidence, and a thorough airing of scientific 'facts' and viewpoints via cross-examination [181]. However, it may be premature and unrealistic to rush to resolution of a controversy where the science is still unfolding.

At this stage, meaningful progress can only be made by replacing the goal of conflict resolution with the more realistic goal of conflict delineation. This type of process would serve to identify and quantify the extent of consensus and controversy as well as highlight knowledge gaps, while establishing a research agenda. For instance, there may be a broader consensus than realized on the heterogeneity of patient or study populations. Identification of this consensus could lead to the discussion of how meaningful classes within the group might be identified. The first step would be to establish a process designed to insure that stakeholders all have an equal voice. Relevant issues here might include transparency, conflicts of interest, confidential voting (to eliminate pressure to conform and to reduce the dominance of forceful personalities or authority figures), proposition framing issues and other group process mechanisms to safeguard fairness and impartiality.

Unfortunately, researchers who adhere to short-term treatment protocols have rebuffed past proposals by members of ILADS for commencing a dialog between the two camps. When invited by legislative bodies to participate in an open forum, these same researchers, by and large, refuse to participate. 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 dialog. 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 dialog and free exchange of ideas vital to the performance of research that addresses the needs of all stakeholders in this controversy.

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

Acknowledgements

The authors thank Bransfield R, Dickson K, Dorward D, Fallon B, Gaito A, Gerberding J, Harris N, Harris S, Harvey W, Hoggard M, Johnson B, Kjemtrup A, Lane R, Liegner K, Lull R, Moore D, Morrow S, Phillips S, Prehn W, Sherr V, Smith H, Sugarman G and Winger E for helpful discussion. The authors are grateful to attorneys Greaves L, Maurer I, and Shepler L for medicolegal commentary, and to Hoggard M for technical assistance. The authors would also like to thank Smith P of the Lyme Disease Association, Mervine P, Lull L, Leonard P and Barsocchini B of the California Lyme Disease Association, and Forschner K of the Lyme Disease Foundation for continuing support. This article is dedicated to the memory of Paul Lavoie.

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 grey 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, outcomes 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.
- Where two standards of care exist, treatment in accordance with either standard is acceptable for malpractice purposes.
- Where two standards of care exist, the treatment decision belongs to the patient under the medical ethical principle of autonomy and the legal doctrine of informed consent.
- Physicians must provide adequate information about treatment options, their probable outcomes, and the risks and benefits associated with each for patients to be able to act autonomously or give informed consent.

References

Papers of special note have been highlighted as:
- • of interest
- •• of considerable interest

1 Marcus LC, Steere AC, Duray PH, Anderson AE, Mahoney EB. Fatal pancarditis in a patient with coexistent Lyme disease and babesiosis. Demonstration of spirochetes in the myocardium. *Ann. Intern. Med.* 103(3), 374–376 (1985).

2 Krause PJ, Telford SR 3rd, Spielman A *et al.* Concurrent Lyme disease and babesiosis. Evidence for increased severity and duration of illness. *J. Am. Med. Assoc.* 275(21), 1657–1660 (1996).

• **Evidence that coinfection increases the severity of Lyme disease.**

3 Schoeler GB, Wikel SK. Modulation of host immunity by haematophagous arthropods. *Ann. Trop. Med. Parasitol.* 95(8), 755–771 (2001).

4 Hannier S, Liversidge J, Sternberg JM, Bowman AS. Ixodes ricinus tick salivary gland extract inhibits IL-10 secretion and CD69 expression by mitogen-stimulated murine splenocytes and induces hyporesponsiveness in B-lymphocytes. *Parasite Immunol.* 25(1), 27–37 (2003).

5 Guner ES. Complement evasion by the Lyme disease spirochete *Borrelia burgdorferi* grown in host-derived tissue cocultures: role of fibronectin in complement-resistance. *Experientia* 52(4), 364–372 (1996).

6 Liang FT, Jacobs MB, Bowers LC, Philipp MT. An immune evasion mechanism for spirochetal persistence in Lyme borreliosis. *J. Exp. Med.* 195(4), 415–422 (2002).

7 Rhen M, Eriksson S, Clements M, Bergstrom S, Normark SJ. The basis of persistent bacterial infections. *Trends Microbiol.* 11(2), 80–86 (2003).

• **Excellent review of the mechanisms of chronic infection.**

8 Harvey WT, Salvato P. Lyme disease: ancient engine of an unrecognized borreliosis pandemic? *Med. Hypotheses* 60(5), 742–759 (2003).

•• **Seminal analysis of the Lyme disease epidemic.**

9 Stricker R, Moore D, Winger E. Clinical and immunologic evidence for the transmission of Lyme disease through intimate human contact. *J. Invest. Med.* 52(1), S151 (2004).

10 Nadelman RB, Sherer C, Mack L, Pavia CS, Wormser GP. Survival of *Borrelia burgdorferi* in human blood stored under blood banking conditions. *Transfusion* 30(4), 298–301 (1990).

11 MacDonald AB. Gestational Lyme borreliosis. Implications for the fetus. *Rheum. Dis. Clin. North Am.* 15(4), 657–677 (1989).

12 Centers for Disease Control and Prevention (CDC). Recommendations for the use of a Lyme disease vaccine. *Morb. Mortal. Wkly Rep.* 48(RR-7) (1999).

13 Centers for Disease Control and Prevention (CDC). Lyme Disease – USA, 2001–2002. *Morb. Mortal. Wkly Rep.* 53(17), 365–369 (2004).

14 Klempner MS, Hu LT, Evans J *et al.* Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N. Engl. J. Med.* 345(2), 85–92 (2001).

15 Sigler S, Kershaw P, Scheuch R, Sklarek H, Halperin J. Respiratory failure due to Lyme meningoradiculitis. *Am. J. Med.* 103(6), 544–547 (1997).

16 Oksi J, Kalimo H, Marttila RJ *et al.* Inflammatory brain changes in Lyme borreliosis. A report on three patients and review of literature. *Brain* (1996) 119(Pt 6), 2143–2154 (2003).

17 Fallon BA, Nields JA. Lyme disease: a neuropsychiatric illness. *Am. J. Psychiatry* 151(11), 1571–1583 (1994).

• **Excellent review of neuropsychiatric symptoms in Lyme disease.**

18 Lebech AM, Hansen K, Wilske B, Theisen M. Taxonomic classification of 29 *Borrelia burgdorferi* strains isolated from patients with Lyme borreliosis: a comparison of five different phenotypic and genotypic typing schemes. *Med. Microbiol. Immunol. (Berlin)* 183(6), 325–341 (1994).

19 Fallon BA, Schwartzberg M, Bransfield R *et al.* Late-stage neuropsychiatric Lyme borreliosis. Differential diagnosis and treatment. *Psychosomatics* 36(3), 295–300 (1995).

20 Coyle PK, Schutzer SE, Deng Z *et al.* Detection of *Borrelia burgdorferi*-specific antigen in antibody-negative cerebrospinal fluid in neurologic Lyme disease. *Neurology* 45(11), 2010–2015 (1995).

21 Food and Drug Administration. Lyme disease test kits: potential for misdiagnosis. *FDA Med. Bull.* (1999).

22 Coyle PK. Neurologic complications of Lyme disease. *Rheum. Dis. Clin. North Am.* 19(4), 993–1009 (1993).

23 Liveris D, Wang G, Girao G *et al.* Quantitative detection of *Borrelia burgdorferi* in 2 mm skin samples of erythema migrans lesions: correlation of results with clinical and laboratory findings. *J. Clin. Microbiol.* 40(4), 1249–1253 (2002).

24 Zore A, Ruzic-Sabljic E, Maraspin V *et al.* Sensitivity of culture and polymerase chain reaction for the etiologic diagnosis of erythema migrans. *Wien Klin. Wochenschr.* 114(13–14), 606–609 (2002).

25 Liegner KB. Lyme disease: the sensible pursuit of answers. *J. Clin. Microbiol.* 31(8), 1961–1963 (1993).

26 Schutzer SE, Coyle PK, Belman AL *et al.* Sequestration of antibody to *Borrelia burgdorferi* in immune complexes in seronegative Lyme disease. *Lancet* 335(8685), 312–315 (1990).

27 Preac-Mursic V, Weber K, Pfister HW *et al.* Survival of *Borrelia burgdorferi* in antibiotically treated patients with Lyme borreliosis. *Infection* 17(6), 355–359 (1989).

28 Mursic VP, Wanner G, Reinhardt S, Wilske B, Busch U, Marget W. Formation and cultivation of *Borrelia burgdorferi* spheroplast-L-form variants. *Infection* 24(3), 218–226 (1996).

29 Bakken LL, Callister SM, Wand PJ, Schell RF. Interlaboratory comparison of test results for detection of Lyme disease by 516 participants in the Wisconsin State Laboratory of Hygiene/College of American Pathologists Proficiency Testing Program. *J. Clin. Microbiol.* 35(3), 537–543 (1997).

30 Donta ST. Late and chronic Lyme disease. *Med. Clin. North Am.* 86(2), 341–349 (2002).

31 Donta ST. The existence of chronic Lyme disease. *Curr. Treat. Op. Infect. Dis.* 3, 261–262 (2001).

32 Donta ST. Tetracycline therapy for chronic Lyme disease. *Clin. Infect. Dis.* 25(Suppl. 1), S52–S56 (1997).

33 Craft JE, Fischer DK, Shimamoto GT *et al.* Antigens of *Borrelia burgdorferi* recognized during Lyme disease. Appearance of a new immunoglobulin M response and expansion of the immunoglobulin G response late in the illness. *J. Clin. Invest.* 78(4), 934–939 (1986).

34 Coyle PK, Schutzer SE, Belman AL, Krupp LB, Golightly MG. Cerebrospinal fluid immune complexes in patients exposed to *Borrelia burgdorferi*: detection of *Borrelia*-specific and -nonspecific complexes. *Ann. Neurol.* 28(6), 739–744 (1990).

35 Jain VK, Hilton E, Maytal J, Dorante G, Ilowite NT, Sood SK. Immunoglobulin M immunoblot for diagnosis of *Borrelia burgdorferi* infection in patients with acute facial palsy. *J. Clin. Microbiol.* 34(8), 2033–2035 (1996).

36 Treib J, Fernandez A, Haass A, Grauer MT, Holzer G, Woessner R. Clinical and serologic follow-up in patients with neuroborreliosis. *Neurology* 51(5), 1489–1491 (1998).

37 The International Lyme and Associated Diseases Society (ILADS). Evidence-based guidelines for the management of Lyme disease. *Expert Rev. Anti-infect. Ther.* 2(Suppl.), S1–S13 (2004).

•• **First comprehensive guidelines for the diagnosis and treatment of Lyme disease.**

38 Engstrom SM, Shoop E, Johnson RC. Immunoblot interpretation criteria for serodiagnosis of early Lyme disease. *J. Clin. Microbiol.* 33(2), 419–427 (1995).

39 Ma B, Christen B, Leung D, Vigo-Pelfrey C. Serodiagnosis of Lyme borreliosis by western immunoblot: reactivity of various significant antibodies against *Borrelia burgdorferi*. *J. Clin. Microbiol.* 30(2), 370–376 (1992).

• **Excellent review of Lyme disease serodiagnosis.**

40 Rawlings JA, Fournier PV, Teltow GJ. Isolation of *Borrelia spirochetes* from patients in Texas. *J. Clin. Microbiol.* 25(7), 1148–1150 (1987).

41 Aguero-Rosenfeld ME, Nowakowski J, Bittker S, Cooper D, Nadelman RB, Wormser GP. Evolution of the serologic response to *Borrelia burgdorferi* in treated patients with culture-confirmed erythema migrans. *J. Clin. Microbiol.* 34(1), 1–9 (1996).

42 Aguero-Rosenfeld ME, Nowakowski J, McKenna DF, Carbonaro CA, Wormser GP. Serodiagnosis in early Lyme disease. *J. Clin. Microbiol.* 31(12), 3090–3095 (1993).

43 Goodman JL, Bradley JF, Ross AE *et al.* Bloodstream invasion in early Lyme disease: results from a prospective, controlled, blinded study using the polymerase chain reaction. *Am. J. Med.* 99(1), 6–12 (1995).

44 Straubinger RK. PCR-based quantification of *Borrelia burgdorferi* organisms in canine tissues over a 500-day postinfection period. *J. Clin. Microbiol.* 38(6), 2191–2199 (2000).

• **Evidence for persistent Lyme disease in dogs.**

45 Ziska MH, Donta ST, Demarest FC. Physician preferences in the diagnosis and treatment of Lyme disease in the USA. *Infection* 24(2), 182–186 (1996).

46 Johnson BJ, Robbins KE, Bailey RE *et al.* Serodiagnosis of Lyme disease: accuracy of a two-step approach using a flagella-based ELISA and immunoblotting. *J. Infect. Dis.* 174(2), 346–353 (1996).

47 Centers for Disease Control and Prevention (CDC). Case definition for infectious conditions under public health surveillance (Lyme disease surveillance case definition). *Morb. Mortal. Wkly Rep.* 46(RR10, 1–3), 15–16 (1997).

48 Porcella SF, Schwan TG. *Borrelia burgdorferi* and *Treponema pallidum*: a comparison of functional genomics, environmental adaptations, and pathogenic mechanisms. *J. Clin. Invest.* 107(6), 651–656 (2004).

• **Good description of the complexity of *Borrelia burgdorferi*.**

49 Georgilis K, Peacocke M, Klempner MS. Fibroblasts protect the Lyme disease spirochete, *Borrelia burgdorferi*, from ceftriaxone *in vitro*. *J. Infect. Dis.* 166(2), 440–444 (1992).

50 Coyle PK. *Borrelia burgdorferi* infection: clinical diagnostic techniques. *Immunol. Invest.* 26(1–2), 117–128 (1997).

51 Brouqui P, Badiaga S, Raoult D. Eucaryotic cells protect *Borrelia burgdorferi* from the action of penicillin and ceftriaxone but not from the action of doxycycline and erythromycin. *Antimicrob. Agents. Chemother.* 40(6), 1552–1554 (1996).

52 Mahmoud AA. The challenge of intracellular pathogens. *N. Engl. J. Med.* 326(11), 761–762 (1992).

53 Beaman BL, Scates SM. Role of L-forms of Nocardia caviae in the development of chronic mycetomas in normal and immunodeficient murine models. *Infect. Immun.* 33(3), 893–907 (1981).

54 Cook J, Fincham WJ, Lack CH. Chronic arthritis produced by streptococcal L-forms. *J. Pathol.* 99(4), 283–297 (1969).

55 Brorson O, Brorson SH. A rapid method for generating cystic forms of *Borrelia burgdorferi*, and their reversal to mobile spirochetes. *Apmis* 106(12), 1131–1141 (1998).

• **Evidence for cell wall-deficient forms of *Borrelia burgdorferi*.**

56 Aberer E, Koszik F, Silberer M. Why is chronic Lyme borreliosis chronic? *Clin. Infect. Dis.* 25(Suppl. 1), S64–S70 (1997).

57 Zajkowska JM, Hermanowska-Szpakowicz T, Kondrusik M, Pancewicz SA. Neurologic syndromes in Lyme disease. *Pol. Merkuriusz. Lek.* 9(50), 584–588 (2000).

58 Zajkowska JM, Hermanowska-Szpakowicz T, Pancewicz SA, Kondrusik M. Selected aspects of immunopathogenesis in Lyme disease. *Pol. Merkuriusz. Lek.* 9(50), 579–583 (2000).

59 Dorward DW, Fischer ER, Brooks DM. Invasion and cytopathic killing of human lymphocytes by spirochetes causing Lyme disease. *Clin. Infect. Dis.* 25(Suppl. 1) S2–S8 (1997).

60 Chiao JW, Pavia C, Riley M *et al.* Antigens of Lyme disease of spirochaete *Borrelia burgdorferi* inhibits antigen or mitogen-induced lymphocyte proliferation. *FEMS Immunol. Med. Microbiol.* 8(2), 151–155 (1994).

61 Seiler KP, Weis JJ. Immunity to Lyme disease: protection, pathology and persistence. *Curr. Opin. Immunol.* 8(4), 503–509 (1996).

62 Stricker RB, Burrascano J, Winger E. Longterm decrease in the CD57 lymphocyte subset in a patient with chronic Lyme disease. *Ann. Agric. Environ. Med.* 9(1), 111–113 (2002).

63 Hunfeld KP, Kraiczy P, Kekoukh E, Schafer V, Brade V. Standardised *in vitro* susceptibility testing of *Borrelia burgdorferi* against well-known and newly developed antimicrobial agents – possible implications for new therapeutic approaches to Lyme disease. *Int. J. Med. Microbiol.* 291(Suppl. 33), 125–137 (2002).

64 Preac Mursic V, Marget W, Busch U, Pleterski Rigler D, Hagl S. Kill kinetics of *Borrelia burgdorferi* and bacterial findings in relation to the treatment of Lyme borreliosis. *Infection* 24(1), 9–16 (1996).

65 Henneberg JP, Neubert U. *Borrelia burgdorferi* group: *in vitro* antibiotic sensitivity. *Ort. Hetil.* 143(21), 1195–1198 (2002).

66 Burrascano J. Lyme disease complexities. Kennett Friends Meeting, sponsored by the Lyme Disease Association of Southeastern Pennsylvania, Kennett Square, PA, USA. 3 May 2003.

67 Brown SL, Hansen SL, Langone JJ. Role of serology in the diagnosis of Lyme disease. *J. Am. Med. Assoc.* 282(1), 62–66 (1999).

• **US Food and Drug Administration view of Lyme disease testing.**

68 Bakken LL, Case KL, Callister SM, Bourdeau NJ, Schell RF. Performance of 45 laboratories participating in a proficiency testing program for Lyme disease serology. *J. Am. Med. Assoc.* 268(7), 891–895 (1992).

• **Review of problems with Lyme disease testing.**

69 Wormser GP, Nadelman RB, Dattwyler RJ *et al.* Practice guidelines for the treatment of Lyme disease. The Infectious Diseases Society of America. *Clin. Infect. Dis.* 31(Suppl. 1), 1–14 (2000).

70 Feder HM Jr. Differences are voiced by two Lyme camps at a Connecticut public hearing on insurance coverage of Lyme disease. *Pediatrics* 105(4 Pt 1), 855–857 (2000).

71 Straubinger RK, Summers BA, Chang YF, Appel MJ. Persistence of *Borrelia burgdorferi* in experimentally infected dogs after antibiotic treatment. *J. Clin. Microbiol.* 35(1), 111–116 (1997).

72 Liegner KB, Kochevar J. Guidelines for the clinical diagnosis of Lyme disease. *Ann. Intern. Med.* 129(5), 422 (1998).

73 Pachner AR, Delaney E, O'Neill T. Neuroborreliosis in the nonhuman primate: *Borrelia burgdorferi* persists in the central nervous system. *Ann. Neurol.* 38(4), 667–669 (1995).

74 Burrascano J. Lyme Disease. In: *Conn's Current Therapy.* Rakel R (Ed.), Saunders, PA, USA (1997).

* Excellent review of Lyme disease diagnosis and treatment.

75 Labro MT, Abdelghaffar H. Immunomodulation by macrolide antibiotics. *J. Chemother.* 13(1), 3–8 (2001).

76 Freedman RM. The two Lyme camps. *Pediatrics* 107(6), 1495 (2001).

77 Magri JM, Johnson MT, Herring TA, Greenblatt JF. Lyme disease knowledge, beliefs, and practices of New Hampshire primary care physicians. *J. Am. Board. Fam. Pract.* 15(4), 277–284 (2001).

78 Straubinger RK, Straubinger AF, Summers BA, Jacobson RH. Status of *Borrelia burgdorferi* infection after antibiotic treatment and the effects of corticosteroids: an experimental study. *J. Infect. Dis.* 181(3), 1069–1081 (2000).

79 Shadick NA, Phillips CB, Logigian EL *et al.* The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. *Ann. Intern. Med.* 121(8), 560–567 (1994).

80 Liegner KB. Culture confirmed treatment failure of cefotaxime and minocycline in a case of Lyme meningoencephalomyelitis. In: *Program and abstracts of the Fifth International Conference on Lyme Borreliosis.* Arlington, VA, USA (1992).

81 Krupp LB, Masur D, Schwartz J *et al.* Cognitive functioning in late Lyme borreliosis. *Arch. Neurol.* 48(11), 1125–1129 (1991).

82 Haupl T, Hahn G, Rittig M *et al.* Persistence of *Borrelia burgdorferi* in ligamentous tissue from a patient with chronic Lyme borreliosis. *Arthritis Rheum.* 36(11), 1621–1626 (1993).

83 Hassler D, Riedel K, Zorn J, Preac-Mursic V. Pulsed high-dose cefotaxime therapy in refractory Lyme borreliosis. *Lancet* 338(8760), 193 (1991).

84 Pfister HW, Preac-Mursic V, Wilske B, Schielke E, Sorgel F, Einhaupl KM. Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. *J. Infect. Dis.* 163(2), 311–318 (1991).

85 Liegner KB. Chronic persistent infection and chronic persistent denial of chronic persistent infection in Lyme disease. *Annual Lyme Disease Scientific Conference.* Atlantic City, NJ, USA. May 5–6 1993.

86 Halperin JJ. Neuroborreliosis: central nervous system involvement. *Semin. Neurol.* 17(1), 19–24 (1997).

87 Ketsten A, Poitschek C, Rauch S, Aberer E. Effects of penicillin, ceftriaxone, and doxycycline on morphology of *Borrelia burgdorferi*. *Antimicrob. Agents. Chemother.* 39(5), 1127–1133 (1995).

88 Preac-Mursic V, Pfister HW, Spiegel H *et al.* First isolation of *Borrelia burgdorferi* from an iris biopsy. *J. Clin. Neuroophthalmol.* 13(3), 155–161 (1993).

89 Young D, Hussell T, Dougan G. Chronic bacterial infections: living with unwanted guests. *Nature Immunol.* 3(11), 1026–1032 (2002).

90 Shadick NA, Phillips CB, Sangha O *et al.* Musculoskeletal and neurologic outcomes in patients with previously treated Lyme disease. *Ann. Intern. Med.* 131(12), 919–926 (1999).

91 Fallon BA. *Testimony at public hearing in re Lyme disease, State of Connecticut.* Department of Public Health 29th January 2004.

92 Schmid GP. Epidemiology and clinical similarities of human spirochetal diseases. *Rev. Infect. Dis.* 11(Suppl. 6), S1460–S1469 (1989).

93 Jacobs RA. Syphilis. In: *Current Medical Diagnosis and Treatment, 42nd Edition.* Tierney LM, McPhee SJ, Papadakis MA (Eds), McGraw Hill, NY, USA (2003).

94 Katzel J. Is there a consensus in treatment of Lyme borreliosis? In: *Lyme Disease 1991 Patient/Physician Perspectives from the US and Canada.* Mermin L (Ed.), Madison, WI, USA (1991).

95 Cimmino MA, Moggiana GL, Parisi M, Accardo S. Treatment of Lyme arthritis. *Infection* 24(1), 91–93 (1996).

96 Raoult D, Houpikian P, Tissot Dupont H, Riss JM, Arditi-Djiane J, Brouqui P. Treatment of Q fever endocarditis: comparison of two regimens containing doxycycline and ofloxacin or hydroxychloroquine. *Arch. Intern. Med.* 159(2), 167–173 (1999).

97 Goto M. Chemotherapy of leprosy: theoretical basis of new guideline in Japan. *Nihon Hansenbyo Gakkai Zasshi* 70(3), 151–155 (2001).

98 Shaw IN, Natrajan MM, Rao GS, Jesudasan K, Christian M, Kavitha M. Long-term follow-up of multibacillary leprosy patients with high BI treated with WHO/MDT regimen for a fixed duration of 2 years. *Int. J. Lepr. Mycobact. Dis.* 68(4), 405–409 (2000).

99 Small PM, Fujiwara PI. Management of tuberculosis in the USA. *N. Engl. J. Med.* 345(3), 189–200 (2001).

100 Stricker RB, Lautin A. The Lyme wars: time to listen. *Expert Opin. Investig. Drugs* 12(10), 1609–1614 (2003).

** Excellent analysis of the Lyme disease controversy.

101 Wahlberg P, Granlund H, Nyman D, Panelius J, Seppala I. Treatment of late Lyme borreliosis. *J. Infect.* 29(3), 255–261 (1994).

102 Oksi J, Marjamaki M, Nikoskelainen J, Viljanen MK. *Borrelia burgdorferi* detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. *Ann. Med.* 31(3), 225–232 (1999).

103 Krupp LB, Hyman LG, Grimson R *et al.* Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. *Neurology* 60(12), 1923–1930 (2003).

104 Haycox A, Bagust A, Walley T. Clinical guidelines – the hidden costs. *Br. Med. J.* 318(7180), 391–393 (1999).

** Short but cogent analysis of the interests of different stakeholders in the process of drafting guidelines.

105 Ernst E, Canter PH. Investigator bias and false positive findings in medical research. *Trends Pharmacol. Sci.* 24(5), 219–221 (2003).

106 Morriem E. From the clinics to the courts: the role evidence should play in litigating medical care. *J. Health Polit. Policy Law* 26(2), 409 (2001).

107 Steiner I. Treating post Lyme disease: trying to solve one equation with too many unknowns. *Neurology* 60(12), 1888–1889 (2003).

108 Halperin JJ, Heyes MP. Neuroactive kynurenines in Lyme borreliosis. *Neurology* 42(1), 43–50 (1992).

109 Noah L. Informed consent and the elusive dichotomy between standard and experimental therapy. *Am. J. Law Med.* 28(4), 361–408 (2002).

•• Excellent overview of the distinction between experimental and nonexperimental medicine, the weight that should be afforded to different types of evidence and the need for informed consent.

110 Britton C. Remarks before the NYS Assembly Committee on Health chaired by Richard Gottfried. *New York State Assembly, Standing Committee On Health, public hearing: chronic Lyme disease and long-term antibiotic treatment.* NY, USA, 27th November 2001.

111 Zeuzem S. A comparison of standard treatment versus dynamically individualized treatment in patients with chronic hepatitis C. *54th Annual Meeting of the American Association for the Study of Liver Diseases* MA USA. October 24–28, 2003.

112 Parola P, Raoult D. Ticks and tickborne bacterial diseases in humans: an emerging infectious threat. *Clin. Infect. Dis.* 32(6), 897–928 (2001).

113 Schabereiter-Gurtner C, Lubitz W, Rolleke S. Application of broad-range 16S rRNA PCR amplification and DGGE fingerprinting for detection of tick-infecting bacteria. *J. Microbiol. Methods* 52(2), 251–260 (2003).

114 Schouls LM, Van De Pol I, Rijpkema SG, Schot CS. Detection and identification of *Ehrlichia, Borrelia burgdorferi* sensu lato, and *Bartonella* spp. in Dutch *Ixodes ricinus* ticks. *J. Clin. Microbiol.* 37(7), 2215–2222 (1999).

115 Kaiser R. False-negative serology in patients with neuroborreliosis and the value of employing of different borrelial strains in serological assays. *J. Med. Microbiol.* 49(10), 911–915 (2000).

116 Steere AC, Dwyer E, Winchester R. Association of chronic Lyme arthritis with HLA-DR4 and HLA-DR2 alleles. *N. Engl. J. Med.* 323(4), 219–223 (1990).

117 Institute of Medicine. *Guidelines for clinical practice: from development to use.* Field M, Lohr K (Eds), National Academy Press, Washington, DC, USA (1992).

•• Excellent overview of the relative roles of evidence and consensus in medical practice and how to guard against bias in the drafting of treatment guidelines.

118 Hitt J. The year in ideas: A to Z evidence-based medicine. *New York Times* December 9 (2001).

119 Wennberg JE, Fisher JS, Skinner JS. Geography and the debate over Medicare reform. *Health. Aff. (Millwood)* (Suppl. Web Exclusives), W96–114 (2002).

•• Includes an excellent analysis of small-area variations caused by patient preference issues and the appropriate way to address this variation (outcomes research and informed patient consent).

120 Arlen J, MacLeod W. Malpractice liability for physicians and managed care organizations. *NY Uni. Law Rev.* (2003).

•• Excellent analysis of negligence liability for physicians and managed care organizations and the essential role that such sanctions play in regulating noncontractable postcontractual medical actions to establish optimal care.

121 Mulrow C, Lohr K. Proof and Policy from Medical Research Evidence Journal of Health Politics, Policy and Law, entitled Evidence: its meanings in health care and in law. (Summary of the 10 April 2000 IOM and AHRQ Workshop). *J. Health Polit. Policy Law* (2000).

•• Analysis of the subjective contribution of judgment, values, probability, and uncertainty in medical decision making.

122 Muir Gray J. *Evidence-Based Healthcare. How to Make Health Policy and Management Decisions.* Churchill Livingstone, London, UK (1997).

123 Hayward RS, Wilson MC, Tunis SR, Bass EB, Guyatt G. Users' guides to the medical literature. How to use clinical practice guidelines. Are the recommendations valid? The Evidence-Based Medicine Working Group. *J. Am. Med. Assoc.* 274(7), 570–574 (1995).

124 Nichol G, Dennis DT, Steere AC. Test-treatment strategies for patients suspected of having Lyme disease: a cost-effectiveness analysis. *Ann. Intern. Med.* 128(1), 37–48 (1998).

125 Martinez B. Care guidelines used by insurers face scrutiny. *Wall Street Journal*, September 14 (2000).

126 Bransfield R. *NYS Assembly Committee on Health chaired by Richard Gottfried.* Albany, NY, USA 27 November 2001.

127 Van de Weyden M. Clinical practice guidelines: time to move the debate from the how to the who. *Med. J. Aust.* 176(7), 304–305 (2002).

128 Grilli R, Magrini N, Penna A, Mura G, Liberati A. Practice guidelines developed by specialty societies: the need for critical appraisal. *Lancet* 355, 103–106 (2000).

129 Silver W. The Inadequacy of state legislative responses to ERISA preemption of managed care liability. *NY Uni. Law Rev.* 78(2), 845–873 (2003).

130 Stolberg S. Study says clinical guides often hide ties of doctors. *New York Times* 6 February (2003).

131 Choudhry N, Stelfox H, Detsky A. Relationships between authors of clinical practice guidelines and the pharmaceutical industry. *J. Am. Med. Assoc.* 287, 612–617 (2002).

132 Mello M. Of swords and shields: the use of clinical practice guidelines in medical malpractice litigation. *Uni Penn. Law Rev.* 149(3), 645–710 (2000).

133 Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. *Br. Med. J.* 318(7182), 527–530 (1999).

134 Fletcher S, Fletcher R. Development of clinical guidelines. *Lancet* 352(9144), 1876 (1998)

135 Haycox A, Bagust A, Walley P. Clinical guidelines – the hidden costs. *Br. Med. J.* 318, 391–393 (1999).

136 Rosenbaum S, Kamoie B. Managed care and public health: conflict and collaboration. *J. Law Med. Ethics* 30(2), 191–200 (2002).

137 Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Potential benefits, limitations, and harms of clinical guidelines. *Br. Med. J.* 318, 527–530 (1999).

138 California Jury Instruction Civil Committee. Duty of Physicians. In: *California Jury Instructions, Civil: Book Of Approved Jury Instructions.* West Publishing Co., MN, USA (2002).

139 Mello M. Using statistical evidence to prove the malpractice standard of care: bridging legal, clinical, and statistical thinking. *Wake Forest Law Rev.* 37(3), 821–859 (2002).

140 California Jury Instruction Civil Committee. Medical negligence – standard of care determined by expert testimony. In: *California Jury Instructions, Civil: Book of Approved Jury Instructions.* West Publishing Co., MN, USA (2002).

141 Hurwitz B. Clinical guidelines and the law. *Br. Med. J.* 311, 1517–1518 (1995).

142 Mulrow C, Lohr K. Proof and policy from medical research evidence. *J. Health Politics Policy Law* 26(2) (2001).

143 California Jury Instruction Civil Committee. Alternative methods of diagnosis or treatment. In: *California Jury Instructions, Civil: Book of Approved Jury Instructions.* West Publishing Co., St. Paul, MN, USA (2002).

144 *Leech v. Bralliar* 275 F. Supp. 897 (D. Ariz. 1967).

145 *Natole v. Michigan Board of Medicine*, (File no. 96-015560 AA-2) (1998) (2001).

146 Office of Technology Assessment (US Congress). Defensive Medicine: definition and causes. In: *Defensive Medicine and Medical Malpractice.* USA Government Printing Office, Washington, DC, USA (1994).

• Interesting analysis of defensive versus nondefensive medicine and in what situations it is appropriate for a physician to employ defensive medicine to improve treatment outcomes.

147 Quill TE, Brody H. Physician recommendations and patient autonomy: finding a balance between physician power and patient choice. *Ann. Intern. Med.* 125(9), 763–769 (1996).

148 Amanda R, Marcia A, Richard WD *et al.* What is a good decision? *Effective Clin. Prac.* July/August (1999).

149 *Cobbs v. Grant*, 104 Cal. Rptr. 505 (Cal. 1972).

150 *Matthies v. Mastromonaco*, 733 A. 2d 456 (N.J. 1999).

151 *Mathis v. Morrissey*, 13 Cal. Rptr. 2d 819 (1992).

152 Wennburg JE, Peters GP. Unwarranted variations in the quality of healthcare: can the law help medicine provide a remedy/remedies? *Wake Forest Law Rev.* 37(3), 925–941 (2002).

153 Wang M. Resurgent Paternalism. Virtual Mentor-Ethics *J. Am. Med. Assoc.* 6(2) (1994).

154 Liegner KB, Lyme disease controversy: use and misuse of language. *Ann. Intern. Med.* 137(9), 775–777 (2002).

155 *Hughes v. Blue Cross of Northern California*, 263 Cal. Rptr. 850 (1989)

156 *Wickline v. State of California*, 239 Cal. Rptr. 810 (1986)

157 *Wilson v. Blue Cross of Southern California*, 271 Cal. Rptr. 876 (1990).

• The Wilson court points out that language in Wickline suggesting that liability rests solely within the treating physician's responsibility constitutes nonbinding dicta and holds that an insurance review company may be held responsible when its conduct is a substantial factor in the plaintiff's injury or death.

158 *Van Vactor v. Blue Cross Assoc.*, 365 N.E.2d 638,645 (Ill. App. Ct. 1977).

159 Furrow BR. The problem of medical misadventures: a review of E Haavi Morreim's Holding Healthcare Accountable. *J. Law Med. Ethics* 29(3–4), 381–393 (2001).

160 *Murray v. Chesapeake*, No. 07C99000129mm. (Cecil county, MD 2000).

161 *Sarchett v. Blue Shield of California*, 223 Cal. Rptr. 76 (1987).

162 Valesova H, Mailer J, Havlik J, Hulinska D, Hercogova J. Long-term results in patients with Lyme arthritis following treatment with ceftriaxone. *Infection* 24(1), 98–102 (1996).

163 Asch ES, Bujak DI, Weiss M, Peterson MG, Weinstein A. Lyme disease: an infectious and postinfectious syndrome. *J. Rheumatol.* 21(3), 454–461 (1994).

164 Logigian EL, Kaplan RF, Steere AC. Chronic neurologic manifestations of Lyme disease. *N. Engl. J. Med.* 323(21), 1438–1444 (1990).

165 Breier F, Khanakah G, Stanek G *et al.* Isolation and polymerase chain reaction typing of *Borrelia afzelii* from a skin lesion in a seronegative patient with generalized ulcerating bullous lichen sclerosus et atrophicus. *Br. J. Dermatol.* 144(2), 387–392 (2001).

166 Horowitz R. Chronic persistent Lyme borreliosis: PCR evidence of chronic infection despite extended antibiotic therapy – a retrospective review. *13th International Scientific Conference on Lyme Disease and Other Tick-Borne Disorders.* CT, USA 24–26 March 2000.

167 Bayer ME, Zhang L, Bayer MH. *Borrelia burgdorferi* DNA in the urine of treated patients with chronic Lyme disease symptoms. A PCR study of 97 cases. *Infection* 24(5), 347–353 (1996).

168 Burrascano J. Failure of aggressive antibiotic therapy to protect the placenta from invasion by B burgdorferi in a pregnant patient with Lyme Borreliosis. *6th Annual International Science Conference on Lyme Disease and other Tick-borne Diseases.* (1993) (Abstract).

169 Battafarano DF, Combs JA, Enzenauer RJ, Fitzpatrick JE. Chronic septic arthritis caused by *Borrelia burgdorferi*. *Clin. Orthop.* 297, 238–241 (1993).

170 Petrovic M, Vogelaers D, Van Renterghem L, Carton D, De Reuck J, Afschrift M. Lyme borreliosis – a review of the late stages and treatment of four cases. *Acta. Clin. Belg.* 53(3), 178–183 (1998).

171 Ferris Tortajada J, Lopez Andreu JA, Salcede Vivo J, Sala Lizarraga JV. Lyme Borreliosis (Letter). *Lancet* 345(8962), 1436–1437 (1995).

172 Lopez-Andreu JA, Ferris J, Canosa CA, Sala-Lizarraga JV. Treatment of late Lyme disease: a challenge to accept. *J. Clin. Microbiol.* 32(5), 1415–1416 (1994).

173 Oksi J, Nikoskelainen J, Viljanen MK. Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. *Eur. J. Clin. Microbiol. Infect. Dis.* 17(10), 715–719 (1998).

174 Fallon BA. Repeated antibiotic treatment in chronic Lyme disease. *J Spirochet Tick Borne Dis.* 6, 94–101 (1999).

175 Lawrence C, Lipton RB, Lowy FD, Coyle PK. Seronegative chronic relapsing neuroborreliosis. *Eur. Neurol.* 35(2), 113–117 (1995).

176 Masters E. Spirochetemia after continuous high-dose oral amoxicillin therapy. *Infect. Dis. Clin. Prac.* 3(3), 207–208 (1994).

177 Cimmino MA, Accardo S. Long-term treatment of chronic Lyme arthritis with benzathine penicillin. *Ann. Rheum. Dis.* 51(8), 1007–1008 (1992).

178 Connor S. Glaxo chief: our drugs do not work on most patients. *The Independent* 8 December (2003).

179 Edmonds J, Day O, Bertouch J. In reply: The road to consensus: consideraton for the safe use and prescribing of COX-2 specific inhibitors. *Med. J. Aust.* 176(7), 332–334 (2002).

•• Excellent discussion of the hazards and pitfalls of guideline development within contentious groups.

180 Jacoby I. Consensus development at NIH: What went wrong? *Risk* 4, 133 (1993).

181 Jacoby I. Resolving medical controversies. *Risk* 6, 139 (1994).

182 Morris GH. Dissing disclosure: just what the doctor ordered. *Ariz. Law Rev.* 44, 313 (2002).

• Provides an extensive and well-reasoned analysis of the history, current status, and legal issues lurking in the doctrine of informed consent.

183 The American Urological Association. Prostate cancer clinical guidelines panel summary report on the management of clinically localized prostate cancer. *J. Urol.* 154(6):2144–2148 (1995).

Websites

201 Rubel J. Lyme disease symptoms and characteristics: a compilation of peer-reviewed literature reports (compilation of 19 Lyme related deaths). www.lymeinfo.net/LDSymptoms.pdf (Accessed July 2004)

202 Edlow J. Tick borne diseases, Lyme. eMedicine www.emedicine.com/emerg/topic588.htm (Accessed July 2004)

203 National Institute of Allergy and Infectious Diseases (National Institute of Health) profile, fiscal year 2001 www.niaid.nih.gov/publications/NIAIDProfile/ (Accessed July 2004)

204 Liegner KB. *Remarks before the New York State Assembly Committee on Health, Public Hearing. Chronic Lyme Disease and Long-term Antibiotic Treatment*, NY, USA, 27 November 2001. www.canlyme.com/leigner.html (Accessed July 2004)

205 National Institute of Allergy and Infectious Diseases (National Institute of Health). Diagnosis of Lyme Disease. www.niaid.nih.gov/dmid/lyme/diagnosis.htm (Accessed July 2004)

206 Mead P. Statement by Paul Mead MD, M.P.H., Medical Epidemiologist, Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Center for Disease Control and Prevention, US Department of Health and Human Services on Hearing: CDC's Lyme Disease Prevention and Control Activities at public hearing in re Lyme disease, State of Connecticut, Department of Public Health, 29 January 2004. www.hhs.gov/asl/testify/t040129.html (Accessed July 2004)

207 Rawlings J Goldhagens H. Lyme Disease Controversies. Medscape coverage of the *14th International Scientific Conference on Lyme Disease and Other Tick-Borne Disorders*. www.medscape.com/viewprogram/482_childindex (Accessed July 2004)

208 Lyme Disease Foundation. The controversies surrounding Lyme disease diagnosis and treatment and why it is not uncommon for patients to experience persistent symptoms despite receiving conventional' (short-term) antibiotic therapy for Lyme disease. www.lyme.org/lymelight/trtcontrov.html (Accessed July 2004)

209 Cooper C. Safety of long-term therapy with penicillin and penicillin derivatives. Center for Drug Evaluation and Research. www.fda.gov/cder/drugprepare/penlongsafety.htm (Accessed July 2004)

210 Burrascano JJ. Diagnostic hints and treatment guidelines for Lyme and other tick-borne illnesses. (2002). http://www.ilads.org/burrascano_1102.htm (Accessed July 2004)

** **Comprehensive guide to Lyme disease diagnosis and treatment.**

211 The International Lyme and Associated Diseases Society (ILADS). Evaluation of antibiotic treatment in patients with persistent symptoms of Lyme disease. www.ilads.org/position2.htm (Accessed July 2004)

** Must-read rebuttal to the flawed study of 'long-term' antibiotic therapy published in the *N. Engl. J. Med.* [14].

212 Grier T. ELISA and western blot lies that can kill you? www.centurytel.net/tjs11/bug/blot1.htm (Accessed July 2004)

213 Morgan M. Independent review of managed care decisions. csha.calhealth.org/ (Accessed July 2004)

214 Booth A. What proportion of healthcare is evidence based? www.shef.ac.uk/scharr/ir/percent.html (Accessed July 2004)

* **Valuable compilation of discussion on evidence-based medicine from many studies and comments, including the distinction between randomized clinical trial-based and compelling nonexperimental evidence.**

215 Lewis D. National guideline clearinghouse: extensive resource underused, in managed care. www.managedcaremag.com/archives/0106/0106.guidelines.htm (Accessed July 2004)

216 Jemsek JG. Lyme disease in the Carolinas (1998) www.jemsekclinic.com/lymedisease.php. (Accessed July 2004)

217 Centre for Evidence Based Medicine. What are the limitations of EBM? www.cebm.utoronto.ca/intro/limit.htm (Accessed July 2004)

218 In the Matter of *Joseph Burrascano v. New York State Bd.* for Professional Medical Conduct, Determination and Order (No. 01–265) of the Hearing Committee dated November 6 2003 w3.health.state.ny.us/opmc/factions.nsf/58220x%20%20%20%20a7f9eeaafab85256b180058c032/7f57f08d61de929c85256a4a0047c6da/$FILE/ATTIDOPD/lc145623.pdf (Accessed July 2004)

219 Hamilton, C. LymeNet Law Pages, Lyme Related Legal Matters. Jury awards $1.7 million to Cecil teen (December 20, 2000). www2.lymenet.org/domino/law.nsf/0/2d03309dc8e1088d052569bd0061a28b?OpenDocument (Accessed July 2004)

220 American Medical Association, Code of Medical Ethics. Current opinions with annotations 2002–2003. www.ama-assn.org/apps/pf_new/pf_online?category= CEJA&assn = AMA&f_n=mSearch&s_t=&st_p=&nth=1& (Accessed July 2004)

221 Fowler F. The role of patient preferences in medical care. www.fimdm.org/downloads/Patient_Preferences_Fowler.pdf (Accessed July 2004)

Affiliations

- *Lorraine Johnson, JD, MBA*
  California Lyme Disease Association,
  P.O. Box 1423, Ukiah, CA 95482, USA
  Tel.: +1 323 461 6184
  Fax: +1 323 461 6143
  lbj1@pacbell.net
- *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

