Testimony for Public Hearing on Pennsylvania House Bill #272

Lyme Disease and Related Tick-Borne Disease Education, Prevention and Treatment

August 30, 2011

(To be read by Mrs. Julia Wagner with my permission)

I am honored to be asked to testify before this hearing. I am a practicing physician and infectious disease specialist who has been treating patients with the Chronic Lyme Disease Syndrome for 21 years.

First I would like to share a few thoughts about this syndrome. The Chronic Lyme Disease Syndrome is a disease caused by its vector, a tick who injects into a human three classes of microorganisms. These have historically been enemies of humans on this planet for centuries. They are spirochetes of the syphilis family ie: Borrelia; ie: Babesia; and small bacteria of the Rickettsia family, that is, Bartonella (cat scratch disease) and Erhlichia.

This triad of organisms, and there may be others, causes a chronic illness of debilitating nature that includes weakness, fatigue, mental difficulties, fever, joint and muscle pains, and multiple sclerosis-like findings. Literally thousands of people in this country appear to have this syndrome. Many of these patients are waiting anxiously for this hearing to take place. Unfortunately, at present there is no generally accepted method to prove that a person has this syndrome.

I will soon be publishing a book detailing my experiences with 51 cases including essays in their regard. The vast majority of these patients were told by well-trained physicians that because their "Lyme tests" were negative, they couldn't have this disease. The particular test that was a culprit in this respect is the Western blot Borrelia antibody test which has been arbitrarily discounted by government edict unless a certain titer in its response has been documented.

It boggles my mind that, because of this, literally thousands of patients in this country have been unable to find physicians who would LISTEN to their complaints. My experience in treating Chronic Lyme Disease is that, in certain instances, long-term therapy given on an empirical basis may help some of these patients.

These treatments must overcome the invasive triad by the following maneuvers:
(1) they must attack the cell wall of some of the invaders, particularly the Borellia,
(2) they must attack the intracellular metabolism of other invaders;
(3) they must attack the life cycles of some of the invaders; and
(4) they must attend to the autoimmunity involved with this syndrome.

All of these treatments must be instituted to theoretically eradicate the invading triad. To date there is no way that it can be proven that these treatments will be successful.

My experience and that of many others who have listened to and tried to help individuals with this syndrome is that there are some who appear to get better under empirical treatments of this type. Many also have noted, as I have, that therapeutic results may disappear when long-term therapy is no longer given.

In my experience, when recurrence occurs, Dr. Fry at the Fry clinic in Arizona can see both protozoa and Bartonella in the blood smears in patients whose disease does reoccur. We may be coming to the point that agreement is reached that treatment will be continued until no organisms can be seen or demonstrated.

When one should stop repressive therapy should be decided upon by the physician who has instituted the empirical program and by the patients who are carefully briefed regarding observations made by those who are treating this syndrome. In my opinion, the fact of arbitrarily stopping therapy being decided upon by those who are not directly involved in patient care, is unconscionable.

I want to thank this committee for allowing me to share my heartfelt feelings regarding the Chronic Lyme Disease Syndrome with you.

It is a mystery to me that some of those who have carefully listened to patients with complaints related to this syndrome, can come to the conclusion that it does not exist.

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Attachments:

(1) The Emperor's New Clothes, Chronic Lyme Disease, and the Infectious Disease Society of America, an essay by Burton Waisbren, MD, FACP, FIDSA
(2) Contested Guidelines Recommendations, IDSA Guidelines Review Hearing, July 30, 2009, by Stephen Phillips, MD

The Emperor's New Clothes, Chronic Lyme Disease, and the Infectious Disease Society of America

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This essay will start with a definition of Chronic Lyme disease: Chronic Lyme disease is a syndrome that results when individuals who have been inoculated with multiple microorganisms by infected ticks and who have not responded to an initial course of doxycycline develop extreme fatigue, intermittent fever, joint pain, muscle pain, brain fog, concentration difficulties, skin rashes, and in many instances symptoms of autoimmune disease to the extent that they impinge upon their quality of life.

When one comes face to face with patients of this type in whom other diseases are ruled out, it is obvious that something serious is amiss.

It's a conundrum why a group of respected physicians who are members of the Infectious Disease Society of America have not recognized this and have, instead, written a guideline that essentially denies that the syndrome exists. This guideline has resulted in literally hundreds of patients unable to be treated for Chronic Lyme disease.

Conclusions regarding this conundrum may be:
1) The physicians who wrote and signed the guidelines of the Infectious Disease Society of America may have seen what they expected to see in the manner of the populace described in the Hans Christian Anderson's perceptive fairy tale, "The Emperor's New Clothes."
2) Perhaps the authors of the guidelines had too much respect for authority and decided to sign the guidelines based on the opinion of some of the members of the society without having personal involvement in the treatment of the syndrome.
3) Perhaps they were unduly influenced by the expenses incurred in the many factors concerned in the empirical treatment of Chronic Lyme Disease.
4) Most probably they were influenced by controlled studies in the medical literature, which were based on Deductive conclusions rather than Inductive conclusions as described by Francis Bacon in 1622. Have they forgotten the well accepted statistical dictum – absence of proof does not equal proof of absence.

Deductive conclusions in regard to Chronic Lyme disease are suspect because there is no way to prove that a person has Chronic Lyme disease. Personal observations (inductive) are what has to be relied upon to conclude that an individual has Chronic Lyme disease.

In Hans Christian Anderson's story, a little boy turns the tide by yelling out, "But the emperor has no clothes!" At the present time we must await the time when many will yell out "These patients are sick!"

This point will have to be proven by inductive observational studies of patients subjected to empirical treatment for chronic Lyme disease. For these inductive studies to reach a level of scientific certainty

great enough to indicate empirical multifactorial treatment of chronic Lyme disease, physicians will have to once again believe what their patients tell them. To do this they will have to remove the "double blind" blinders put on their eyes by Claude Bernard in his monumental book of experimental medicine.

The Internet will provide service in this regard if physicians who treat chronic Lyme disease will present to their colleagues and patients detailed case reports regarding this experience on the internet as well as in the medical literature. Respected medical journals still reluctantly present case reports. Unfortunately, when they do so they usually warn about anecdotal evidence. In this respect isn't it ironic that huge numbers of individuals strongly accept ideas based on anecdotes presented in religious tomes and serious literature.

Phillips, in a brilliant critique of the IDSA guidelines, has separated out numerous observational studies that suggest the occurrence of chronic Lyme disease as described in this essay.

http://www.ilads.org/lyme_disease/media/lyme_video_phillips.html

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RESEARCH LETTER

Consequences of treatment delay in Lyme disease

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Introduction

Lyme disease is the fastest growing vector-borne disease in the Northern hemisphere, with enzootic cycles that can be maintained in a wide range of ecological conditions. According to the Centers for Disease Control and Prevention (CDC), 40 792 cases were reported in the USA in 2001–2002, a 40% increase over the previous year [1]. Data from individual Lyme clinics indicate that the number of actual cases may be as many as 10 times higher, especially in the north-eastern states [2]. Cases are also growing at a substantial rate in the UK (a fivefold increase between 1986 and 1998), and in certain areas of Europe (particularly Sweden and Slovakia) [3].

Surprisingly long treatment delays of 3 years and more have been described in patients enrolled in a National Institute of Health Lyme disease clinical trial [4]. A series of Lyme patients with neuropsychiatric presentations failed to receive treatment for 1 year after onset, despite an average of two previous doctor evaluations [5]. Shorter but still significant delays averaging 6 weeks were reported in each of three cohorts – 215 consecutively evaluated patients in a Lyme clinic [6], patients with neurologic presentations [7], and patients misdiagnosed with cellulitis rather than Lyme disease [8]. To date, the role of treatment delay in determining the outcome of treatment of Lyme disease has not been established. However, a growing database now enables us to address this important question.

Methods

Patient population

We focused on consecutively treated subjects in order to reduce selection bias. The study includes 100 adolescents and adults who were treated in a community-based setting from July 1997 to January 2000. All had a clear diagnosis of Lyme disease and conformed with the Centers for Disease Control and Prevention (CDC) national surveillance case definition [1]. Chronic Lyme disease [6,7] cases were also included to enable comparison with previous studies of chronic Lyme disease [1,6] and to improve the generalizability of the Lyme disease population [7].

The CDC epidemiologic criteria consists of an erythema migrans rash, Bell's palsy, heart block, and/or arthritis [1]. There is, as yet, no other widely agreed upon definition for chronic Lyme disease. Chronic Lyme patients present with a variety of symptoms, including memory loss, poor concentration, irritability, and sleep disturbances. Absence of another diagnosis, and confirmatory serology are also key considerations [6,7].

This is the largest case-controlled study to examine subjects confirmed by the CDC's recommended two-tier diagnostic criteria. Analysis was limited to subjects with a positive IgG Western blot serology to reduce the bias of case ascertainment. The enzyme-linked immunosorbent assay testing was performed at the laboratory for the Diagnosis of Tick Borne Diseases at Stony Brook University School of Medicine. The Western blot testing was performed at Quest Diagnostics.

Subjects who failed initial treatment comprised the case group and subjects who were successfully treated, the control group. An unmatched case–control design also allowed an examination of the role of age and sex in treatment failure. All study subjects and controls received uniform Lyme disease management through a single internal medicine practice.

Clinical history

The onset of Lyme disease was determined by clinical history. This method has been widely used by Lyme researchers to date [6,7,9], and similar criteria have been used in two double-blind placebo-controlled trials [10].

Outcomes

Outcome assessment was also based on clinical impression, as in the majority of the previous studies from 1988 to 2005 [7,9]. At present, there is no alternative clinical or serologic test to deter-

mine outcome. Examination of cerebrospinal fluid fails as an outcome measure as only two of 27 neurological cases show an abnormal spinal tap at onset [7]. Further, neuropsychological tests are not usually administered before initiating treatment.

Clinical judgement for determining success has been previously described as follows: none to moderate gains were considered treatment failure, significant to complete gains were considered successes [7,9].

Statistics

Previous studies show 34–63% failure rates on long-term follow-up of Lyme disease treatment [6,7,9,10]. This sample is large enough to detect an odds ratio (OR) of 4 with 80% power and an alpha level of 0.05. We used chi-square or Student's *t*-test to identify differences between groups in demographic characteristics, clinical characteristics, treatment delay and outcome (SPSS 11.5.1, Chicago, IL, USA).

The effectiveness of antibiotic treatment was evaluated by means of logistic regression analysis with adjustments for sex, tick bite, erythema migrans rash, treatment delay, and treatment duration (SPSS 11.5.1).

The use of this surveillance database was approved by the Western Institutional Review Board. Because this was a retrospective analysis of an existing data set, written informed consent was not necessary from the participating subjects.

Results

Table 1 shows the different characteristics of cases and controls. Gender and age were similar in both groups. However, cases were significantly less likely to report a tick bite (29% vs. 47%, $P = 0.12$) or erythema migrans rash (33% vs. 49%, $P = 0.12$). Cases were much more likely to have been treated previously with steroids (17% vs. 3%, $P = 0.12$).

Fifteen of 24 cases (63%) failing treatment received delayed treatment (Table 2). Treatment delay was more common among cases (58%) than controls (24%, $P = 0.002$) (Table 1). The delay was also significantly longer for cases than controls (518 ± 851 and 92 ± 362 days, $P = 0.001$).

The majority (60%) of cases (cases 1, 3–5, 7, 11–15) with delayed treatment conformed to CDC epidemiological standards, presenting with a rash, Bell's palsy, or arthritis (Table 2). Five of the cases meeting CDC epidemiological standards had been diagnosed with meniscus tear, oedema, 'water on the knee', pericarditis, asthmatic bronchitis, and cellulitis (cases 3, 12–15). Four of these cases were told by their doctors they did not have Lyme disease. Two of the five presented with a classic erythema migrans rash (cases 1, 5). The third had an atypical rash but other symptoms typical of Lyme and a positive Lyme test (case 11); the fourth had Bell's palsy (case 7). Another case meeting CDC epidemiological standards, with Bell's palsy followed by typical symptoms, did not seek medical care (case 4).

The remaining third of our cases had characteristic clinical presentations confirmed by two-tier serologic criteria (cases 2, 6, 8–10) yet did not meet CDC epidemiological case definition. Steroids were prescribed in four of these cases (cases 12–15).

Table 3 shows that treatment delay, steroid treatment and the absence of an erythema migrans rash are associated with the greatest risk of treatment failure by univariate analysis. They are also independent risk factors for treatment failure by logistic regression (OR = 6.3, CI 2.1–19; OR = 10.3, CI 1.2–87 and OR = 0.2, CI 0.1–0.8 respectively.)

Discussion

These results indicate that treatment delay is strongly associated with treatment failure for patients with Lyme disease. The average 1.8 years treatment delay recorded here is consistent with previous reports of treatment delays spanning 6 weeks to 3 years [4–6]. Two-thirds of the delays occurred even though patients conformed to the well-defined CDC case definition. An additional third presented with well-described clinical presentations of Lyme disease, including fatigue, memory and concentration problems, irritability and headaches [7].

The poor outcome after treatment delay supports the hypothesis that treatment delay is a major risk factor for developing chronic Lyme disease.

Delayed treatment was identified in 58% of the cases with treatment failure. Failure was more than twice as likely to occur with delayed treatment than with timely treatment ($P < 0.002$). The association between treatment delay and chronic Lyme disease remains strong even after adjustment for age, sex, tick bite, erythema migrans and steroid use variables.

Two-thirds of our subjects received timely treatment. Their failure rate was only 24%. That is less than half the failure rate for

Table 1 Characteristics of 24 cases of treatment failure and 76 controls of successful treatment

Characteristic	Treatment failure ($n = 24$)	Treatment success ($n = 76$)	*P*-value
Age (years), mean (SD)	38 (19)	42 (15)	0.2
Male	14 (58)	42 (55)	0.79
Tick bite	7 (29)	36 (47)	0.11
Erythema migrans rash	8 (33)	37 (49)	0.12
Steroid use	4 (17)	2 (3)	0.12
Treatment delay	14 (58)	18 (24)	0.002
Treatment duration (days), mean (SD)	85 (134)	70 (83)	0.031
Treatment delay (days), mean (SD)	518 (851)	92 (362)	0.001

Values are numbers (percentages) unless stated otherwise

Table 2 Clinical presentation of the 15 cases failing treatment with delayed treatment by treatment delay

Case	Delay (days)	Age (year)	Sex	Clinical characteristics
1	2920	35	M	Erythema migrans rash, tested 1 week after rash and never retested.
2	2920	16	F	Epstein Barr and Strep infection. Tonsils subsequently removed.
3	2190	57	F	Tick bite followed by swollen right knee diagnosed as meniscus tear.
4	2190	16	M	Bell's palsy, poor in school.
5	1460	31	M	6 by 6 inch rash.
6	1095	35	M	Typical symptoms, told not Lyme disease by two doctors.
7	1095	42	F	Bell's palsy, told not Lyme based on a negative spinal tap.
8	515	22	M	Sinusitis, followed by two sinus operations.
9	455	75	M	Aches, pains and walking difficulties, told related to a previous heart attack for stroke.
10	240	50	M	Rotator cuff injury and meniscus tear.
11	210	36	F	Ill defined rash with a positive test, told not Lyme by their doctor.
12	120	75	M	Edema given diuretics and later 'water on knee' given cortisone.
13	90	18	F	4 by 4 inch rash followed by pericarditis, treated with steroids instead of antibiotics.
14	60	37	M	Disseminated Lyme rashes and asthmatic bronchitis, treated with steroids instead of antibiotics.
15	60	20	F	Cellulitis treated three times.

F, female, M, male.

Table 3 Relation between history variables and treatment failure in 100 Lyme disease patients

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age	1.5 (0.2 to 9.5)	Not included
Sex	0.6 (0.2 to 1.7)	Not included
History of tick bite	0.6 (0.2 to 1.9)	Not included
Erythema migrans rash	0.2 (0.6 to 0.8)*	0.2 (0.1 to 0.8)*
Steroid use	9.6 (1.0 to 91)*	10.3 (1.2 to 87)*
Treatment delay	7.0 (2.2 to 23)**	6.3 (2.1 to 19)**

*Significance <0.05 **Significance <0.001

patients with delayed treatment in our study (58%), and dramatically lower than the 63% failure rate for patients with delayed treatment in two clinical trials [10].

It is worth noting that in our study, the overall failure rate was closer to the 12% to 33% rate documented for patients with neurological Lyme disease [7,9]. The lower failure of 24% in those who received timely treatment underscores the importance of immediate and accurate diagnosis.

To avoid recall bias, we counted doctor contact only if a clear diagnosis was made by the previous doctor. Patient delays were included only if a clear rash or characteristic symptom complex developed. Longer delays by patients with ill-defined, non-specific symptoms would likely only strengthen the association between treatment delay and treatment failure.

This study was retrospective because it is not ethically or legally possible to design a research project with patients who receive no treatment.

Finally, it must be noted that study was not intended to determine if a treatment failure resulted from persistent infection or immune mediation. Additional trials are needed to understand the mechanism for treatment failure.

In summary, clinicians must ensure that patients receive prompt treatment as delays cause unnecessary suffering and expense. Doctors in Lyme endemic regions should inform patients about the risks and symptoms of Lyme disease. There is a pressing need for doctor education programmes designed to help clinicians recognize and treat Lyme disease at onset.

References

1. MMWR (2002) Lyme disease – United States, 2000. *Morbidityand Mortality Weekly Report*, 51 (2), 29–31.
2. Campbell, G. L., Fritz, C. L., Fish, D., Nowakowski, J., Nadelman, R. B. & Wormser, G. P. (1998) Estimation of the incidence of Lyme disease. *American Journal of Epidemiology*, 148 (10), 1018–1026.
3. Smith, R., O'Connell, S. & Palmer, S. (2000) Lyme disease surveillance in England and Wales, 1986–1998. *Emerging infectious diseases*, 6 (4), 404–407.
4. Fallon, B. A. (2001) *Profiles of Chronic Lyme Disease from the NIH Clinical Trial*. Presentation 15th International Scientific Conference on Lyme Disease and Other Tick-Borne Disorders, 22 April 2001, Farmington, CT, USA.
5. Fallon, B. A., Nields, J. A. & Delbene, D. (1991) Depression and Lyme disease: a controlled survey (abstract#NR119). In New Research and Program Abstracts of the 144th Annual Meeting of the American Psychiatric Association, p. 76. Washington, DC: American Psychiatric Association.
6. Asch, E. S., Bujak, D. I., Weiss, M., Peterson, M. G. & Weinstein, A. (1994) Lyme disease: an infectious and postinfectious syndrome. *Journal of Rheumatology*, 21 (3), 454–461.
7. Logigian, E. L., Kaplan, R. F. & Steere, A. C. (1990) Chronic neurologic manifestations of Lyme disease. *New England Journal of Medicine*, 323 (21), 1438–1444.
8. Feder, H. M. Jr & Whitaker, D. L. (1995) Misdiagnosis of erythema migrans. *American Journal of Medicine*, 99 (4), 412–419.
9. Logigian, E. L., Kaplan, R. F. & Steere, A. C. (1999) Successful treatment of Lyme encephalopathy with intravenous ceftriaxone. *Journal of Infectious Diseases*, 180 (2), 377–383.
10. Klempner, M. S., Hu, L. T., Evans, J. *et al.* (2001) Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *New England Journal of Medicine*, 345 (2), 85–92.

The Need for Clinical Judgment in the Diagnosis and Treatment of Lyme Disease

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ABSTRACT

Clinical practice guidelines are increasing in number. Unfortunately, when scientific evidence is uncertain, limited, or evolving, as is often the case, conflict often arises between guideline committees and practicing physicians, who bear the direct responsibility for the care of individual patients. The 2006 Infectious Diseases Society of America guidelines for Lyme disease, which have limited scientific support, could, if implemented, limit the clinical discretion of treating physicians and the treatment options available to patients.

Introduction

Clinical practice guidelines are now ubiquitous throughout the United States. The National Guidelines Clearing House, under the category "diseases," currently lists 2,126 separate guidelines on its website.[1] Clinical guidelines are intended to assist physicians in patient care by clearly communicating the results of the guideline committees' evaluation of available therapeutic options. However, the processes by which individual guidelines are constructed may be less clear, leading to disagreements between the issuing committee and the physicians who treat patients—physicians who may well be as experienced and knowledgeable as the guideline committee.

The 2006 Infectious Diseases Society of America (IDSA) guidelines for Lyme disease were released in the fall of that year and were soon the focus of an antitrust suit brought by Connecticut's attorney general.[2] A settlement between the two sides was announced on May 1, 2008; it called for the seating of a new panel and a comprehensive review of the evidence, including a hearing to allow for presentation of divergent medical points of view.[3] This article reviews the 2006 IDSA Lyme guidelines regarding the impact various recommendations may have on the use of clinical judgment in the diagnosis and treatment of patients with Lyme disease.

Clinical Judgment in the Diagnosis of Lyme Disease

The IDSA in its 2006 Lyme disease guidelines states:

> Clinical findings are sufficient for the diagnosis of erythema migrans, but clinical findings alone are not sufficient for diagnosis of extracutaneous manifestations of Lyme disease or for diagnosis of [human granulocytic anaplasmosis] HGA or babesiosis. Diagnostic testing performed in laboratories with excellent quality-control procedures is required for confirmation of extra cutaneous Lyme disease, HGA, and babesiosis.[4]

Initially, the statement appears innocuous; laboratory confirmation of any diagnosis is always reassuring. But here the guidelines panel goes a step further. By requiring lab confirmation, it sets up a diagnostic hierarchy in which testing supersedes clinical judgment, negative results on indirect laboratory assessments of infection overrule carefully constructed clinical assessments, and tests are deemed infallible.

Yet, this diagnostic scheme is fallible. Consider the situation in which 100 patients with undiagnosed Lyme disease seek medical attention for evaluation of fever, headache, fatigue, and body aches occurring at the end of June. Recall that CDC data indicate that erythema migrans (EM) rashes are reported in 68% of patients meeting the surveillance case definition, and that the guidelines recommend two-tier serologic testing of patients lacking the diagnostic rash.[4,5] In the two-tier scheme, patients are first tested with an enzyme-linked immunoabsorbant assay (ELISA) or indirect fluorescent antibody (IFA) test, and those with positive or equivocal results are then tested with Western blotting; patients who are negative on ELISA are not tested further. Trevejo et al.[6] found the sensitivity of two-tier testing in early Lyme disease to be 29%-32%; Bacon et al.[7] found it to be 38%. As Table 1 demonstrates, the laboratory confirmation requirement is problematic; as many as 22% of early Lyme disease patients would go untreated.

Clearly, this is unacceptable; patients would be left untreated at the stage when therapy is most efficacious. Owing to the potential for false negative results in these circumstances, Steere et al.[8] suggested that physicians consider treating patients with "summertime flu" symptoms. The need for such a suggestion emphasizes the principal reason for this challenge—laboratory confirmation requirements undermine the value and primacy of clinical data and may impede care, as would be the case in this very common clinical scenario.

The same problem with laboratory confirmation holds true for late neurologic Lyme disease. Starting again with 100 patients who have undiagnosed Lyme disease and objective, non-EM findings, 43%-56% would be misdiagnosed because of deficits in laboratory capabilities, as shown in Table 2. In late Lyme, sensitivity of the testing procedure was found to be 44% by Ledue et al.[9], and 57% by Dressler et al.[10]

The low sensitivity of two-tier testing in late neurologic Lyme disease can be traced back to the original paper by Dressler et al.,[10] from which the Centers for Disease Control and Prevention (CDC)

Table 1. Outcomes for 100 Patients with Early Lyme Disease, Following IDSA Recommendations

Description	Number	Positive two-tier	Negative two-tier	Outcome
EM positive	68	NA	NA	Treat
EM absent	32	10-12	20-22	10 treated; **22 untreated**

Table 2. Outcomes for 100 Patients with Late Neurologic Lyme Disease, Following IDSA Recommendations

Description	Positive two-tier	Negative two-tier	Outcome
Late disease, objective positive	44-57	43-56	Roughly half would go untreated

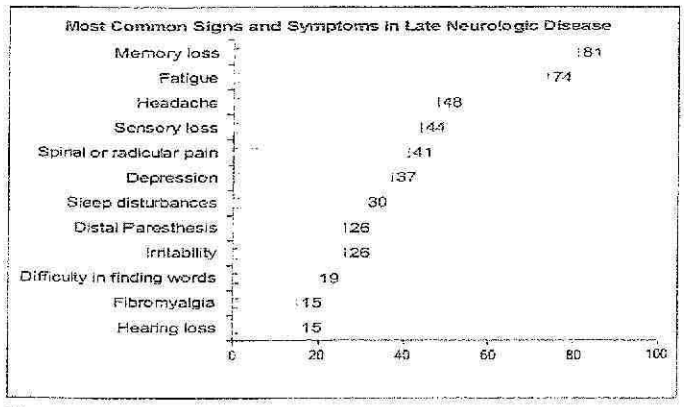

Figure 1. Frequency of Various Signs and Symptoms in Late Neurologic Lyme Disease

took its IgG Western blot criteria. After identifying the 10 bands on Western blotting that yielded the highest specificity in a retrospective study, Dressler et al. then tested the criteria in a prospective study. In that study, the paper reports that 21 of 29 patients with neuroborreliosis had positive IgG Western blot results, yielding a sensitivity of 72%.[10] The ELISA used by Dressler et al. had a sensitivity of 79%. Performing the tests sequentially, as is done in two-tier testing, results in an overall sensitivity of 57% (79% x 72%). With the two-tier sensitivity for late Lyme disease roughly 50%, a negative result does not inform physicians, but may easily lead them astray.

Other studies on the two-tier strategy yield different and higher values for sensitivity.[6,10-13] Some studies speak of the "relative sensitivity" of a test rather than the true sensitivity.[13] The disagreement between studies investigating the sensitivity of various testing methodologies for Lyme disease indicates a problem with test reliability, which has been the subject of other papers.[14,15] If the serologic tests for Lyme disease were equally reliable, sensitivity would be nearly identical across studies of similar, and appropriate, design. (A full discussion on the limitations of serologic testing is beyond the scope of this paper.)

Other methods available to support or confirm a clinical diagnosis of Lyme disease in the absence of an EM have low sensitivity (polymerase chain reaction [PCR] of cerebrospinal fluid and blood), may be invasive, or are not clinically available.[16-20]

With serologic testing being insensitive, clinical data—the history and physical examination—become even more important. Relying on clinical data to make a diagnosis is not unique to Lyme disease. One study on the relative values of history, physical examination, and diagnostic studies found that internists used history alone to establish the correct diagnosis in 76% of test cases.[21] Another found that in distributing a 100% total relative value between these three types of data, clinical faculty valued history at 63.3%, physical examination at 19.2%, and laboratory/imaging data at 17.5%.[22] Such evidence establishes that the diagnostic hierarchy proposed by the guidelines is inconsistent with the way medicine is practiced.

A Lyme disease history begins with the potential for exposure. This history, while a key element, is not always enlightening. Patients may be unaware of whether they live/work/recreate in a Lyme-endemic area; they may forget about vacations in endemic areas. Questions regarding tick bites may lead to inappropriately ruling out Lyme disease; in one study on erythema migrans, only 14% of the patients recalled being bitten by a tick.[23]

Clinically, and in keeping with its multisystemic nature, Lyme disease has been described as being "symptom rich, exam poor." Symptoms may be specific or nonspecific, mundane or unusual, acute or chronic; some are prognostic. Some physicians have been criticized for "seeing Lyme everywhere" in that they recognize scores of symptoms beyond EM rashes, Bell's palsy, and arthritis as being associated with Lyme disease.[24,25] Yet, early researchers also noted these symptoms. In a treatment trial on early Lyme disease, Massarotti et al. found that subjects reported the following symptoms: 56% had headache; 42%, stiff neck, with 19% having pain with neck flexion; 14%, dysesthesias; 11%, photophobia; and 4%, facial palsy.[26] Consider these symptoms from Logigian et al., shown in Figure 1.[27]

The wide array of Lyme disease symptoms is consistent with *Borrelia burgdorferi's* ability to infect multiple organ systems; nervous system involvement creates the potential for varied and atypical symptoms.[28-35] Common symptoms include: EM rash, fever, fatigue, headache, neck pain, joint or muscle pain, paresthesias, memory impairment, weakness of facial muscles, mood disorders, neuropathic pain.[8,16,23,26-41] A compendium of manifestations by system is given in Table 3.

Table 3. Lyme Disease Manifestations[16,27,35,42-88]

General	Gastrointestinal and Genitourinary Systems	Psychological
Fever Night sweats Fatigue, lack of endurance Unexplained weight gain/loss Generalized, unprovoked pain Migratory pain	Nausea/pain/gastroesophageal reflux Recurrent vomiting Diarrhea/constipation Irritable bladder or interstitial cystitis Testicular or pelvic pain Decreased libido Unexplained menstrual irregularity Unexplained galactorrhea	Mood swings, irritability Patient feels as "if losing my mind" Overly emotional reactions, cries easily Depression Bipolar disorder Panic attacks, anxiety Obsessive-compulsive disorder Psychosis
Head, Face, Neck	**Musculoskeletal System**	**Mental Capability**
Headache, mild or severe Facial flushing Pressure in head Jaw pain or stiffness Unexplained hair loss Dental problems/pain (unexplained) Facial muscle fasciculations Stiff or painful neck Facial paralysis (Bell's Palsy) Sore throat, hoarseness Tingling of nose, tongue, cheek	Bone pain, joint pain or swelling Carpal tunnel syndrome Stiffness of joints, back, or neck Frequent tendonitis, lateral epicondylitis Myalgia or cramps, muscle spasms Sore smiles, especially in morning	Memory loss (short or long-term) Disorientation (getting or feeling lost Confusion, difficulty in thinking Apraxia Difficulty concentrating or reading Dementia
Eyes/Vision and Ears/Hearing	**Respiratory and Circulatory Systems**	**Nervous System**
Diplopia or blurry vision Difficulty with night vision Increased floating spots Pain in eyes, or swelling around eyes Photophobia Flashing lights/Peripheral waves/phantom images Change in color vision Decreased hearing in one or both ears Tinnitus Pain in ears, hyperacusis Auditory hallucinations	Shortness of breath, cough Endocarditis, myocarditis, heart failure Peripheral vascular abnormalities Rhythm disturbances—PVCs, PACs, SVTs, palpitations, heart block	Burning, stabbing, aching, or shock sensations Lightheadedness, syncope Paresthesias Increased motion sickness Peripheral neuropathies Abnormalities of vision, hearing, taste, smell, or touch Muscle weakness Muscle atrophy Muscle fasciculations Speech difficulty (slurred or slow) Stammering speech Word searching, misspeaking Poor balance Dizziness Difficulty walking, gait problems Tremors Seizures Sleep problems (excessive sleep, insomnia, sleep apnea, narcolepsy, unusual sleep behaviors)

It is the multisystemic nature of the illness that provides physicians with useful diagnostic information. In fact, with the exception of an isolated EM rash or swollen joint, patients with symptoms restricted to a single system are unlikely to have Lyme disease. Recognizing the potential for disease is different from "seeing it everywhere." Failure to recognize Lyme disease may lead to serious harm, as antibiotics are delayed and the infection is unchecked.[89]

The nonspecific nature of many Lyme disease symptoms leads some to suggest that such symptoms hold no diagnostic value.[91] Lyme disease is like many other illnesses that present with nonspecific and often subtle symptoms—symptoms that may go unrecognized by physicians. Examples include hypothyroidism, ovarian cancer, and acute subendocardial myocardial infarction. What gives the individual symptoms of Lyme disease value is their occurrence in clusters; a single symptom means little but four or five may, for all practical purposes, make the case. Just as abdominal bloating, urinary urgency, and pelvic pain raise "red flags" for gynecologists, the combination of fatigue, paresthesias, arthralgias, and memory complaints presenting in a single patient commands the attention of physicians aware of these potential Lyme disease symptoms.

Steere et al. noted that patients with early Lyme disease who lacked an EM rash presented with an average of four or more symptoms.[8] Fever, chills, malaise, and myalgia, all nonspecific, were present in 46%-71% of the patients with definite Lyme disease alone. In this group, it was the clustering of nonspecific symptoms in the appropriate setting that led to the correct diagnosis of Lyme disease. Logigian et al. also noted the nonspecific nature of identi-fying symptoms: "The most common form of chronic central nervous system involvement in our patients was subacute encephalopathy affecting memory, mood, and sleep, sometimes with subtle disturbances in language. *Diagnosis of this condition may be difficult because the typical symptoms are nonspecific*" [emphasis added].[27] To provide a clinical level of diagnostic sensitivity higher than two-tier testing, physicians need to recognize the symptom clusters and maintain a high index of suspicion for Lyme disease.

Symptoms not only form the basis of disease identification, they may also inform on prognosis. Dysesthesias,[26] paresthesias,[36] multiple EM lesions,[36,38] increased irritability,[37] persistent fatigue,[38] headache,[38] stiff neck,[38] and increased severity of the initial illness[38] were associated by various investigators in the early Lyme disease treatment trials with an increased risk of treatment failure. Symptoms were also used in the trials as indicators that a strategy was working or needed to be altered.[26,36,38,39]

Findings on physical exam are usually subtle and limited; they may be variably present.[29,32] The more common findings include: solitary or multiple EM lesions,[23,26,33,36-41] manifestations of cranial neuritis (such as extraocular palsies, ptosis, decreased facial sensation, facial nerve palsy, decreased hearing),[4,26,29,32,33] swollen and tender joints,[4,27,33] diminished sensation, and motor weakness.[27,29,30,32,35] Cognitive deficits are usually not readily apparent on mental status testing, but patients may be disorganized or slow to respond to questions.[16,17,27,34] A lack of physical findings does not necessarily indicate that the symptoms in those cases cannot be corroborated with objective evidence. Halperin et al. studied 14 patients with complaints of distal paresthesias;[35] 10 had completely normal sensory, motor and reflex findings on examination, three had only mild sensory loss, and one had moderate sensory and motor loss coupled with decreased reflexes. All underwent EMG testing; 13 of the 14 had "significant neurophysiologic findings." Logigian et al. also found that detailed neuropsychometric testing could reveal cognitive deficits that were not apparent on routine mental status testing.[16,27,34] Cost and time constraints do not allow for such complete testing in a community setting, but the studies suggests that with sufficiently detailed testing, objective evidence may be discovered and the subjective data supported. The absence of findings does not equal absence of disease.

Even the EM rash has a variable presentation that may cause less informed physicians to miss it. An EM lesion may have one or more of the following characteristics: homogeneously erythematous color, prominent central clearing, target-like appearance, central vesicles or pustules, partially purpuric, and not scaly, unless topical corticosteroid creams have been applied or the rash is old and fading.[4,23,33] An EM rash must be distinguished from: tick bite hypersensitivity reactions, insect or spider bites, contact dermatitis, bacterial cellulitis, and tinea.[4,33] An interesting study in *JAMA* compared responses from physicians in endemic and nonendemic areas with regard to what percentage of EM rashes in their practices had central clearing.[41] Physicians from endemic areas thought it only 19%, while those from nonendemic estimated 80%. The authors did not give a reason for the disparity; possibilities include *B. burgdorferi* strain variation or physician experience. The variable presentation of the EM rash, coupled with the fact that it does not manifest in 32% of patients,[5] makes it unwise to rely on EM as the only manifestation of Lyme disease that has clinical diagnostic utility.

Physicians use pattern recognition as a common diagnostic heuristic.[92] These cognitive "shortcuts," when used properly, allow physicians to move quickly to the correct diagnosis. Pattern recognition transforms exposure, individual symptoms, and the course of illness into a unified diagnosis; it is why some physicians specifically see "Lyme disease" when colleagues see only a generalized "positive review of systems." For physicians unfamiliar with the pattern of Lyme disease, serologic testing, combined with clinical data, offers the potential for reaching the correct diagnosis. However, serology alone cannot confirm or deny presence of infection.[93] In Lyme disease, there is no testing shortcut.

Furthermore, diagnostic criteria are situational. Clinical criteria are constructed to diagnose and treat ill patients. Research criteria are constructed to test a hypothesis in a uniform group of subjects; researchers have no duty to those excluded from the trial. Surveillance criteria are much the same, the goal being selection of a homogeneous patient subset that can be observed over time and treatment. The difference between these situations is an important consideration. This distinction is highlighted by these comments from CDC epidemiologist Dr. Paul Mead:

> A clinical diagnosis is made for the purpose of treating an individual patient and should consider the many details associated with that patient's illness. Surveillance case definitions are created for the purpose of standardization, not patient care; they exist so that health officials can reasonably compare the number and distribution of "cases" over space and time. 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.[94]

Recognition of the differing goals allows knowledgeable physicians the discretion to diagnose Lyme disease in patients lacking the five of 10 bands required for admittance into the surveillance group.[95] Failure to acknowledge the distinction results in many patients with Lyme disease remaining undiagnosed and untreated.

Mandatory laboratory confirmation of clinical diagnoses, as advanced in the 2006 IDSA guidelines, reverses the roles of clinical and laboratory data in the diagnostic process and hierarchy. Substituting laboratory tests for physician judgment is not clinically sound, particularly when laboratory tests lack sensitivity. This recommendation is a change from the 2000 IDSA guidelines on Lyme disease, but the 2006 panel did not discuss the reasons for this change nor cite any references from the literature to support it.[4,96] Guideline developers have identified the need for reconciliation between new and former versions of the same disease guidelines;[97] the IDSA, itself, endorsed the reconciliation process, yet it did not occur in this instance.

Correctly diagnosing extracutaneous Lyme disease can be difficult. The importance of clinically derived data has been demonstrated repeatedly, as have the weaknesses of serologic testing. At this time, Lyme disease should remain a clinical diagnosis, with testing playing a supportive role.

Clinical Judgment in Management of Patients with Lyme Disease

Clinical judgment is required to appropriately manage patient care. Patient management is an evolutionary process, not a static state; ongoing assessment allows for refinement of the original diagnosis or the search for new one. Lyme disease is no exception to this rule; yet the 2006 IDSA guidelines reduce clinical management to a one-size-fits-all approach quickly chosen from a table.[4] Clinical judgment is especially important when the clinical picture is unclear and laboratory data unhelpful. After careful investigation of other potential diagnoses, physicians may need to perform an empiric treatment trial as a diagnostic modality. The use of such trials extends well beyond Lyme disease. For example, patients with nonspecific epigastric pain may be offered "GI cocktails" as a means to both diagnose and treat the condition.

Clinical decision-making in Lyme disease requires ongoing information; the longitudinal treatment trials on Lyme disease demonstrated the value of this data. Historical and physical examination data were gathered at defined points; on some occasions the information was used to alter the treatment protocol (investigators withdrew or re-treated some subjects).[26,34,36,38] Follow-up visits in many of the studies on Lyme disease demonstrated a positive correlation between reported symptomatic changes and subsequent physical findings or test results.[27,35] Long-term follow-up extending beyond the active treatment phase provides researchers, as well as physicians in clinical practice, the ability to discern the difference between placebo and treatment effects.[27]

Clinical judgment in Lyme disease requires physicians to weigh risk-benefit concerns with individual patients.[98] Treatment risks for the patient include potential adverse effects from antibiotic therapy (including risks associated with medication administration), costs associated with therapy, and lifestyle changes to accommodate treatment.[99-101] Patient benefits include improved health with attendant improvement in quality of life and lower medical costs following recovery. Antibiotic therapy, including long-term oral antibiotics, is generally safe and well tolerated.[101,102] A meta-analysis on the risks associated with intravenous (IV) access of various types found that peripheral intravenous catheters cause 0.5 bloodstream infections per 1,000 intravascular device (IVD) days while surgically implanted long-term central venous devices—cuffed and tunneled catheters—cause 1.6 infections per 1,000 IVD-days.[102] Data from Lyme disease treatment trials can inform on the risk of IV antibiotic therapy in this patient population. Table 4 reports the complication rates in the treatment groups of Lyme disease studies which used IV ceftriaxone for a minimum of 30 days.[34,104-106] Significant adverse events included medication-related events (severe allergic reactions, gall bladder toxicity, *Clostridium difficile* enterocolitis, renal failure) and catheter-related events (skin infiltration, infection, and thrombosis).

Table 4. Medication and IV Device Complications in Studies of Lyme Disease

Study	N	Days of IV antibiotic	IVD Days	Significant Adverse Events (%)	Adverse Event Rate/ 1,000 IVD Days
Logigian1999[34]	18	30	540	0	0
Klempner 2001[104]	64	30	1920	2 (3.1%)	1.0
Krupp 2003[105]	28	30	840	1 (3.6%)	1.2
Fallon 2008[106]	23	70	1610	6 (26.1%)	4.3
Total	133		4910	9 (6.8%)	1.83

Adverse events in the Fallon study[106] are considerably higher than in the others; reasons are unknown, and the small sample size makes it difficult to draw conclusions. There were three cases of ceftriaxone allergy in the 23 patients; this 13% allergic rate is higher than expected.[107] Thrombi developed in two patients, but the paper does not provide details of the site of the peripherally inserted central catheter (PICC) or its specific type. Additional studies are needed to delineate the risk of IV antibiotic therapy extending beyond 30 days in better detail, and to determine whether there would be opportunities to minimize those factors contributing to the total risk.

There are also risks to the patient associated with failure to treat a continuing infection.[108] These include declining health, decreased productivity, a potential for increased costs as more health-related services are required, and costs related to palliative medications (including their potential adverse effects).[99-101]

The IDSA guidelines raise concerns about the impact longer treatment regimens may have on society.[4] While these concerns should not sway treating physicians who are entrusted with the care of individual patients, the concerns merit some comments. The guidelines authors focus attention on treatment risks to society, citing additional costs and the potential for increased bacterial resistance in the community.[4] However, the authors ignored potential benefits to society from such treatment regimens. These benefits include improved health in the community, increased production from previously ill patients, and potential for success in this patient population to inform treatment decisions in other groups.[109]

Additionally, there are societal risks from not treating; these include ever increasing expenses for a chronically ill subpopulation and lost productivity from ill workers.[109]

In the individual patient, the decision to treat or to prolong treatment may depend on the length of time between onset of illness and diagnosis; 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 abilities; presence of untreated co-infections; the patient's immune system status; whether diagnostic tests, symptoms or treatment response suggest ongoing infection; the patient's response to treatment; which medications the patient can tolerate; the specifics of prior treatment regarding antibiotic type, dose, and duration; whether the patient relapses when treatment is withdrawn; the risks/benefits of the treatment approach under consideration; and availability of any alternative treatment approaches and their attendant risks balanced against the risks associated with failing to treat. These highly individualized decisions are best made by the treating physician and the patient.

The controversy over antibiotic treatment duration for patients with Lyme disease exists because there is no test of cure, and individual patient responses to specific therapeutic approaches have been highly variable. Lyme disease, in many patients, is marked by periods when the illness is relatively quiescent.[26,28] Lacking a test of cure, physicians who do not rely on arbitrary cut-off points are faced with a difficult decision when attempting to determine an appropriate stopping point. Mixed results from the treatment trials add to the uncertainty.

The variable response to treatment has been well documented;[16,26,27,29,30,32,34,36-40] the causes remain unclear, as scientific evidence in this area is still evolving. Early hypotheses of autoimmune processes have not been substantiated;[110,111] persistent infection, however, has been demonstrated in case reports and animal studies.[19-20,112,113] Patients with Lyme disease are a heterogeneous group. Genetic variation may play a role in pathogenesis and treatment response. Just as HLA status may be related to treatment response in Lyme arthritis,[114] the response in patients with other types of Lyme disease pathology may be based on some yet to be discovered genetic subtype.

Variation in infecting strains of *B. burgdorferi* certainly is a factor.[115-117] More than 100 strains of *B. burgdorferi* have been identified. Certain strains are more virulent and pathogenic than others;[115,116] instances of antibiotic susceptibility varying between strains is well documented.[117] Coinfections and comorbidities also contribute to the heterogeneity of treatment response seen in Lyme disease.[118] *Ixodes scapularis* is able to carry multiple known bacterial, viral, and parasitic pathogens, and evidence for additional tick-borne pathogens continues to emerge.[119] Different combinations of pathogens require different treatment regimens; failure to identify and treat the specific pathogens causing an illness may partially explain variations in treatment responses.

As explained by Kravitz et al., "[h]eterogeneity of treatment effects reflects patient diversity to risk of disease, responsiveness to treatment, vulnerability to adverse effects, and utility for different outcomes."[108] Kravitz et al. discuss the application of generalized, or averaged, results from treatment trials to the care of an individual patient, and pitfalls inherent in applying them too strictly, noting that "misapplying averages can cause harm, by either giving patients treatments which do not help or denying patients treatments that would help them."[108] The individual patient is not a numeric average but, rather, falls somewhere on the continuum of the bell curve and, hence, requires individualized care.

Clinical guidelines should not supplant the judgment of treating physicians. Quality patient care requires the physician to consider management decisions in light of the details unique to each patient. When guideline recommendations are substituted for carefully derived, individualized decisions, there is a potential for harm.[120] The American Academy of Pediatrics policy statement on guideline development recognizes this principle.[121] The document outlines how evidentiary strength and risk-benefit analyses are integrated to yield a specific recommendation level. For example, strongly positive recommendations require benefits to clearly exceed risks, and supporting evidence must be of excellent quality.

In this scheme, strong recommendations are not made based on low-quality evidence or expert opinion. Options identify treatment alternatives. Options recognize patient preferences and respect the clinician's decision-making process. The U.S. Preventive Services Task Force also recognizes scenarios in which the certainty of the evidence is low.[122] In those situations, no recommendation is made, regardless of the perceived net magnitude of benefit or harm. Additionally, the Task Force advocates shared decision-making between individual patients and their physicians, instead of population-based recommendations, when issues under consideration are highly sensitive to patient utilities.[122]

Guideline committees are not in a position to perform risk-benefit analyses for specific patients.[121,123] Patient-specific risk-benefit analyses are the essence of clinical judgment. Such judgments are the domain of individual treating physicians; guideline committees may inform judgments through their evaluation of therapeutic options, but they may not substitute their judgments for those of the treating physicians. A recent *JAMA* editorial by Shaneyfelt and Centor said as much: "Guidelines are not patient-specific enough to be useful and rarely allow for individualization of care. Most guidelines have a one-size-fits-all mentality and do not build flexibility or contextualization into the recommendations."[123] While the 2006 IDSA guidelines contain the typical legal disclaimer that "they are not intended to supplant physician judgment with respect to particular patients or special clinical situations," formulaic disclaimers cannot overcome the failure of the guidelines to provide treatment options and to recognize the role of clinical judgment in individualized care. These shortcomings cannot be addressed in boilerplate disclaimers; they can only be addressed in the substance of the guidelines.

Available laboratory tests for Lyme disease have poor sensitivity.[5-14] Treatment trials cited in the guidelines for early Lyme disease were dissimilar, making it hard to compare outcomes;[26,36-40,124-126] those for late neurologic Lyme disease involved only 96 patients whose treatment responses can be analyzed.[27,34,127,128] Both the early and late treatment trials yielded poor outcome rates for complete recovery. The prophylaxis recommendation is based on a single

study performed under conditions unlikely to be reproduced in community practices, and the list of "not recommended" therapeutic modalities is apparently based on panel opinion.[4,139] Given the limits of guidelines in general, and the specific shortcomings of the 2006 IDSA guidelines on Lyme disease, patients and their physicians should be free to act without interference; many may justifiably decide to decide for themselves which strategy to embrace.

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REFERENCES

1. U.S. Department of Health and Human Services. National Guideline Clearinghouse. Available at: sww.guideline.gov/browse/browsemode.aspx?node=29255&type=1. Accessed Aug 18, 2009.
2. Landers SJ. Lyme disease debate provokes treatment divide, legal action. *AM News*, Dec 25, 2006. Available at: www.ama-assn.org/amednews/2006/12/25/hlsa1225.htm. Accessed Aug 19, 2009.
3. State of Connecticut Attorney General's Office. Press release, May 1, 2008. Available at www.ct.gov/ag/cwp/view.asp?Q=414284&A=2795. Accessed Jul 15, 2008.
4. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006;43:1089-1134.
5. CDC. Lyme disease—United States 2001-2002. *MMWR* 2004;53(17):365-369.
6. Trevejo RT, Krause PJ, Sikand VK, et al. Evaluation of two-test serodiagnostic method for early Lyme disease in clinical practice. *J Infect Dis* 1999;179:931-938.
7. Bacon RM, Bickerstaff BJ, Schreifer ME, et al. Serodiagnosis of Lyme disease by kinetic enzyme-linked immunosorbent assay using recombinant VlsE1 or peptide antigens of *Borrelia burgdorferi* compared with two-tiered testing using whole cell lysates. *J Infect Dis* 2003;187:1187-1199.
8. Steere A, Dhar A, Hernandez J, et al. Systemic symptoms without erythema migrans as the presenting picture of early Lyme disease. *Am J Med* 2003;114:58-62.
9. Ledue TB, Collins MF, Craig WY. New laboratory guidelines for serologic diagnosis of Lyme disease: evaluation of the two-test protocol. *J Clin Microbiol* 1996;34:2343-50.
10. Dressler F, Whalen JA, Reinhardt BN, Steere AC. Western blotting in the serodiagnosis of Lyme disease. *J Infect Dis* 1993;167:392-400.
11. Steere AC, McHugh G, Damle N, Sikand VK. Prospective study of serologic tests for Lyme disease. *Clin Infect Dis* 2008;47:188-195.
12. Tilton RC, Sand MN, Manak M. The Western immunoblot for Lyme disease: determination of sensitivity, specificity, and interpretive criteria with use of commercially available performance panels. *Clin Infect Dis* 1997;25(Jul Suppl 1):S31-S34.
13. Mogilyansky E, Loa CC, Adelson ME, Mordechai E, Tilton RC. Comparison of Western immunoblotting and the C6 Lyme antibody test for laboratory detection of Lyme disease. *Clin Diagn Lab Immunol* 2004;11:924-929.
14. Bakken LL, Callister SM, Wand PJ, Schell RF. Intralaboratory 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* 1997;35:537-543.
15. Hunfeld KP, Stanek G, Straube E, et al. Quality of Lyme disease serology. Lessons from the German Proficiency Testing Program 1999-2001. a preliminary report. *Wien Klin Wochenschr* 2002;114(13-14):591-600.
16. Logigian EL. Reversible cerebral hypoperfusion in Lyme encephalopathy. *Neurology* 1997;49:1661-1670.
17. Fallon BA, Das S, Plutchok JJ, et al. Functional brain imaging and neuropsychological testing in Lyme disease. *Clin Infect Dis* 1997;25(Suppl 1):S57-S63.
18. Oksi J, Uksila J, Marjamäki M, Nikoskelainen J, Viljanen MK. Antibodies against whole sonicated Borrelia burgdorferi spirochetes, 41-kilodalton flagellin, and P39 protein in patients with PCR- or culture-proven late Lyme borreliosis. *J Clin Microbiol* 1995;33:2260-2264.
19. Nocton JJ, Dressler F, Rutledge BJ, et al. Detection of *Borrelia burgdorferi* DNA by polymerase chain reaction in synovial fluid from patients with Lyme arthritis. *N Engl J Med* 1994;330:229-234.
20. Nocton JJ, Bloom BJ, Rutledge BJ, et al. Detection of *Borrelia burgdorferi* DNA by polymerase chain reaction in cerebrospinal fluid in Lyme neuroborreliosis. *J Infect Dis* 1996;174:623-627.
21. Peterson MC, Holbrook JH, Hales D, Smith NL, Von Staker LV. Contributions of the history, physical examination, and laboratory investigation in making medical diagnoses. *West J Med* 1992;156:163-165.
22. Markert RJ, Haist SA, Hillson HD, et al. Comparative value of clinical information in making a diagnosis. *Med Gen Med* 2004;6:64.
23. Berger BW. Dermatologic manifestations of Lyme disease. *Rev Infect Dis* 1989;11(Suppl 6):6:S1475-S1481
24. Sigal LH. Summary of the first 100 patients seen at a Lyme disease referral center. *Am J Med* 1990;88:577-581.
25. Steere AC, Taylor E, McHugh GL, et al. The overdiagnosis of Lyme disease. *JAMA* 1993;269:1812-1816.
26. Massarotti EM, Luger SW, Rahn DW, et al. Treatment of early Lyme disease. *Am J Med* 1992;92:396-403.
27. Logigian EL, Kaplan RF, Steere AC. Chronic neurologic manifestations of Lyme disease. *N Engl J Med* 1990;323:1438-1444.
28. Cook SP, Macartney KK, et al. Lyme disease and seventh nerve paralysis in children. *Am J Otolaryngol* 1997;18:320-323.
29. Coyle PK. Neurologic aspects of Lyme disease. *Med Clin North Am* 2002;86:261-284.
30. Halperin JJ. Lyme disease and the peripheral nervous system. *Muscle Nerve* 2003;28:133-143.
31. Dotevall L. Pain as presenting symptom in Lyme neuroborreliosis. *Eur J Pain* 2003;7:235-239.
32. Fallon, BA. Lyme borreliosis: neuropsychiatric aspects and neuropathology. *Psychiatric Ann* 2006;36:120-128.
33. Hengge UR. Lyme Borreliosis. *Lancet Infect Dis* 2003;3:489-500.
34. Logigian EL, Kaplan RF, Steere AC. Successful treatment of Lyme encephalopathy with intravenous ceftriaxone. *J Infect Dis* 1999; 180:377-383.
35. Halperin JJ, Little BW, Coyle PK, Dattwyler RJ. Lyme disease: cause of a treatable peripheral neuropathy. *Neurology* 1987;37:1700-1706.
36. Nadelman RB, Luger SW, Frank E, et al. Comparison of cefuroxime axetil and doxycycline in the treatment of early Lyme disease. *Ann Intern Med* 1992;117:273-280.
37. Luger SW, Paparone P, Wormser GP, et al. Comparison of cefuroxime axetil and doxycycline in treatment of patients with early Lyme disease associated with erythema migrans. *Antimicrob Agents Chemother* 1995;39:661-667.

[39] Steere AC, Hutchinson GJ, Rahn DW, et al. Treatment of early manifestations of Lyme disease. *Ann Intern Med* 1983;99:22-26.
[38] Luft BJ, Dattwyler RJ, Johnson RC, et al. Azithromycin compared with amoxicillin in the treatment of erythema migrans: a double blind, randomized, controlled trial. *Ann Intern Med* 1996;124:785-791.
[40] Dattwyler RJ, Volkman DJ, Conaty SM, Platkin SP, Luft BJ. Amoxicillin plus probenecid versus doxycycline for treatment of erythema migrans borreliosis. *Lancet* 1990;336:1404-1406.
[41] Tibbles CD, Edlow JA. Does this patient have erythema migrans? *JAMA* 2007;297:2617-2627.
[42] Ackermann R, Rehse-Kupper B, Gollmer E, Schmidt R. Chronic neurologic manifestations of erythema migrans borreliosis. *Ann NY Acad Sci* 1988;539:16-23.
[43] Arav-Boger R, Crawford T, Steere AC, Halsey NA. Cerebellar ataxia as the presenting manifestation of Lyme disease. *Pediatr Infect Dis J* 2002;21:353-356.
[44] Bhambhani N, Disla E, Cupperi G. Lyme disease presenting with sequential episodes of ruptured baker cysts. *J Clin Rheumatol* 2006;12:160-162.
[45] Bloom BJ, Wyckoff PM, Meissner HC, Steere AC. Neurocognitive abnormalities in children after classic manifestations of Lyme disease. *Pediatr Infect Dis J* 1998;17:189-196.
[46] Cassarino DS, Quezado MM, Ghatak NR, Duray PH. Lyme-associated parkinsonism: a neuropathologic case study and review of the literature. *Arch Pathol Lab Med* 2003;127:1204-1206.
[47] Chancellor MB, McGinnis DE, Shenot PJ, Kiilholma P, Hirsch IH. Urinary dysfunction in Lyme disease. *J Urol* 1993;149:26-30.
[48] Dinerman H, Steere AC. Lyme disease associated with fibromyalgia. *Ann Intern Med* 1992;117:281-285.
[49] Duray PH, Steere AC. Clinical pathologic correlations of Lyme disease by stage. *Ann NY Acad Sci* 1988;539:65-79.
[50] Faller J, Thompson F, Hamilton W. Foot and ankle disorders resulting from Lyme disease. *Foot Ankle* 1991;11:236-238.
[51] Fallon BA, Kochevar JM, Gaito A, Nields J. The underdiagnosis of neuropsychiatric Lyme disease in children and adults. *Psychiatr Clin N Am* 1998;21:693-703.
[52] Fallon BA, Nields JA. Lyme disease: a neuropsychiatric illness. *Am J Psychiat* 1994;151:1571-1583.
[53] Fallon BA, Nields JA, Liegner K, DelBene D, Liebowtitz MR. The neuropsychiatric manifestations of Lyme borreliosis. *Psychiatr Q* 1992;63:95-117.
[54] Gasser R, Horn S, Reisinger E, et al. First description of recurrent pericardial effusion associated with *Borrelia burgdorferi* infection. *Int J Cardiol* 1998;64:309-310.
[55] Halperin JJ. Neuroborreliosis. *Am J Med* 1995;98(4A):52S-56S.
[56] Halperin JJ, Kaplan GP, Brazinsky S, et al. Immunologic reactivity against *Borrelia burgdorferi* in patients with motor neuron disease. *Arch Neurol* 1990;47:586-594.
[57] Halperin JJ, Volkman DJ, Luft BJ, Dattwyler RJ. Carpal tunnel syndrome in Lyme borreliosis. *Muscle Nerve* 1989;12:397-400.
[58] Haupl T, Hahn G, Rittig M, et al. Persistence of *Borrelia burgdorferi* in ligamentous tissue from a patient with chronic Lyme borreliosis. *Arthritis Rheum* 1993;36:1621-1626.
[59] Horowitz HW, Sanghera K, Goldberg N, et al. Dermatomyositis associated with Lyme disease: case report and review of Lyme myositis. *Clin Infect Dis* 1994;18:166-171.
[60] Karma A, Seppala I, Mikkila H, et al. Diagnosis and clinical characteristics of ocular Lyme borreliosis. *Am J Ophthalmol* 1995;119:127-135.
[61] Kirsch M, Ruben FL, Steere AC, et al. Fatal adult respiratory distress syndrome in a patient with Lyme disease. *JAMA* 1988;259:2737-2739.
[62] Krupp LB, Masur D, Schwartz J, et al. Cognitive functioning in late Lyme borreliosis. *Arch Neurol* 1991;48:1125-1129.
[63] Lader E. Lyme disease misdiagnosed as a temporomandibular joint disorder. *J Prosthet Dent* 1990;63:82-85.
[64] Lo R, Menzies DJ, Archer H, Cohen TJ. Complete heart block due to Lyme carditis. *J Invasive Cardiol* 2003;15:367-369.
[65] MacDonald AB. Concurrent neocortical borreliosis and Alzheimer's disease: Demonstration of a spirochetal cyst form. *Ann NY Acad Sci* 1988;539:468-470.
[66] Mikkila HO, Seppala IJ, Viljanen MK, Peltomaa MP, Karma A. The expanding clinical spectrum of ocular Lyme borreliosis. *Ophthalmology* 2000;107:581-587.
[67] Mormont E, Esselinckx W, De Ronde T, et al. Abdominal wall weakness and lumboabdominal pain revealing neuroborreliosis: a report of three cases. *Clin Rheumatol* 2001;20:447-450.
[68] Moscatello AL, Worden DL, Nadelman RB, Wormser G, Lucente F. Otolaryngologic aspects of Lyme disease. *Laryngoscope* 1991;101(6 Pt 1):592-595.
[69] Nord JA, Karter D. Lyme disease complicated with pseudotumor cerebri. *Clin Infect Dis* 2003;37:E25-E26.
[70] Oksi J, Marjamaki M, Nikoskelainen J, Viljanen MK. *Borrelia burgdorferi* detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. *Ann Med* 1999;31:225-232.
[71] Oksi J, Voipio-Pulkki L-M, Uksila J, et al. *Borrelia burgdorferi* infection in patients with suspected acute myocardial infarction. *Lancet* 1997;350:1447-1448.
[72] Pachner AR, Steere AC. The triad of neurological manifestations of Lyme disease: meningitis, cranial neuritis, and radiculoneuritis. *Neurology* 1985;35:47-53.
[73] Pachner AR, Steiner I. Lyme neuroborreliosis: infection, immunity, and inflammation. *Lancet Neurol* 2007;6:544-552.
[74] Reik L, Steere AC, Bartenhagen NH, Shope RE, Malawista SE. Neurologic abnormalities of Lyme disease. *Medicine* 1979;58:281-294.
[75] Richardson H, Birchall JP, Hill J, McMaster T. Should we routinely screen for Lyme disease in patients with asymmetrical hearing loss? *Br J Audiol* 1994;28:59-61.
[76] Riedel M, Straube A, Schwarz MJ, Wilske BM, Muller N. Lyme disease presenting as Tourette's syndrome. *Lancet* 1998;351:418-419.
[77] Rosenhall U, Hanner P, Kaijser B. Borrelia infection and vertigo. *Acta Otolaryngol* 1988;106:111-116.
[78] Shadick NA, Phillips CB, Logigian EL, et al. The long-term clinical outcomes of Lyme disease. *Ann Intern Med* 1994;121:560-567.
[79] Shamim EA, Shamim SA, Liss G, et al. Constipation heralding neuroborreliosis: an atypical tale of 2 patients. *Arch Neurol* 2005;62:671-673.
[80] Sigal L. Clinical manifestations of Lyme disease. *N J Med* 1990;87:549-555.
[81] Sigler S, Kershaw P, Scheuch R, Sklarek H, Halperin J. Respiratory failure due to Lyme meningopolyradiculitis. *Am J Med* 1997;103:544-547.
[82] Siwula JM, Mathieu G. Acute onset of facial nerve palsy associated with Lyme disease in a 6-year-old child. *Pediatr Dent* 2002;24:572-574.
[83] Smith JL, Winward KE, Nicholson DF, Albert DW. Retinal vasculitis in Lyme borreliosis. *J Clin Neuroophthalmol* 1991;11(1):7-15.
[84] Steere AC. Lyme disease. *N Engl J Med* 1989;321:586-596.
[85] Steere AC, Bartenhagen NH, Craft JE, et al. The early clinical manifestations of Lyme disease. *Ann Intern Med* 1983;99:76-82.
[86] Steere AC, Malawista SE, Hardin JA, et al. Erythema chronicum migrans and Lyme arthritis: the enlarging clinical spectrum. *Ann Intern Med* 1977;86:685-698.

[87] Steere AC, Malawista SE et al. The clinical spectrum and treatment of Lyme disease. *Yale J Biol Med* 1984;57:453-464.

[88] Tager FA, Fallon BA, Keilp J, et al. A controlled study of cognitive deficits in children with chronic Lyme disease. *J Neuropsychiatry Clin Neurosci* 2001;13:500-507.

[89] Weissenbacher S, Ring J, Hofmann H. Gabapentin for the symptomatic treatment of chronic neuropathic pain in patients with late-stage Lyme borreliosis: a pilot study. *Dermatology* 2005;211:123-127.

[90] Cameron DJ. Consequences of treatment delay in Lyme disease. *J Eval Clin Pract* 2007;13:470-472.

[91] Feder HM Jr, Johnson BJ, O'Connell S, et al. A critical appraisal of "chronic Lyme disease." *N Engl J Med* 2007;357:1422-1430.

[92] Groopman J. *How Doctors Think*. New York, N.Y.: Houghton Mifflin; 2007.

[93] Brown SL, Hansen SL, Langone JJ. Role of serology in the diagnosis of Lyme disease. *JAMA* 1999;282:62-66.

[94] Mead P. Statement by Paul Mead M.D., M.P.H., on Hearing: CDC's Lyme Disease Prevention and Control Activities before the Connecticut Department of Public Health and the Connecticut Attorney General's Office; Jan 29, 2004. Available at: www.hhs.gov/asl/testify/1040129.html. Accessed Aug 19, 2009.

[95] Reed K. Laboratory testing for Lyme disease: possibilities and practicalities. *J Clin Microbiol* 2002;40:319-324.

[96] Wormser GP, Nadelman RB, Dattwyler RJ, et al. Practice guidelines for the treatment of Lyme disease. *Clin Infect Dis* 2000;31 (Suppl 1):S1-S14.

[97] Kish M. Guide to development of practice guidelines. *Clin Infect Dis* 2001;32:851-854.

[98] AMA Principles of Medical Ethics. E-8.08 Informed Consent. Available at: www.ama-assn.org. Accessed Feb 20, 2009.

[99] Zhang X, Meltzer MI, Peña CA, et al. Economic impact of Lyme disease. *Emerg Infect Dis* 2006;12:653-660.

[100] Meltzer MI, Dennis DT, Orloski KA. The cost effectiveness of vaccinating against Lyme disease. *Emerg Infect Dis* 1999;5:321-328.

[101] Maes E, Lecomte P, Ray N. A cost-of-illness study of Lyme disease in the United States. *Clin Ther* 1998;20:993-1008.

[102] Cooper C. Safety of long-term therapy with penicillin and penicillin derivatives. U.S. Food and Drug Administration; Apr 30, 2009. Available at: http://www.fda.gov/Drugs/EmergencyPreparedness/Bioterrorism andDrug Preparedness/ucm072755.htm. Accessed Aug 19, 2009.

[103] Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc* 2006;81:1159-1171.

[104] 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* 2001;345:85-92.

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

[106] Fallon BA, Keilp JG, Corbera KM, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology* 2008;70:992-1003.

[107] Pichichero ME. Cephalosporins can be prescribed safely for penicillin-allergic patients. *J Fam Pract* 2006;55(2):106-112.

[108] Kravitz RL, Duan N, Braslow J. Evidenced-based medicine, heterogeneity of treatment effects, and the trouble with averages. *Milbank Q* 2004;82:661-687.

[109] Joss AW, Davidson MM, Ho-Yen DO, Ludbrook A. Lyme disease—what is the cost for Scotland? *Public Health* 2003;117(4):264-273.

[110] Steere AC, Malawista SE, Newman JH, Spieler PN, Bartenhagen NH. Antibiotic therapy in Lyme disease. *Ann Intern Med* 1980;93:1-8.

[111] Stricker RB, Johnson L. Searching for autoimmunity in "antibiotic-refractory" Lyme arthritis. *Mol Immunol*. 2008;45:3023-3024.

[112] Oksi J, Marjamäki M, Nikoskelainen J, Viljanen MK. *Borrelia burgdorferi* detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. *Ann Med* 1999;31:225-332.

[113] Hodzic E, Feng S, Holden K, Freet KJ, Barthold SW. Persistence of *Borrelia burgdorferi* following antibiotic treatment in mice. *Antimicrob Agents Chemother* 2008;52:1728-1736.

[114] Steere AC, Dwyer E, Winchester R. Association of chronic Lyme arthritis with HLA-DR4 and HLA-DR2 alleles. *N Engl J Med* 1990;323:219-223.

[115] Seinost G., Dykhuizen DE, Dattwyler RJ, et al. Four clones of *Borrelia burgdorferi* sensu stricto cause invasive infection in humans. *Infect Immun* 1999;67:3518-3524.

[116] Wormser G. P., Liveris D., Nowakowski J., et al. Association of specific subtypes of *Borrelia burgdorferi* with hematogenous dissemination in early Lyme disease. *J Infect Dis* 1999;180:720-725.

[117] 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*. 1996;24(1):9-16. Erratum in: *Infection* 1996;24(2):169.

[118] Krause PJ, Telford SR III, Spielman A, et al. Concurrent Lyme disease and babesiosis: evidence for increased severity and duration of illness. *JAMA* 1996;275:1657-60.

[119] Billeter SA, Levy MG, Chomel BB, Breitschwerdt EB. Vector transmission of Bartonella species with emphasis on the potential for tick transmission. *Med Vet Entomol* 2008;22:1-15.

[120] Tobin M. Counterpoint: Evidence-based medicine lacks a sound scientific base. *Chest* 2008;133:1071-1974.

[121] American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics* 2004;114:874-877.

[122] U.S. Preventive Services Task Force Procedure Manual, AHRQ Publication No. 08-05118-EF; July 2008:46.

[123] Shaneyfelt TM, Centor RM. Reassessment of clinical practice guidelines: go gently into that good night. *JAMA* 2009;301:868-869.

[124] Dattwyler RJ, Luft BJ, Kunkel M, et al.. Ceftriaxone compared with doxycycline for the treatment of acute disseminated Lyme disease. *N Engl J Med* 1997;337:289-294.

[125] Eppes SC, Childs JA. Comparative study of cefuroxime axetil versus amoxicillin in children with early Lyme disease. *Pediatrics* 2002;109:1173-1177.

[126] Wormser GP, Ramanathan R, Nowakowski J, et al.. Duration of antibiotic therapy for early Lyme disease: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2003;138:697-704.

[127] Dattwyler RJ, Halperin JJ, Pass H, Luft BJ. Ceftriaxone as effective therapy for refractory Lyme disease. *J Infect Dis* 1987;155:1322-1325.

[128] Dattwyler RJ, Halperin JJ, Volkman DJ, Luft BJ. Treatment of late Lyme borreliosis—randomized comparison of ceftriaxone and penicillin. *Lancet* 1988;1(8596):1191-1194.

[129] Nadelman RB, Nowakowski J, Fish D, et al.. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite. *N Engl J Med* 2001; 345:79-84.

RESEARCH LETTER

Consequences of treatment delay in Lyme disease

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Introduction

Lyme disease is the fastest growing vector-borne disease in the Northern hemisphere, with enzootic cycles that can be maintained in a wide range of ecological conditions. According to the Centers for Disease Control and Prevention (CDC), 40 792 cases were reported in the USA in 2001–2002, a 40% increase over the previous year [1]. Data from individual Lyme clinics indicate that the number of actual cases may be as many as 10 times higher, especially in the north-eastern states [2]. Cases are also growing at a substantial rate in the UK (a fivefold increase between 1986 and 1998), and in certain areas of Europe (particularly Sweden and Slovakia) [3].

Surprisingly long treatment delays of 3 years and more have been described in patients enrolled in a National Institute of Health Lyme disease clinical trial [4]. A series of Lyme patients with neuropsychiatric presentations failed to receive treatment for 1 year after onset, despite an average of two previous doctor evaluations [5]. Shorter but still significant delays averaging 6 weeks were reported in each of three cohorts – 215 consecutively evaluated patients in a Lyme clinic [6], patients with neurologic presentations [7], and patients misdiagnosed with cellulitis rather than Lyme disease [8]. To date, the role of treatment delay in determining the outcome of treatment of Lyme disease has not been established. However, a growing database now enables us to address this important question.

Methods

Patient population

We focused on consecutively treated subjects in order to reduce selection bias. The study includes 100 adolescents and adults who were treated in a community-based setting from July 1997 to January 2000. All had a clear diagnosis of Lyme disease and conformed with the Centers for Disease Control and Prevention (CDC) national surveillance case definition [1]. Chronic Lyme disease [6,7] cases were also included to enable comparison with previous studies of chronic Lyme disease [1,6] and to improve the generalizability of the Lyme disease population [7].

The CDC epidemiologic criteria consists of an erythema migrans rash, Bell's palsy, heart block, and/or arthritis [1]. There is, as yet, no other widely agreed upon definition for chronic Lyme disease. Chronic Lyme patients present with a variety of symptoms, including memory loss, poor concentration, irritability, and sleep disturbances. Absence of another diagnosis, and confirmatory serology are also key considerations [6,7].

This is the largest case-controlled study to examine subjects confirmed by the CDC's recommended two-tier diagnostic criteria. Analysis was limited to subjects with a positive IgG Western blot serology to reduce the bias of case ascertainment. The enzyme-linked immunosorbent assay testing was performed at the laboratory for the Diagnosis of Tick Borne Diseases at Stony Brook University School of Medicine. The Western blot testing was performed at Quest Diagnostics.

Subjects who failed initial treatment comprised the case group and subjects who were successfully treated, the control group. An unmatched case–control design also allowed an examination of the role of age and sex in treatment failure. All study subjects and controls received uniform Lyme disease management through a single internal medicine practice.

Clinical history

The onset of Lyme disease was determined by clinical history. This method has been widely used by Lyme researchers to date [6,7,9], and similar criteria have been used in two double-blind placebo-controlled trials [10].

Outcomes

Outcome assessment was also based on clinical impression, as in the majority of the previous studies from 1988 to 2005 [7,9]. At present, there is no alternative clinical or serologic test to deter-

mine outcome. Examination of cerebrospinal fluid fails as an outcome measure as only two of 27 neurological cases show an abnormal spinal tap at onset [7]. Further, neuropsychological tests are not usually administered before initiating treatment.

Clinical judgement for determining success has been previously described as follows: none to moderate gains were considered treatment failure, significant to complete gains were considered successes [7,9].

Statistics

Previous studies show 34–63% failure rates on long-term follow-up of Lyme disease treatment [6,7,9,10]. This sample is large enough to detect an odds ratio (OR) of 4 with 80% power and an alpha level of 0.05. We used chi-square or Student's *t*-test to identify differences between groups in demographic characteristics, clinical characteristics, treatment delay and outcome (SPSS 11.5.1, Chicago, IL, USA).

The effectiveness of antibiotic treatment was evaluated by means of logistic regression analysis with adjustments for sex, tick bite, erythema migrans rash, treatment delay, and treatment duration (SPSS 11.5.1).

The use of this surveillance database was approved by the Western Institutional Review Board. Because this was a retrospective analysis of an existing data set, written informed consent was not necessary from the participating subjects.

Results

Table 1 shows the different characteristics of cases and controls. Gender and age were similar in both groups. However, cases were significantly less likely to report a tick bite (29% vs. 47%, $P = 0.12$) or erythema migrans rash (33% vs. 49%, $P = 0.12$). Cases were much more likely to have been treated previously with steroids (17% vs. 3%, $P = 0.12$).

Fifteen of 24 cases (63%) failing treatment received delayed treatment (Table 2). Treatment delay was more common among cases (58%) than controls (24%, $P = 0.002$) (Table 1). The delay was also significantly longer for cases than controls (518 ± 851 and 92 ± 362 days, $P = 0.001$).

The majority (60%) of cases (cases 1, 3–5, 7, 11–15) with delayed treatment conformed to CDC epidemiological standards, presenting with a rash, Bell's palsy, or arthritis (Table 2). Five of the cases meeting CDC epidemiological standards had been diagnosed with meniscus tear, oedema, 'water on the knee', pericarditis, asthmatic bronchitis, and cellulitis (cases 3, 12–15). Four of these cases were told by their doctors they did not have Lyme disease. Two of the five presented with a classic erythema migrans rash (cases 1, 5). The third had an atypical rash but other symptoms typical of Lyme and a positive Lyme test (case 11); the fourth had Bell's palsy (case 7). Another case meeting CDC epidemiological standards, with Bell's palsy followed by typical symptoms, did not seek medical care (case 4).

The remaining third of our cases had characteristic clinical presentations confirmed by two-tier serologic criteria (cases 2, 6, 8–10) yet did not meet CDC epidemiological case definition. Steroids were prescribed in four of these cases (cases 12–15).

Table 3 shows that treatment delay, steroid treatment and the absence of an erythema migrans rash are associated with the greatest risk of treatment failure by univariate analysis. They are also independent risk factors for treatment failure by logistic regression (OR = 6.3, CI 2.1–19; OR = 10.3, CI 1.2–87 and OR = 0.2, CI 0.1–0.8 respectively.)

Discussion

These results indicate that treatment delay is strongly associated with treatment failure for patients with Lyme disease. The average 1.8 years treatment delay recorded here is consistent with previous reports of treatment delays spanning 6 weeks to 3 years [4–6]. Two-thirds of the delays occurred even though patients conformed to the well-defined CDC case definition. An additional third presented with well-described clinical presentations of Lyme disease, including fatigue, memory and concentration problems, irritability and headaches [7].

The poor outcome after treatment delay supports the hypothesis that treatment delay is a major risk factor for developing chronic Lyme disease.

Delayed treatment was identified in 58% of the cases with treatment failure. Failure was more than twice as likely to occur with delayed treatment than with timely treatment ($P < 0.002$). The association between treatment delay and chronic Lyme disease remains strong even after adjustment for age, sex, tick bite, erythema migrans and steroid use variables.

Two-thirds of our subjects received timely treatment. Their failure rate was only 24%. That is less than half the failure rate for

Table 1 Characteristics of 24 cases of treatment failure and 76 controls of successful treatment

Characteristic	Treatment failure ($n = 24$)	Treatment success ($n = 76$)	*P*-value
Age (years), mean (SD)	38 (19)	42 (15)	0.2
Male	14 (58)	42 (55)	0.79
Tick bite	7 (29)	36 (47)	0.11
Erythema migrans rash	8 (33)	37 (49)	0.12
Steroid use	4 (17)	2 (3)	0.12
Treatment delay	14 (58)	18 (24)	0.002
Treatment duration (days), mean (SD)	85 (134)	70 (83)	0.031
Treatment delay (days), mean (SD)	518 (851)	92 (362)	0.001

Values are numbers (percentages) unless stated otherwise

Table 2 Clinical presentation of the 15 cases failing treatment with delayed treatment by treatment delay

Case	Delay (days)	Age (year)	Sex	Clinical characteristics
1	2920	35	M	Erythema migrans rash, tested 1 week after rash and never retested.
2	2920	16	F	Epstein Barr and Strep infection. Tonsils subsequently removed.
3	2190	57	F	Tick bite followed by swollen right knee diagnosed as meniscus tear.
4	2190	16	M	Bell's palsy, poor in school.
5	1460	31	M	6 by 6 inch rash.
6	1095	35	M	Typical symptoms, told not Lyme disease by two doctors.
7	1095	42	F	Bell's palsy, told not Lyme based on a negative spinal tap.
8	515	22	M	Sinusitis, followed by two sinus operations.
9	455	75	M	Aches, pains and walking difficulties, told related to a previous heart attack for stroke.
10	240	50	M	Rotator cuff injury and meniscus tear.
11	210	36	F	Ill defined rash with a positive test, told not Lyme by their doctor.
12	120	75	M	Edema given diuretics and later 'water on knee' given cortisone.
13	90	18	F	4 by 4 inch rash followed by pericarditis, treated with steroids instead of antibiotics.
14	60	37	M	Disseminated Lyme rashes and asthmatic bronchitis, treated with steroids instead of antibiotics.
15	60	20	F	Cellulitis treated three times.

F, female, M, male.

Table 3 Relation between history variables and treatment failure in 100 Lyme disease patients

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age	1.5 (0.2 to 9.5)	Not included
Sex	0.6 (0.2 to 1.7)	Not included
History of tick bite	0.6 (0.2 to 1.9)	Not included
Erythema migrans rash	0.2 (0.6 to 0.8)*	0.2 (0.1 to 0.8)*
Steroid use	9.6 (1.0 to 91)*	10.3 (1.2 to 87)*
Treatment delay	7.0 (2.2 to 23)**	6.3 (2.1 to 19)**

*Significance <0.05 **Significance <0.001

patients with delayed treatment in our study (58%), and dramatically lower than the 63% failure rate for patients with delayed treatment in two clinical trials [10].

It is worth noting that in our study, the overall failure rate was closer to the 12% to 33% rate documented for patients with neurological Lyme disease [7,9]. The lower failure of 24% in those who received timely treatment underscores the importance of immediate and accurate diagnosis.

To avoid recall bias, we counted doctor contact only if a clear diagnosis was made by the previous doctor. Patient delays were included only if a clear rash or characteristic symptom complex developed. Longer delays by patients with ill-defined, non-specific symptoms would likely only strengthen the association between treatment delay and treatment failure.

This study was retrospective because it is not ethically or legally possible to design a research project with patients who receive no treatment.

Finally, it must be noted that study was not intended to determine if a treatment failure resulted from persistent infection or immune mediation. Additional trials are needed to understand the mechanism for treatment failure.

In summary, clinicians must ensure that patients receive prompt treatment as delays cause unnecessary suffering and expense. Doctors in Lyme endemic regions should inform patients about the risks and symptoms of Lyme disease. There is a pressing need for doctor education programmes designed to help clinicians recognize and treat Lyme disease at onset.

References

1. MMWR (2002) Lyme disease – United States, 2000. *Morbidityand Mortality Weekly Report*, 51 (2), 29–31.
2. Campbell, G. L., Fritz, C. L., Fish, D., Nowakowski, J., Nadelman, R. B. & Wormser, G. P. (1998) Estimation of the incidence of Lyme disease. *American Journal of Epidemiology*, 148 (10), 1018–1026.
3. Smith, R., O'Connell, S. & Palmer, S. (2000) Lyme disease surveillance in England and Wales, 1986–1998. *Emerging infectious diseases*, 6 (4), 404–407.
4. Fallon, B. A. (2001) *Profiles of Chronic Lyme Disease from the NIH Clinical Trial*. Presentation 15th International Scientific Conference on Lyme Disease and Other Tick-Borne Disorders, 22 April 2001, Farmington, CT, USA.
5. Fallon, B. A., Nields, J. A. & Delbene, D. (1991) Depression and Lyme disease: a controlled survey (abstract#NR119). In New Research and Program Abstracts of the 144th Annual Meeting of the American Psychiatric Association, p. 76. Washington, DC: American Psychiatric Association.
6. Asch, E. S., Bujak, D. I., Weiss, M., Peterson, M. G. & Weinstein, A. (1994) Lyme disease: an infectious and postinfectious syndrome. *Journal of Rheumatology*, 21 (3), 454–461.
7. Logigian, E. L., Kaplan, R. F. & Steere, A. C. (1990) Chronic neurologic manifestations of Lyme disease. *New England Journal of Medicine*, 323 (21), 1438–1444.
8. Feder, H. M. Jr & Whitaker, D. L. (1995) Misdiagnosis of erythema migrans. *American Journal of Medicine*, 99 (4), 412–419.
9. Logigian, E. L., Kaplan, R. F. & Steere, A. C. (1999) Successful treatment of Lyme encephalopathy with intravenous ceftriaxone. *Journal of Infectious Diseases*, 180 (2), 377–383.
10. Klempner, M. S., Hu, L. T., Evans, J. *et al.* (2001) Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *New England Journal of Medicine*, 345 (2), 85–92.

Internal Medicine News

News and Views that Matter to Physicians

Infectious Diseases

Infectious Disease Recommendations Largely Based on Low-Quality Evidence

By: MARY ANN MOON, Internal Medicine News Digital Network

01/10/11

FROM ARCHIVES OF INTERNAL MEDICINE

VITALS

Major Finding: Only 14% of 4,218 individual recommendations in 41 Infectious Diseases Society of America clinical practice guidelines are based on level I evidence such as that from randomized clinical trials, while more than half are based on level III evidence, such as that from expert opinion or descriptive studies.

Data Source: A review of 41 current IDSA clinical practice guidelines aimed at assessing the quality of evidence on which each recommendation is based.

Disclosures: Dr. Lee and Dr. Vielemeyer, of Drexel University reported that they had no relevant financial disclosures.

Practice Guidelines Are Only a Starting Point

More than half of the current recommendations in practice guidelines concerning infectious disease are based on evidence derived only from expert opinion or descriptive studies, according to a report in the Jan. 10 issue of the Archives of Internal Medicine.

Only 14% of the 4,218 individual recommendations included in 41 Infectious Diseases Society of America (IDSA) guidelines published in 1994-2010 are based on the highest-quality, or level I, evidence, such as that from randomized controlled trials, said Dr. Dong Heun Lee and Dr. Ole Vielemeyer of Drexel University, Philadelphia.

"Guidelines can only summarize the best available evidence, which often may be weak. Thus, even more than 50 years since the inception of evidence-based medicine, following guidelines cannot always be equated with practicing medicine that is founded on robust data," the investigators noted.

"Physicians and policy makers should remain cautious when using current guidelines as the sole source guiding decisions in patient care."

The study authors assessed the quality of evidence underlying 41 of the 52 IDSA guidelines currently available, which cover a wide range of topics and use an IDSA evidence-grading system. About half of these 41 guidelines are new and half are updates of earlier guidelines.

In addition to the highest-quality (level I) evidence, the IDSA grading system designates evidence from well-designed, but nonrandomized clinical trials, from cohort studies, from case-controlled analytical studies, or "dramatic results from uncontrolled experiments" as intermediate-quality (level II) evidence. The lowest-quality (level III) evidence is that "from the opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees," the investigators said.

They identified 4,218 individual recommendations among the 41 guidelines that could be charted according to the strength of the recommendation and the quality of the evidence supporting it. Only 14% were supported by level I evidence, 31% by level II evidence, and 55% by level III evidence (Arch. Intern. Med. 2011;171:18-22).

For example, greater than 80% of the recommendations concerning blastomycosis, which were published in 2008, were based on level III evidence and did not have any level I support. The findings were the same for recommendations concerning sporotrichosis, published in 2007.

The investigators also assessed the extent to which the quality of evidence has improved over time by selecting five guidelines that had recently been updated and comparing them with their respective earlier versions. The updates did include evidence from more studies, as well as evidence from more recent studies, than did the earlier guidelines. "However, only two updated guidelines had a significant increase in the number of level I quality-of-evidence recommendations; most additional recommendations were supported by level II or III quality of evidence only," Dr. Lee and Dr. Vielemeyer said.

In addition, "we came across imprecisions on more than one occasion and for more than one guideline, including illogical, erroneous, or missing references for recommendations and their associated grades," they added.

These findings are particularly concerning because guidelines are used not only for decision making in clinical practice but also "as benchmarks in the appraisal of quality of care provision," they said.

"We believe that the current clinical practice guidelines released by the IDSA constitute a great and reliable source of information that should be used. However, in circumstances when patient outcome is less than desirable, or when colleagues use diagnostic or therapeutic choices not included in the recommendations, it is prudent to remember that many of the individual recommendations are not supported by solid evidence.

"In such cases, we encourage reviewing the primary literature and using one's clinical judgment rather than relying solely on recommendations," they concluded.

Dr. Lee and Dr. Vielemeyer reported that they had no relevant financial disclosures.

Practice Guidelines Are Only a Starting Point

"Perhaps the main point we should take from the studies on quality of evidence is to be wary of falling into the trap of 'cookbook medicine,'?" said Dr. John H. Powers.

"The existence of guidelines is probably better than no guidelines, but guidelines will never replace critical thinking in patient care."

For clinicians, guidelines "may provide a starting point for searching for information, but they are not the finish line.

"As with individual research studies, providers should critically evaluate guidelines and the evidence on which they are based and how relevant recommendations are locally at their institutions and in their patients," he said.

DR. POWERS *is with the division of clinical research at the Scientific Applications International Corp. (SAIC) in support of the National Institutes of Health. He reports receiving consulting fees from several pharmaceutical companies. These comments were taken from his editorial accompanying the report by Dr. Lee and Dr. Vielemeyer (Arch. Intern. Med. 2010;171:15-17).*

Relapses and Failure Rates Using Short Term Approaches.

In animals, the failure of 30 day antibiotic approaches was demonstrated by Straubinger[1], while in humans, the culture confirmed failure of standard courses of antibiotics was demonstrated by Preac-Mursic et al.[2] Studies consistently show high failure rates, ranging from 26% to 50%, using short term antibiotic approaches. (See table below.) As a recent review of Lyme disease points out: "The question with persistent Lyme disease has never been what to do with the 50-76% who find short-term treatment approaches successful. The issue is how to treat those 24 to 50% who fail under this treatment approach."[3]

Treatment Relapses and Failures on Short Term Therapy[3]

Study/ Relapse or Failure %	Comments
Shadick (1999) [4] 37%	69 of 184 previously treated patients (37%) reported a previous relapse.
Treib (1998) [5] >50%	After 4.2 years, more than ½ of 44 treated patients with clinical signs of neuroborreliosis and specific intrathecal antibody production were symptomatic.
Logigian (1990) [6] 37%	After 6 months, 10 of 27 patients treated relapsed or failed treatment. 17 (63%) improved, 6 (22 percent) improved, then relapsed, 4 (15%) had no response."
Pfister (1991) [7] 37%	33 patients with neuroborreliosis treated. After a mean of 8.1 months, 10 of 27 were symptomatic and borrelia persisted in the CSF of one patient.
Shadick (1994) [8] 26%	10 of the 38 patients ... relapsed within 1 year of treatment and had had repeated antibiotic treatment."
Valesova (1996) [9] 38%	At 36 months, 10 of 26 had relapsed or progressed: complete response or marked improvement in 19, relapse in 6, and new symptoms in 4.
Asch (1994) [10] 28%	3.2 years after initial treatment: 28% relapsed with major organ involvement; 18% were reinfected. Persistent symptoms of arthralgia, arthritis, cardiac or neurologic involvement, were present in 114 (53%) patients."

References

1. Straubinger, R.K., *PCR-Based quantification of Borrelia burgdorferi organisms in canine tissues over a 500-Day postinfection period.* J Clin Microbiol, 2000. **38**(6): p. 2191-9.
2. Preac-Mursic, V., et al., *Survival of Borrelia burgdorferi in antibiotically treated patients with Lyme borreliosis.* Infection, 1989. **17**(6): p. 355-9.
3. Johnson, L.B. and R.B. Stricker, *Treatment of Lyme disease--a medicolegal assessment.* Expert Rev Anti-infect Ther, 2004. **2**(4): p. 533-57.
4. Shadick, N.A., et al., *Musculoskeletal and neurologic outcomes in patients with previously treated Lyme disease.* Ann Intern Med, 1999. **131**(12): p. 919-26.
5. Treib, J., et al., *Clinical and serologic follow-up in patients with neuroborreliosis.* Neurology, 1998. **51**(5): p. 1489-91.
6. Logigian, E.L., R.F. Kaplan, and A.C. Steere, *Chronic neurologic manifestations of Lyme disease.* N Engl J Med, 1990. **323**(21): p. 1438-44.
7. Pfister, H.W., et al., *Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis.* J Infect Dis, 1991. **163**(2): p. 311-8.
8. Shadick, N.A., et al., *The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study.* Ann Intern Med, 1994. **121**(8): p. 560-7.
9. Valesova, H., et al., *Long-term results in patients with Lyme arthritis following treatment with ceftriaxone.* Infection, 1996. **24**(1): p. 98-102.
10. Asch, E.S., et al., *Lyme disease: an infectious and postinfectious syndrome.* J Rheumatol, 1994. **21**(3): p. 454-61.

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From: Patricia V. Smith, President, Lyme Disease Association, Inc.
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June 22, 2010
Testimony to: The PA Senate Banking & Insurance Committee
The Honorable Senator Donald C. White, Chairman

As background on Patricia V. Smith: President LDA
Strategic Advisory Board, Columbia University Medical Center Lyme & TBD Research Center
Advisor to Time for Lyme (CT)
Former Chair, [NJ] Governor's Lyme Disease Advisory Council
Washington DC- met with HHS, CDC, NIH, military
Invited to CDC Ft Collins, Vector-Borne Diseases Division (Lyme Program Headquarters)
Testified/invited to educate officials > dozen states

Thank you for the opportunity to testify favorably on this very important issue, Lyme disease bill SB 1199.

The Lyme Disease Association (LDA) is all-volunteer national non profit devoted to education, research funding, prevention & patient support with 37 allied organizations nationwide, including in Pennsylvania an affiliate, a Chapter, and a coalition. LDA is part of the 2010 Combined Federal Campaign (CFC) as an approved national charity, has sponsored 10 fully CME accredited scientific conferences, with the 11th to be in Philadelphia in October 2010.

LDA's *LymeAid 4 Kids* fund dispenses money for children without insurance – 19 Pennsylvania children have benefited to date from this fund. LDA provides research grants coast-to-coast with its projects published in 18 peer reviewed journals to date and has funded several projects in Pennsylvania with researchers at Fox Chase Cancer Center, University of Pennsylvania, Edinboro University of Pennsylvania, and University of Pittsburg School of Nursing and partnered with its affiliate to endow a Center at Columbia to study chronic Lyme. LDA is an Environmental Protection Agency (EPA) PESP partner and sits on a working group with EPA and with CDC developing measures to help reduce exposure to Lyme disease.

Lyme is now found in 65 countries worldwide. According to the 2009 Armed Forces Health Surveillance Center report, confirmed cases of Lyme disease in the services were diagnosed at more than 120 military locations worldwide.[i] A UN commissioned study indicates ticks in Sweden have moved almost as far north as the Arctic Circle and are being found in January.[ii] Reports from researchers and patients confirm that latter finding in the Northeast. For example, in January 2005, a fully engorged deer tick was removed from the ear of my then 5-year old granddaughter. It was 25°.

According to CDC, ages 5-9 are at the greatest risk of acquiring Lyme,[iii] the most prevalent vector-borne disease in the US, reported from all 50 states. From 1990-2008, CDC reported 51,266 cases of

Pennsylvania Lyme disease, a number including my late parents. Since only 10% that meet the CDC's narrow surveillance criteria are reported, more than 1/2M (512, 660) cases occurred in PA–that does not count those who are clinically diagnosed, the patients we are here about today, the ones who most often develop chronic Lyme disease. A CDC Lyme review from 1990-2006 showed a geographic expansion in PA, indicated that the percent of cases with signs of disseminated infection didn't go down and that there needs to be continued education on early disease recognition and treatment.

ILADS' (International Lyme & Associated Diseases Society) treating physicians recognize that patients who are not diagnosed quickly or not treated appropriately can become chronically ill– one study shows that the impact of Lyme disease on physical health was at least equal to the disability of patients with congestive heart failure and osteoarthritis.[iv] Yet many of these patients, often multiple members of one family,[v] now have to travel many hours outside Pennsylvania to find care for their Lyme. They don't have the resources nor the health to fight the vested interests stacked against them, which is why legislation is often necessary to protect doctors who treat, ensuring that in-state treating doctors cannot be prosecuted solely for providing long-term treatment based on clinical judgment. Rhode Island, Connecticut and California have passed protective legislation and Massachusetts is awaiting the Governor's signature on a bill.

Following IDSA (Infectious Diseases Society of America) Guidelines can lead to delayed diagnosis and treatment and to chronic Lyme disease. Depending on the literature, an estimated 10-15 up to 34-62% [vi] of patients develop chronic disease, although treating doctors seem to feel it's about 20%. According to an actuarial study on Lyme costs, "37% of the financial costs of this disease is incurred before the correct diagnosis is made." [vii] A delay in diagnosis also leads to more chronic disease since the Lyme bacterium can get into the brain within 24 hours of a tick bite.[viii] Chronic Lyme is more costly to patients physically, mentally, and financially. According to a 1998 CDC journal study, early Lyme costs averaged $161 per patient and neurologic longstanding Lyme disease averaged $61,243.[ix] Chronic Lyme is also more costly to the state and federal government in terms of disability and education e.g., special services, home instruction, substitute teachers. [x] Allowing doctor discretion in diagnosing and treating before Lyme disease ravages a patient can cut costs and most importantly, human suffering.

Most opposition to Lyme legislation comes from the IDSA itself. You've heard how doctors who don't follow IDSA Guidelines but use their own clinical skills to diagnose and treat face medical board discipline and hospital sanctions if they do not march lockstep with IDSA, creating a "chilled" treatment climate nationwide.

Complicating that treatment picture, physicians continue to be monitored by insurance companies who say stop prescribing antibiotics for Lyme disease or leave the insurance plan. Some doctors then leave the plan voluntarily, others are forced out. Some continue treating patients without accepting insurance. Other physicians fear scrutiny from the insurance companies and stop treating Lyme disease entirely, leading to a scarcity of physicians.

Patients lack of insurance coverage leads to limited courses of antibiotics, often not effective in eradicating the Lyme bacterium, which has the ability to hide inside cells, kill human lymphocytes and certain B cells and to change into other forms. Legislation requiring insurance companies to cover patients for Lyme treatment has been passed in Rhode Island and Connecticut.

The facts demonstrate the need for more research. A 2006 CDC study proved that it's possible to acquire Lyme through blood transfusion in a mouse model,[xi] although no cases of Lyme have been linked to blood transfusion in humans. However, scientists proved that Lyme bacteria can live in blood that is stored for donation and Red Cross says that individuals being treated with antibiotics for Lyme disease should not donate blood. The co-infection babesiosis can be transmitted through the blood supply, and there have been documented deaths through transfusions, as there is no blood screening for babesia.

The military takes Lyme very seriously. The US Army Public Health Command Tick-Borne Disease Laboratory at Aberdeen Proving Grounds, where LDA has been invited twice to visit, provides free voluntary tick identification and testing service for Department of Defense personnel & dependents, testing several thousand ticks off people every year from about 100 participating military installations. 31% of ticks from 3 PA installations tested positive for Lyme disease over 4 years. Both Lyme and Babesiosis are considered full (100%) disability if contracted during military duty,[xii] and the Air Force aeromedical concerns may require flyers to receive a waiver to fly if they have Lyme disease.[xiii]

To fund more research and education, there are companion bills in Congress which provide $100M over 5 years, particularly for an accurate test to help resolve many Lyme-related issues. IDSA opposes those bills, too, the Lyme & Tick-Borne diseases Prevention, Research and Education Act 2009 [**HR 1179 C. Smith (NJ) 91 co-sponsors, S 1352 C. Dodd (CT) 9 co-sponsors**]. They once told a Congressman's office that all the significant research on Lyme has been done. They opposed the bill in writing because they do not like the constitution of a Lyme and tick-borne diseases federal advisory committee created by the bills, because it contains patient and treating physician reps with viewpoints different from their own. Many other diseases have advisory panels with patient representation. Currently, Lyme patients have no input into the disease despite their being the major stakeholders.

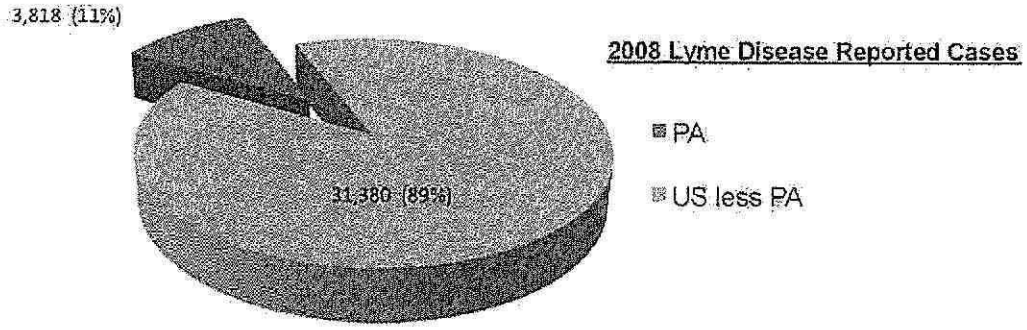
Lyme language was included in the 2010 HHS Appropriations bill signed into law by President Obama, including the terms "chronic Lyme disease" and "persistence" and it provided additional monies for CDC to develop a definitive test, recognizing that existing tests are antiquated. It directs NIH to hold a conference where all sides of the science will be examined. The federal government realizes that Lyme disease patients suffer from unsettled science and from science that has been examined and interpreted through only one lens, a myopic one at that, one which has created a vast number of people unable to get diagnosed, treated, or reimbursed for treatment.

Most of the opposition to Lyme legislation comes from the IDSA itself. You have heard how doctors who don't follow IDSA Guidelines but use their own clinical skills to diagnose and treat face medical board discipline, hospital privilege/post revocation, and insurance plan exclusion if they do not march lockstep with IDSA, creating a "chilled" treatment climate. This has occurred nationwide for many years.

You have the power to change the face of Lyme disease in PA. Contrary to what bill opponents will say, you are NOT legislating treatment but only allowing doctors to practice medicine as they were taught, meshing their clinical skills with the tools they have at hand, antiquated tests, and antibiotics which have been shown for decades to help those with bacterial infections. It is not experimental treatment but a professional judgment call in consultation with the patient as to what antibiotic they use and for what length of time.

Thank you for supporting this bill.

Lyme Disease Association Lyme Disease Analysis
Pennsylvania / National Reportable Cases [1]

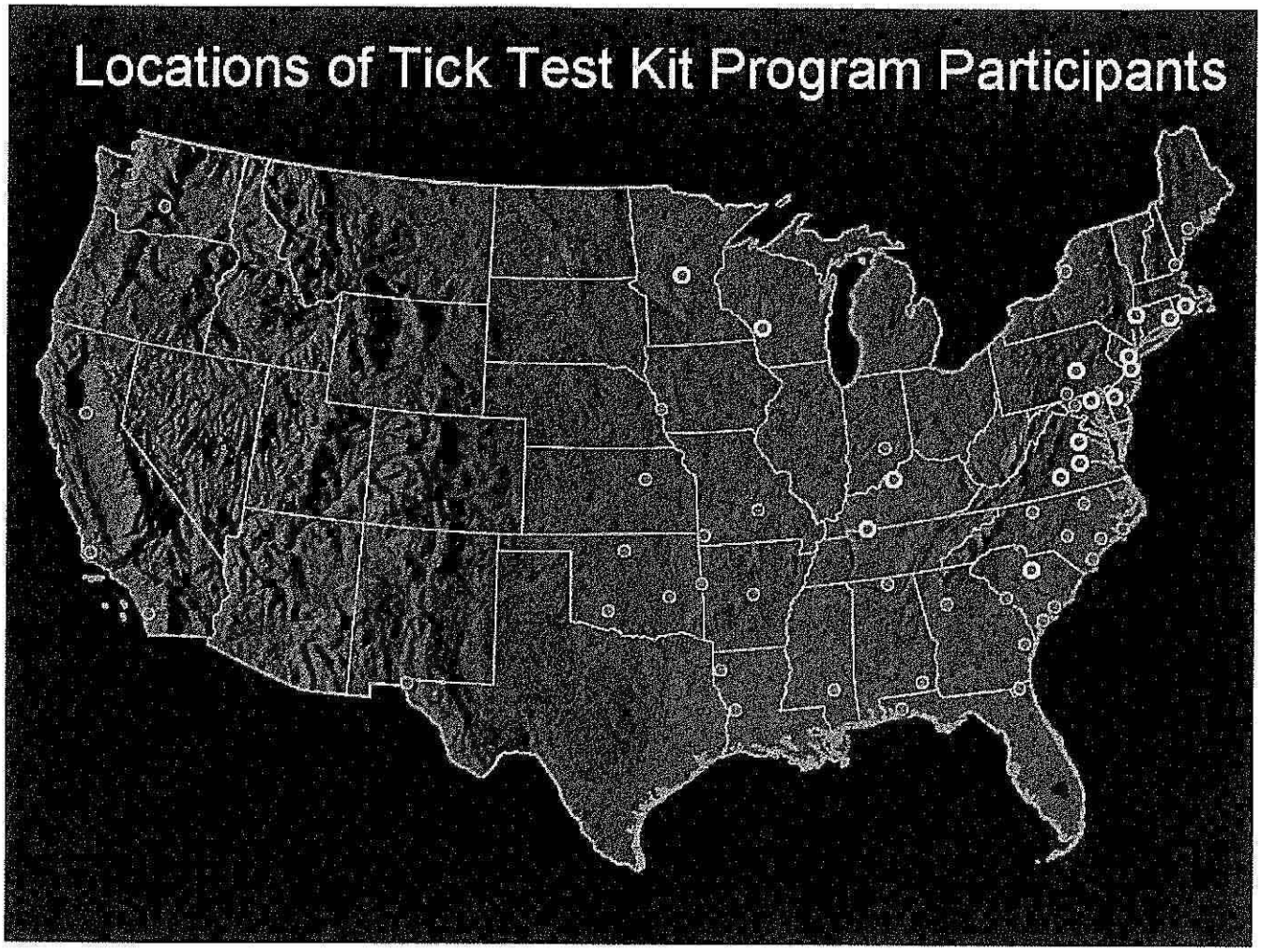


Year	PA Lyme Disease Cases	Adjusted for CDC estimate only 10% cases get reported	US Lyme Disease Cases	Adjusted for CDC estimate only 10% cases get reported
2008 [2]	3,818	38,180	35,198	351,980
2007	3,994	39,940	27,444	274,440
2006	3,242	32,420	19,931	199,310
2005	4,287	42,870	23,305	233,050
2004	3,985	39,850	19,804	198,040
2003	5,730	57,300	21,273	212,730
2002	3,989	39,890	23,763	237,630
2001	2,806	28,060	17,029	170,290
2000	2,343	23,430	17,730	177,300
1999	2,781	27,810	16,273	162,730
1998	2,760	27,600	16,801	168,010
1997	2,188	21,880	12,801	128,010
1996	2,814	28,140	16,455	164,550
1995	1,562	15,620	11,700	117,000
1994	1,438	14,380	13,043	130,430
1993	1,085	10,850	8,257	82,570
1992	1,173	11,730	9,908	99,080
1991	718	7,180	9,470	94,700
1990	553	5,530	7,943	79,430
Total 1990 to 2008	51,266	512,660	328,128	3,281,280

(1) Source data compiled from CDC pub. data (MMWR)

(2) Lyme disease case definition was changed for 2008 and the category of probable was reported for the first time. (US 2008 confirmed = 28,921 / probable = 6,277) (PA 2008 confirmed = 3,818 / probable = 0) The numbers used in 2008 include confirmed and probable cases reported by CDC According to the CDC, only 10% of Lyme disease cases that meet the case definition are reported, meaning if 10,000 cases are reported, 100,000 cases occurred. This data does not include all the cases that fall outside the stringent surveillance case definition.

11/29/09



US Army Public Health Command Tick-Borne Disease Laboratory provides a tick identification and testing service for Department of Defense personnel & dependents. Our program is free; participation is voluntary. We test several thousand ticks every year from around 100 participating military installations. This map shows locations, the big dots (white-rimmed) indicate the installations that send us the most ticks.

LYME DISEASE ASSOCIATION'S
PENNSYLVANIA FACT SHEET

Pennsylvania (PA) has consistently ranked in the top ten states in the US in reported Lyme disease cases. During 2003-2005, Centers for Disease Control and Prevention (CDC) indicates 93% of the cases (59,770) in the U.S. occurred in 10 endemic states: Connecticut, Delaware, Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, Rhode Island, and Wisconsin. Incidence (cases/100,000 pop.) in the 10 went from 29.1 in 2003 to 31.6 in 2005. [xiv] The largest incidence increases in PA in 2006 by county were Cameron (154.03); Elk (107.39) and Chester (101.96). In 2008, PA ranked 3rd nationwide in reported Lyme case numbers (3,818), a 252% increase over 1993, while numbers nationally increased 250%.

The highest reported incidence rate was among children aged 10-14 years and adults 50 and over. According to University of Pennsylvania School of Veterinary Medicine, "Increased risk is associated with living in single family homes, homes with yards or attached land, woods on the land, signs of tick hosts seen on the land, and homes within 100 feet of woodland. Gardening for more than four hours per week was also a risk factor." [xv]

CDC indicates only 10% of the cases that meet its surveillance criteria are actually reported,[xvi] thus about 38,818 cases of Lyme disease that met the CDC surveillance criteria occurred in PA in 2008. Over ¼ million people (289,210) who fit the surveillance criteria developed new Lyme disease in the U.S in 2008. No one tracks numbers of cases that are doctor-diagnosed clinically–the ones that most often develop into chronic disease, an estimated 10-15 to 40% (cases which failed standard treatment course & continue to be symptomatic). [xvii]

According to Johns Hopkins, "cultivation of Borrelia burgdorferi [Lyme] is definitive," and "prior investigations have shown that no single test is optimal for Lyme disease diagnosis." In 2005, Hopkins conducted studies using high-volume blood cultures, skin biopsy culture, PCR, and serodiagnosis on patients with suspected Lyme acquired in PA and Maryland (MD). Hopkins overall results indicate about 75% of Lyme patients tested are negative using the best known testing methods available.[xviii]

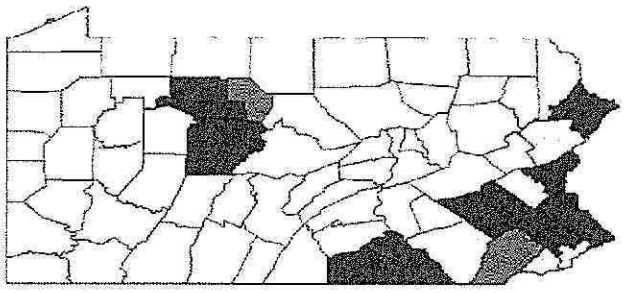
Hopkins also reported from the 118 small mammal tissue or blood cultures they studied from PA and MD, spirochetes were observed in 71 (60.2%), including 27 blood and 44 ear biopsy cultures." These studies "confirm a high degree of *B. burgdorferi* genetic diversity and a lack of concordance between strains identified in animals and humans from the same locations."[xix]

Penn State reports "symptoms of persisting infection may continue or recur, making additional antibiotic treatment necessary. Varying degrees of permanent damage to joints or the nervous system can develop in patients with late chronic Lyme disease. Typically these are patients in whom Lyme disease was unrecognized in the early stages or for whom the initial treatment was unsuccessful. Rare deaths from Lyme disease have been reported."[xx]

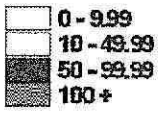
Other tick-borne diseases are on the rise in PA and nationally. Estimates of 20% to 73% of deer tick vectors rampant in states near Philadelphia are infected with at least 1 pathogen. According to a 2004 Medical Hypothesis article by PA physician VT Sherr, "more and more frequently patients are co-infected with Lyme and babesiosis....Until babesiosis is a reportable disease and physicians are alerted and educated, the majority of people sickened by it will remain undiagnosed and therefore untreated. They will continue, innocent of any awareness of this infection, to spread babesia via placenta, blood and/or organ donations."[xxi]

Pennsylvania

Lyme Disease 5-Year Average Incidence

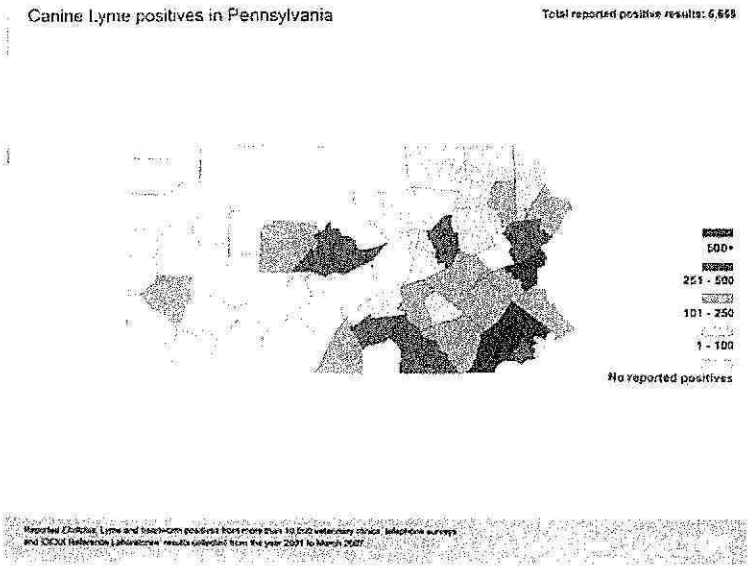


Average Number of New Cases Per Year (2002-2006)



Source: Pennsylvania Department of Health

Canine Lyme Disease Positives by County



Source: IDEXX Veterinary Labs

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[1] CDC MMWR June 15, 2007
[1] http://www.mass.gov/dph/cdc/epii/lyme/lyme_disease_surveillance_2005.doc
[1] Paul Meade CDC NJ Herald
[1] LDA review of various peer review studies
[1] J Clin Microbiol. 2005 Oct;43(10):5080-4. **Two-year evaluation of Borrelia burgdorferi culture and supplemental tests for definitive diagnosis of Lyme disease.** Coulter P, Lema C, Flayhart D, Linhardt AS, Aucott JN, Auwaerter PG, Dumler JS. Division of Medical Microbiology, Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.

[1] ***Borrelia burgdorferi ospC* Heterogeneity among Human and Murine Isolates from a Defined Region of Northern Maryland and Southern Pennsylvania: Lack of Correlation with Invasive and Noninvasive Genotypes** Muneera Y. Alghaferi,[1¶] Jennifer M. Anderson,[1] Jinho Park,[2†] Paul G. Auwaerter,[3] John N. Aucott,[3] Douglas E. Norris,[1] and J. Stephen Dumler[1,2*] J Clin Microbiol. 2005 April; 43(4): 1879–1884.
doi: 10.1128/JCM.43.4.1879-1884.2005.
[1] http://ento.psu.edu/extension/urban/lyme-disease/symptoms-diagnosis-and-treatment?searchterm=reported%2520cases%2520Lyme
[1] http://www.ncbi.nlm.nih.gov/pubmed/15325004?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=22

End Notes to Testimony

[i] Medical Surveillance Monthly Report Armed Forces Health Surveillance Center July 2009 Lyme disease among U.S. military members, active and reserve component, 2001-2008_

[ii] UN Intergovernmental Panel on Climate Change 2007

[iii] Centers for Disease Control & Prevention, *Average Annual Incidence of Reported Cases of Lyme Disease by Age Group & Sex*, http://www.cdc.gov/ncidod/dvbid/lyme/ld_MeanAnnualIncidence.htm.

[iv] MS Klempner et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *New England Journal of Medicine* vol. 345(2), July 12, 2001.

[v] CDC unpub. study data presented in Congressional forum, Wall NJ Oct 1992 (Later pub. in Lyme Times)

[vi] Shadick NA et al Ann. of Internal Medicine '94 ; Asch ES et al Rheumatol. '94

[vii] Irwin Vanderhoof, *Lyme Disease the Cost to Society*, Contingencies January/February 1993.

[viii] Steere, Allen, Mandel, Douglas, and Bennett's *Principals & Practices of Infectious Diseases*, 4th ed. 1995.

[ix] Martin I. Meltzer *The Cost Effectiveness of Vaccinating against Lyme Disease CDC Emerging Infectious Diseases;* Vol.5, No.3; 1999 May-June;5(3)321-8. * This is 1996 costs not adjusted to 2007. The following additional costs to society aren't measured by this table: special education needs for children, disability, increased medical and insurance costs, and livestock losses, etc. Also, there are personal loses: friends, employment, self, esteem, domicile, and breakup of families.

[x] Patricia Smith, Wall Township, NJ, Board of Education member *NJ School District Study on Impact of Lyme Disease on School Districts* presented in Washington DC Congressionally hosted meeting with CDC & NIH, March 12, 1992.

[xi] Persistence of *Borrelia burgdorferi* following Antibiotic Treatment in Mice Emir Hodzic, Sunlian Feng, Kevin Holden, Kimberly J. Freet, and Stephen W. Barthold

xii §4.88b Schedule of ratings-infectious diseases, immune disorders and nutritional deficiencies. http://www.warms.vba.va.gov/regs/38CFR/BOOKC/PART4/S4_88b.DOC