

**25th ANNIVERSARY ISSUE: Science**

# THE LYME TIMES

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*The Journal of LymeDisease.org*

***First Evidence-Based  
Patient-Centered  
Lyme Guidelines***



**Dan Cameron, MD**



**Elizabeth Maloney, MD**



**Lorraine Johnson, JD**

**ILADS RELEASES REVISED GUIDELINES**



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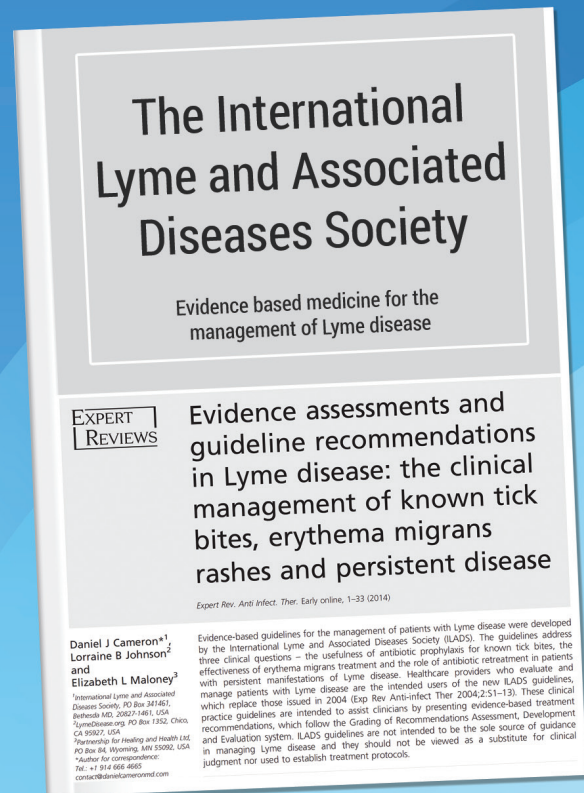
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# LDO ENDORSES NEW ILADS GUIDELINES



**EXPERT  
REVIEWS**  
  
Daniel J Cameron<sup>1</sup>,  
Lorraine B Johnson<sup>2</sup>  
and  
Elizabeth L Maloney<sup>3</sup>  
<sup>1</sup>International Lyme and Associated  
Diseases Society, PO Box 347461,  
Bethesda MD, 20827-1461, USA  
<sup>2</sup>lymedisease.org, PO Box 1352, Chico,  
CA 95927, USA  
<sup>3</sup>Department for Healing and Health Ltd,  
PO Box 84, Wyoming, MN 55092, USA  
\*Author for correspondence:  
Tel: +1 914 666 4665  
correspond@lymedisease.com

Evidence-based guidelines for the management of patients with Lyme disease were developed by the International Lyme and Associated Diseases Society (ILADS). The guidelines address three clinical questions – the usefulness of antibiotic prophylaxis for known tick bites, the effectiveness of erythema migrans treatment and the role of antibiotic retreatment in patients with persistent manifestations of Lyme disease. Healthcare providers who evaluate and manage patients with Lyme disease are the intended users of the new ILADS guidelines which replace those issued in 2004 (Exp Rev Anti-infect Ther 2004;2:51–13). These clinical practice guidelines are intended to assist clinicians by presenting evidence-based treatment recommendations, which follow the Grading of Recommendations Assessment, Development and Evaluation system. ILADS guidelines are not intended to be the sole source of guidance in managing Lyme disease and they should not be viewed as a substitute for clinical judgment nor used to establish treatment protocols.

The International Lyme and Associated Diseases Society (ILADS) published its revised treatment guidelines in August 2014. Developed over a three year period, they reflect the latest science.

Both evidence-based and patient-centered they focus on how best to reduce the risk of developing chronic illness.

### FRONT COVER:

Authors of revised ILADS guidelines reference the latest science  
Cover design by Michele Lott, [MicheleLottDesign.com](http://MicheleLottDesign.com)

**INSIDE FRONT COVER:** LDO endorses the new ILADS guidelines  
Graphic by Laurie Martin, [CauseRoar.com](http://CauseRoar.com)

**BACK COVER:** FDA proposes to regulate Lyme lab tests  
Graphic by Laurie Martin, [CauseRoar.com](http://CauseRoar.com)

# THE LYME TIMES

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Photo courtesy of the National Institute of Health

Wilhelm "Willy" Burgdorfer 1925-2014  
The bacterium he discovered in 1982 that causes Lyme disease is named in his honor: *Borrelia burgdorferi*.

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# Informed Advocates are Strong Advocates

In the third issue of our 25th anniversary series, we are looking at the scope of the science of Lyme disease, from Willy Burgdorfer's discovery of the spirochete in 1982 to ILADS' new evidence-based guidelines.



The big news is the publication of the new guidelines — the first Lyme guidelines to follow the GRADE format, a systematic and transparent analysis of the evidence used by several organizations including Cochrane Collaborative and the World Health Organization (see page 17). They are also the first to comply with the eight standards identified by the prestigious Institute of Medicine as being critical to the development of trustworthy guidelines. The authors built patient-centered care into the guidelines from the ground up and our own executive director, Lorraine Johnson, was part of the working group. We

thank Dan Cameron, Betty Maloney, and Lorraine for volunteering thousands of hours over two intense years, hammering out details and making the guidelines the best they could be. It was a labor of love. We are grateful to ILADS for allowing us to reprint the Executive Summary in this issue. The complete Guidelines are available free online. [[informahealthcare.com/doi/abs/10.1586/14787210.2014.940900](http://informahealthcare.com/doi/abs/10.1586/14787210.2014.940900)]

Informed advocates are strong advocates, and in these pages Betty Maloney, Dan Cameron, Eva Sapi, Robert Lane and Brian Fallon try to give you a sense of the progress we have made while Ray Stricker, Alan MacDonald and Tom Grier highlight areas still crying for attention. Lorraine Johnson ties it all together with her astute analysis and strong patient advocacy. She explains what patient-centered care is and why patients need to be involved in evidence-based guidelines. Every advocate should understand these cutting-edge concepts informing the front lines of medicine.

Today we are facing a new challenge — the FDA is threatening to clamp down on non-FDA-approved tests across the board and to shut down some of the most accurate Lyme labs. Currently, 90% of the FDA-approved Lyme tests are ELISA tests, judged by researchers to be too insensitive for use as screening tests. *LymeDisease.org* is fighting back. We will use the data from our survey when we meet with FDA officials to protest the crackdown. The survey drew over 3,500 responses in the first 48 hours. Please participate! (See back cover)

Other groups also oppose the FDA's proposal, including the American Medical Association, which argues that patients would lose "access to timely life-saving diagnostic services and hinder advancements in the practice of medicine."

We thank all those who generously contributed their time and energy to write the articles for this special issue. These remarkable people are willing to share with us their unique combination of advocacy, scientific investigation and the practice of medicine. They are our heroes.

We hope this issue helps you better understand the "big picture" — what we know, what we don't know, where we have been and where we need to go from here. Join our team, use our resources, find out what you can do to contribute. There is strength in numbers, and we need all the help we can get.

*Phyllis Mervine*

# Evidence-Based Medicine

Knowing where evidence ends and values begin is important to patients

By Lorraine Johnson, JD, MBA

We are in the midst of a sea of change driven largely by healthcare reform and evidence-based medicine (EBM). Public trust is critical to the success of healthcare reform. But many patients believe that EBM is vulnerable to corruption by stakeholders, like insurers seeking to control costs and panel members who have industry conflicts of interest. Distrust in IDSA Lyme guidelines is high because Lyme patients believe that the guidelines panel was corrupted by industry conflicts (diagnostic tests, vaccines and insurance) and researcher self-interest.

Today, a shift from old models of medicine toward patient-centered medicine is emerging. It seeks to focus medical attention on the needs and concerns of the individual patient rather than those of physicians, insurers, pharmaceutical companies and researchers. At [LymeDisease.org](http://LymeDisease.org) we have been up to our eyeballs in EBM and patient-centered care since 2004, when we launched the two standards of care campaign.

From the beginning we have emphasized that when science is uncertain, different research and physician groups can hold different viewpoints about what to do. They can do this based on their interpretation of the evidence and the values they hold about different outcomes. This is not simply a matter of opinion. A recent study found that given identical evidence two groups of expert panels reached contrasting therapeutic recommendations. We know this happens with Lyme disease, but this panel was looking at angina, not Lyme!

Although EBM is defined as “the in-

tegration of best research evidence with clinical expertise and patient values,” patient values are frequently overlooked. This is shifting, however. Government institutions, like the Institute of Medicine (IOM) and Patient Centered Outcomes Research Institute (PCORI), now recognize that trustworthy policies,

patient values are accurately represented in the process.

We cannot do this without entering into the public discussion of EBM. The need for patient involvement is now being recognized by the IOM, which requires patient involvement in guidelines deemed “trustworthy.” It is also being recognized by newly emerging organizations established under healthcare reform, like Patient Centered Research Outcomes Institute (PCORI). PCORI, which had a 2013 research budget of \$350 million, is creating researcher/patient partnerships that bring stakeholders into the process as active partners. National organizations of patient groups, like Consumers United for Evidence-Based Healthcare (CUE), are helping to define the patient’s role in EBM. To this, I say count me in!

The Lyme community needs to be part of the conversation that determines the role of patients in healthcare. Without a seat at the table, our concerns fall on deaf ears.

## Resources

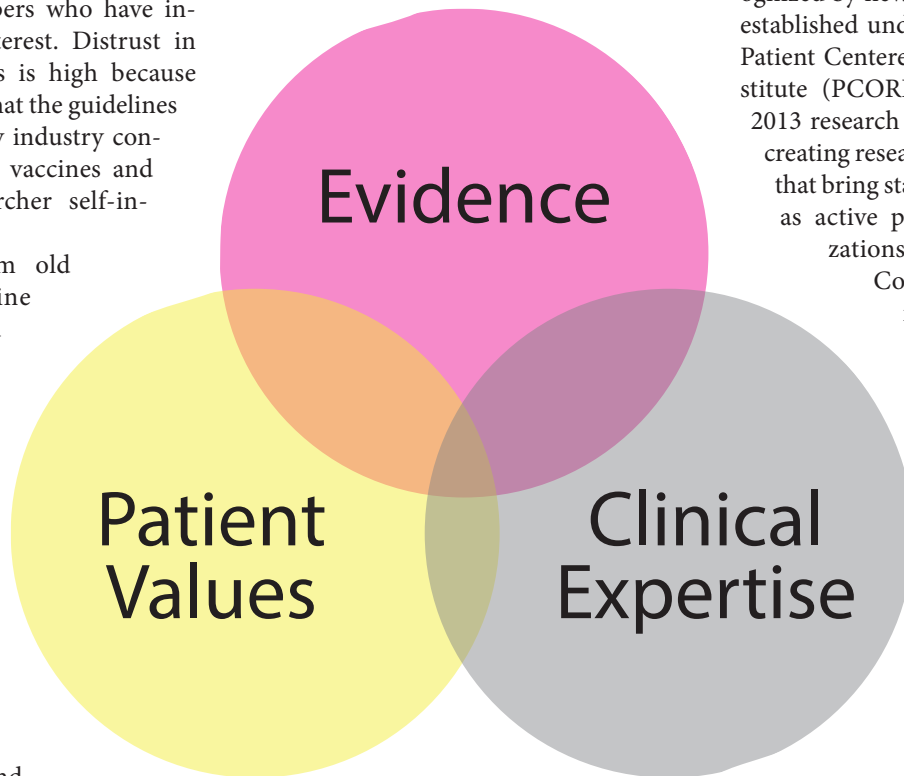
Gerber AS *et al.* A national survey reveals public skepticism about research-based treatment guidelines. *Health Affairs* (Millwood). 2010 Oct;29(10):1882-4.

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*Lorraine Johnson, JD, MBA, serves as the co-chair of CUE and a patient grant reviewer for PCORI. She is the executive director of LymeDisease.org and posts regularly on her blog Lyme Policy Wonk at [Lymedisease.org](http://Lymedisease.org). Contact her at [lbjohnson@lymedisease.org](mailto:lbjohnson@lymedisease.org).*



guidelines and research require the participation of patients.

If we are basing healthcare coverage decisions on EBM, we need to know where the evidence begins and ends. We need to know whose clinical expertise we are relying on. Is it the clinical expertise of treating physicians or that of researchers who see few patients? And we need to know how patient values are taken into account. Are patients involved? Whose values and viewpoints are represented? Patient involvement in EBM is essential to enforce the boundary between evidence and values and to ensure that

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# State of the Science

LLMD presents his "Top-Ten List" of Lyme facts uncovered over the last 25 years

By Raphael Stricker, MD

As we stumble toward 2015, questions about Lyme disease and related tick-borne co-infections have often caused controversy and made headlines. Here is a Top-Ten list of the most significant Lyme-related facts and events of the past 25 years.



Raphael Stricker, MD

1. The Centers for Disease Control and Prevention (CDC) announces that the rate of new Lyme disease cases in the U.S. is greater than 300,000 per year, more than 10 times higher than the previous estimate. Thus the spirochete *Borrelia burgdorferi* (*Bb*), the corkscrew-shaped bacterial agent of Lyme disease, causes illness that is twice as common as breast cancer and six times more common than HIV/AIDS. This statistic confirms that Lyme disease is a major epidemic in the U.S. and underscores the outrageous lack of funding for Lyme disease research compared to other diseases.

2. The abysmal state of commercial testing for Lyme disease becomes obvious, as the tests miss as many as 90% of Lyme disease cases. The myth that this testing is accurate for late Lyme disease gradually falls apart as the flawed reasoning behind this statement is exposed and the number of missed cases continues to rise. Calls for better testing get louder.

3. The U.S. House of Representatives passes HR 4701, the Vector-Borne Disease Research Accountability and Transparency Act of 2014. This is the first major legislation in the U.S. that addresses the Lyme disease epidemic. At this writing, the bill is now in the Senate. The term "chronic Lyme disease" (CLD), previously maligned by the medical establishment, gains recognition in the U.S. Congress.

4. The Infectious Diseases Society of America (IDSA) holds hearings on its opinion-based Lyme disease guidelines following a lawsuit by then-Connecticut Attorney General (now U.S. Senator) Richard Blumenthal. Although the hearing and its "do-nothing" conclusions are rigged in favor of IDSA, the widely-viewed open forum exposes the significant problems with IDSA "science" and impugns the national Lyme disease policy based on that "science." The evidence-based Lyme disease guidelines of the International Lyme and Associated Diseases Society (ILADS) are published and refute much of the IDSA

guidelines. Calls for guidelines reform get louder.

5. Treatment for Lyme disease and related tick-borne co-infections remains limited by the IDSA "28 day rule" claiming that anyone with Lyme disease will be cured with 28 days of antibiotic treatment even if the person is still sick. Studies critical of the poor science behind this rule are published, and evidence for persistent infection via cysts and biofilms in animals and humans with CLD grows stronger. Calls for better treatment trials and more effective antibiotics get louder.

6. A "new" relapsing fever spirochete, *Borrelia miyamotoi*, is found in deer ticks that carry the Lyme disease spirochete throughout the U.S. Although testing for *B. miyamotoi* was developed a decade ago, there is currently no commercial test available to screen for this "new" tick-borne disease.

7. Tick-borne co-infections, including *Babesia*, *Anaplasma*, *Ehrlichia*, *Bartonella* and *Rickettsia*, are increasingly recognized as complicating factors in patients with chronic Lyme disease. The risk of these agents to the blood supply creates growing alarm among blood banks. A study from China describes 237 bacterial agents that are carried by ticks and potentially pathogenic for humans. Based on new evidence, the time required for ticks to transmit Lyme disease and co-infections decreases from 24-48 hours to less than 12 hours (and even as little as 10 minutes) in animals and humans.

8. Transmission of Lyme disease during pregnancy gets increased recognition. Congenital Lyme disease is linked to autism, and prophylactic antibiotic therapy during pregnancy to prevent

Lyme disease transmission is adopted by Lyme-literate practitioners. At the other end of the age spectrum, Lyme disease is linked to Alzheimer's disease, suggesting a possible prevention strategy for this degenerative brain disease.

9. A bizarre chronic skin rash known as Morgellons disease is convincingly linked to Lyme disease. Treatment of Morgellons disease mirrors treatment of CLD with the successful use of prolonged antibiotics.

10. In early 2014, a small study claims that Lyme disease can be sexually transmitted in humans, as it is in animal models. Calls for further investigation of this transmission mode of Lyme disease get louder.

In this issue of *The Lyme Times* you will read more about the many controversial questions related to Lyme disease that are listed above. The calls to answer these questions are getting louder.

Raphael Stricker, MD, a practicing physician in San Francisco, is a past-president of ILADS and a member of the board of Lyme-Disease.org. Email: [rstricker@usmamed.com](mailto:rstricker@usmamed.com).

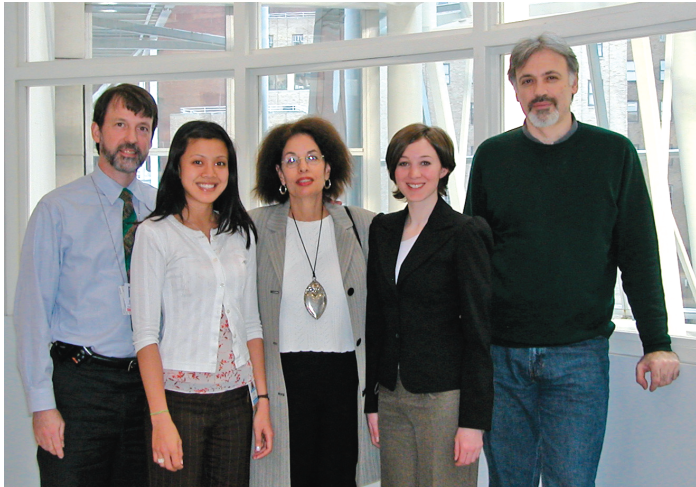


# NIH Clinical trials

## What we learned from four famous trials funded by the National Institutes of Health

By Brian Fallon, MD, MPH

The groundbreaking clinical trials investigating post-treatment Lyme disease syndrome (PTLDS) contributed to our knowledge of tick-borne diseases for several reasons.



Brian Fallon and a team of researchers at Columbia University Medical Center conducted one of the four famous NIH clinical trials in 2003: From left: Dexterrie Ramirez, Kathy Corbera, MD, Megan Romano, and Jordan Slavov, PhD.

All the trials showed that a proportion of patients got better with time (even without medication), i.e., the placebo response. That's good news for patients as it demonstrates that not everyone needs to receive additional antibiotics to get better.

Response to treatment might not be demonstrated immediately after treatment. In the Krupp trial, there was no difference in the percentage of responders to IV ceftriaxone vs IV placebo immediately after treatment; but when these same patients were assessed five months later (off antibiotics), patients receiving IV ceftriaxone were 3.5 times more likely to have meaningful improvement in fatigue compared to those who initially received IV placebo. While antibiotic retreatment can be effective, the impact may not be seen immediately. This finding was later demonstrated again in a European study.

The Krupp trial suggested that a much greater proportion of patients respond to treatment if they are IgG Western blot positive at the time. In this trial, the responder rate was 80% for drug-randomized patients who were IgG Western blot positive vs 46% for those who were not; in other words, patients are almost twice as likely to respond to retreatment if their serologic tests are positive. This finding highlights the importance of careful study design. Had the Krupp trial only recruited individuals who were seronegative, that study may not have shown the positive treatment effect on the primary outcome measure of fatigue observed at six months.

While some have argued that the beneficial response in the Krupp trial should be disregarded, our Lyme encephalopathy

clinical trial (analyzed in the same fashion as the Krupp trial) found nearly identical benefits on the fatigue measure at six months favoring drug over placebo. Finding a nearly identical treatment effect from an independent study conducted at a different university is compelling evidence in support of the validity of the original Krupp results.

Thankfully, the NIH funded these four clinical trials, as without them much less would be known. The NIH should be encouraged to support new clinical trials, however, to draw firm and clear conclusions about the beneficial effects of antibiotic therapy. It is premature to draw conclusions from such a small sample of Lyme patients (37 in the Fallon trial, 55 in Krupp, 51 in Klemmner's seronegative trial, and 78 in Klemmner's seropositive trial).

### Significance of study design

To get a meaningful outcome, it is important to enroll individuals with significant impairment – those who meet a severity cutoff. Too often this key design feature gets violated. For example, the Krupp trial recruited patients who met a severity cutoff on fatigue – and convincingly showed a benefit to drug over placebo. For the Columbia Encephalopathy trial, only patients who met a severity cutoff on cognition were allowed to enroll. While we did not see a sustained improvement in cognition to six months for drug vs placebo, we did see a significantly greater improvement at 12 weeks.

A preset severity cutoff ensures that a true treatment effect can be observed. Simply stating that all who entered the trial reported functional impairment is not the same as saying that all who entered the trial scored at an “impaired level” on the primary outcome measure of interest. Understandably researchers face a huge push to enroll as many people as possible as quickly as possible because such trials cost a lot of money. For the sake of drawing meaningful conclusions, however, impairment must meet a predefined standard.

Among the four NIH trials, the two Klemmner studies had the largest enrollment, (a strong positive) but they were the only trials without a “severity cutoff” for enrollment (a striking negative). Although these trials showed no drug-placebo difference, we don't know what proportion of enrollees would have met a meaningful cutoff for impairment at the start of the study. Future trials must include a severity threshold to maximize the likelihood that their hypothesis is adequately tested.

### Columbia encephalopathy trial

We examined whether certain laboratory biomarkers might predict good or poor outcomes, including the CD 57 marker, inflammatory markers (CRP, ESR), and presence of antibodies against *Babesia* or *Bartonella*. Unfortunately, none of these markers proved helpful in predicting treatment response. Interestingly, the only markers associated with treatment response were clinical markers — not lab test markers. In our trial, we found that the physical exam was one of the best predictors of treatment

*Continued on page 26*



# Understanding Persistence

Columbia University research center pursues a cure for chronic Lyme

By Brian A. Fallon, MD, MPH

The Lyme & Tick-borne Diseases (TBD) Research Center, established in 2007 at the Columbia University Medical Center, benefits from the joint effort of the Lyme Disease Association, the Lyme Research Alliance (previously Time for Lyme), and the trustees of Columbia University. The mission of the Center is to bring together a multidisciplinary team of investigators to study the problem of chronic Lyme disease (CLD) and to serve as an educational resource to the medical community both locally and nationally. Our focus has been to understand the mechanisms of persistence — to examine why patients have persistent symptoms, to identify biomarkers or tests that would be helpful in differentiating the cause, and to identify effective treatments.

One of the great pleasures of this work has been to collaborate with investigators within Columbia University (such as Armin Alaedini, Rafal Tokarz, James Moeller, Serge Cremers, Robert Winchester, Harold Sackeim) as well as those outside such as Steven Schutzer, Madeleine Cunningham, Ben Luft, Tao Liu, Charles Chiu and many others.

On the research front, most satisfying has been our work on the neurologic, neuropsychiatric, and neuroimmunologic aspects of this disease. Research from our Center has identified several key facts about chronic Lyme symptoms.

Patients with post-treatment Lyme disease (PTLD) have objective markers of persistent illness. We have shown this through studies of brain blood flow and metabolism, through studies of immune markers in the peripheral blood and proteomic studies of the spinal fluid, and through clinical studies using neurocognitive testing.

PTLD patients have markers that differentiate Lyme from Chronic Fatigue Syndrome and depression. This finding emerged by proteomic studies of the cerebrospinal fluid and by neurocognitive studies.

While PTLD has brain metabolic deficits, there are also prominent vascular flow



Brian Fallon, MD, (far right), and his multidisciplinary team of investigators continue to study chronic Lyme disease to identify the cause and effective treatments.

deficits. What appears to unite many of these findings is an ongoing abnormally activated immune response and abnormally activated brain networks. Why this aberrant immune activation and brain activation persists and how to down-regulate this response are key questions that shape our new research efforts. Our former NIH postdoctoral fellow Dr. Alla Landa, now an assistant professor at Columbia, is leading a brain imaging, immunologic and treatment study of post-treatment Lyme pain to better understand the Central Sensitization that appears so problematic to these patients. We also have a new NIH postdoctoral fellow who will be establishing a biorepository to investigate Lyme-related and other anti-neuronal antibodies in children, adolescents and young adults as a potential cause of severe neuropsychiatric disease.

## Testing

We have collaborated with researchers in the U.S., England, and Germany to help identify better diagnostic tests for Lyme. These collaborations are in full swing as we embarked this year on a prospective diag-

nostic study that has the advantage of collecting samples from patients with new onset disease from several states and following each of these patients over two years.

With key collaborators nationally and internationally, we are investigating several novel Lyme and co-infection assays — some PCR based, some antibody-based, and some cytokine based. Unlike antibody-based tests, one of the new assays under investigation appears highly sensitive in detecting active infection within days of the tick bite and, importantly, may become negative after the infection has been treated. If results from our study here in the U.S. are as promising as studies in Europe, the Lyme community will have a very useful new diagnostic test in the not too distant future to mark active infection.

Our study is tracking the immune response over time and using state-of-the-art newly developed nationally standardized clinical assessments to more precisely describe the clinical profile of PTLD. This will enable us to explore whether there is a “bi-

*Continued on next page*

# CDC & NIH Webinar

## Persistence of *Borrelia burgdorferi* tops agenda

On May 22, 2014, the Centers for Disease Control and Prevention (CDC) joined the National Institutes of Health (NIH) to sponsor a login/call-in program of speakers highlighting the state of the science surrounding the question of persistence of the *Borrelia burgdorferi* (*Bb*) infection. They proposed that a “better understanding of this topic should lead to improved diagnostics, safer and more durable therapeutics, and improved prevention options.”

The webinar session, convened by Ben Beard, CDC, and moderated by Joseph Breen, NIH, featured a panel of impressive speakers:

- Dr. Stephen Barthold, U.C. Davis. The

Comparative Biology of *Bb* Persistence

- Dr. Linda Bockenstedt, Yale School of Medicine. Design of Animal Studies to Assess *Bb* Persistence
- Dr. Monica Embers, Tulane University. Studies of *Bb* Persistence in the Nonhuman Primate
- Dr. Adriana Marques, NIH. Searching for Persistence of Infection in Lyme disease
- Dr. Linden Hu, Tufts University. *Bb* Persistence: Consensus and Controversy

Questions remain, however. Are residual *Bb* spirochetes capable of causing disease following antibiotic treatment? What are the mechanisms of persistence?

Does persistent infection require live spirochetes or just their DNA? How do we explain the inability to culture *Bb* after antibiotic therapy? Does duration of infection prior to treatment matter? Are there differences in the ability of different strains to persist? Can xenodiagnosis provide a way to study mechanisms of Lyme disease? Among the speakers, Dr. Barthold noted that as *Bb* evolved to survive in the wild without destroying the host, he suspects it can sequester in spaces to evade antibiotics.

View webinar slides at [www.cdc.gov/lyme/pdfs/PersistenceWebinarSlides.pdf](http://www.cdc.gov/lyme/pdfs/PersistenceWebinarSlides.pdf). Read the transcript at [www.cdc.gov/lyme/pdfs/PersistenceTranscript.pdf](http://www.cdc.gov/lyme/pdfs/PersistenceTranscript.pdf)

**Columbia**, from page 7

osignature” in the blood — reflections of disease — that can distinguish recovered Lyme patients from those who have persistent symptoms. Such a biosignature might help clarify the pathophysiology of recovery vs chronicity, thereby enabling more effective treatment interventions.

### Biorepository

Much of our work has been made possible through our biorepository of well-characterized samples from patients with both early and later stages of Lyme. As is now well recognized nationally, such a repository is essential for progress. In addition to the importance of samples from patients with early Lyme, one of the key pressing national needs is for samples from patients with well-established chronic symptoms as well. While the CDC does have a limited supply of samples from patients with Lyme arthritis, there is no central resource for samples from patients with later-disseminated disease. These are hard to gather and require patience, time, and commitment. We are grateful to the Center for providing the resources to allow such an effort.

### Education

On the educational front, with the help of generous donors and the contribution of teaching time by experts in Lyme and TBD, we have recently established a joint Fellowship between the Division of

Family Medicine at the Columbia Medical Center and the Department of Psychiatry. This 2-year fellowship trains a family medicine doctor to become an expert in Lyme and TBD — to think critically, to thoroughly understand the literature on these diseases, to participate in new research studies, to lecture at conferences, and to return to the community as a highly trained professional in the evaluation and treatment of patients with these complex diseases. We continue educating medical students in summer training.

### Annual conference

The national Lyme conference that we organize with the Lyme Disease Association (LDA) continues to be a great pleasure for me personally and a tremendous learning opportunity for all who attend. Over the years our speakers have been luminaries not only in TBD but also in related areas of medicine. Our mission has been not only to teach about what is known but to invite those whose outstanding work in other related areas might have application to TBD. Not only does this conference educate doctors and other healthcare providers but it also provides an opportunity for critical conversation among researchers to allow for new collaborations.

### Federal funding

Perhaps most frustrating to me early

in the Center’s years was the lack of interest by national funding agencies in the problem of chronic Lyme. The tide has turned, however. As a result of outstanding animal research at U.C. Davis, Cornell, Tulane, and other institutions in Europe, it is widely recognized that the *Bb* organism can persist despite antibiotic therapy. That such persisters may be contributing to persistent symptoms is a leading area of investigation. The identification of new organisms, particularly *Borrelia miyamotoi*, raises questions about whether these may be contributing to symptom chronicity or “seronegative” antibiotic responsive Lyme.

A new attitude of collegiality and openness has emerged in the last several years, along with a new interest in private philanthropy to support scientific research. I am hopeful that much will be accomplished in the next five years as a result of major changes in how we view chronicity and TBD.

Brian Fallon, MD, MPH, is the director of the Lyme and Tick-borne Diseases Research Center at Columbia University in New York City and Professor of Clinical Psychiatry at the College of Physicians and Surgeons. His research has focused on neuropsychiatry, the discipline that studies the behavioral and mood effects of diseases that affect the brain. He may be reached at [baf1@columbia.edu](mailto:baf1@columbia.edu).

# Clinical trials

Been there, done that

By Daniel Cameron, MD

In this 25<sup>th</sup> anniversary issue of *The Lyme Times*, Phyllis Mervine and I can both say, “Been there, done that,” when it comes to chronic Lyme disease (CLD) clinical trials. Phyllis was one of two consumers on a review panel to monitor the two Klempner National Institutes of Health (NIH) CLD clinical trials in 1996. The trials validated the severity of CLD an average of 4.7 years after onset despite antibiotic treatment. The Klempner trials also validated the difficulties designing CLD clinical trials.<sup>1,2</sup>

## The Cameron trial

I would like to share my experience as principal investigator of the only community-based double-blind placebo-controlled clinical trial of CLD, referred to as the Cameron trial. I enrolled 84 patients making it the largest clinical trial of CLD. The Fallon, Krupp, and two Klempner trials had previously enrolled 37, 55, 70 and 45 individuals with CLD respectively.

Two-thirds of the 84 individuals in my trial were assigned at random to receive two 500 mg amoxicillin by mouth three times a day for three months, plus one-third placebo. Manifestations of CLD were as severe as those ill with CLD enrolling in the NIH-sponsored trials<sup>3-5</sup> within an average of six months of onset of their Lyme disease. At least 70% in my trial presented with fatigue, painful joints, stiff joints, headaches, poor concentration, sore muscles, disturbed sleep, memory loss, tingling/numbness, irritability, and muscle stiffness.

Individuals randomized to amoxicillin were more likely to improve than the placebo patients (46% vs 18%,  $p=0.007$ )

on a Short Form-36 (SF-36) measure of quality of life (QOL). The 46% success rate for amoxicillin was lower than described in actual practice due in part to shortcomings of the SF-36 as a measure of clinically meaningful benefits. My trial has been criticized for failing to adjust the  $p$  value for the two outcomes - mental and physical health.

The higher than expected dropout rate in my trial offers an insight into the difficulties individuals with CLD face when enrolling in placebo-controlled trials. Individuals with CLD were expected to remain off antibiotics for six months despite symptoms as severe as those described in the Klempner and Fallon trials.

I advised 17 individuals with persistent severe symptoms to leave the placebo-controlled trial within three months to pursue an individualized treatment. I advised an additional six individuals with a positive IgM Western blot test to leave the placebo-controlled trial to avoid the risk that an individual with a persistent infection or reinfection might be randomized to placebo for six months. The decision to drop individuals with a persistent positive IgM Western blot is reinforced by published reports that a positive IgM Western blot test can persist in LD for up to two years.<sup>6-8</sup>

## Conclusions

I concluded that three months of amoxicillin can lead to clinically meaningful benefits without serious adverse events, consistent with the goal of improving patients' Quality of Life (QOL) worthy of further study.<sup>9</sup> In 2012, Fallon came to a similar conclusion, saying that “while repeated IV antibiotic therapy can be effective, safer modes of delivery are needed.”<sup>2</sup>

## Lessons learned

I published the community-based CLD trial in 2008 despite the higher than expected dropout rate to offer insights into designing future innovative compassionate trials. The paper published in the peer-review journal *Medical Minerva* reflected that goal: “Severity of Lyme disease with persistent symptoms”<sup>9</sup>.

Having been there, done that, I remain convinced that we can design innovative trials of CLD to eliminate the design issues in both the NIH and community-based trials. It would be helpful if serious dollars were available to launch such innovative trials.

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Daniel Cameron, MD



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# Embers at a Glance

## Persistent infection in monkeys following antibiotic therapy refutes critical IDSA assumptions

By Lorraine Johnson, JD, MBA

*Editor's Note: A decade after it was conducted, a study of Lyme disease (LD) in Rhesus monkeys was finally published in 2012. It was specifically modeled after the NIH-funded Klemmner trial completed in 2001 that assessed the effectiveness of re-treating patients with chronic Lyme disease (CLD).*

*The idea of conducting a parallel study in monkeys was proposed by an advisory committee to fact-check the human results in the Klemmner trial. The Embers study was funded in 1998. Carl Brenner of the National Research Fund for Tick-Borne Diseases and Phyllis Mervine, president of LymeDisease.org, were patient members of the advisory committee. The hope was that the results of the two studies could be published at the same time. Unfortunately, for reasons yet unknown, publication of the findings of the monkey study, which contradict the Klemmner study, was delayed for 11 years.*

*As this part of the story recently unfolded, Lorraine Johnson posted a 5-part series in her Lyme Policy Wonk blog on [lyme-disease.org](http://lyme-disease.org) explaining the ongoing debate raging over the appropriate treatment of tick-borne diseases. To this day the IDSA continues to deny the existence of persistent infection. Embers is the latest in a number of compelling studies to demonstrate persistence in animal models despite antibiotic treatment.*

In Part 1 of my 4-part series, I identified three critical questions raised by the Embers study. In four blog posts, I explored the implications of the study for chronic LD, early disseminated LD, and antibody testing.

**Q:** Does the IDSA 28-day protocol for treating early disseminated LD (defined as four months after inoculation) eradicate *Bb* or does *Bb* persist notwithstanding short-term treatment?

**A:** *Bb* persisted in 100% of treated monkeys. This suggests that at four months post-infection, 28 days of treatment with doxycycline may be insufficient to eradicate infection. Persistent

infection was demonstrated by other means including PCR, culture, immunofluorescence and xenodiagnosis.

**Q:** Does the Klemmner 90-day treatment protocol (30 days IV Rocephin followed by 60 days oral doxycycline) for treating late disseminated LD (some seven months after inoculation) eradicate *Bb* or does *Bb* persist notwithstanding this treatment?

**A:** *Bb* persisted in approximately 75% of the infected monkeys. This suggests that different treatment approaches - longer or involving different or combined antibiotics - may be more appropriate when LD has been present for more than six months. The authors state: "[T]he use of variable and pulse-dosing regimens of antibiotics may improve efficacy and this warrants testing in an appropriate model."

**Q:** Does the C6 antibody test accurately measure active infection?

**A:** The C6 antibody test detected active infection 100% of the time 27 weeks after inoculation for untreated monkeys. After 27 weeks, however, antibody response began returning to baseline and the test failed to detect active infection in approximately 60% of the untreated monkeys. The antibody test also failed to detect active infection in 100% of the treated monkeys. This suggests that the C6 test is not sensitive enough to detect active disease in those having the disease for more than a few months or those who treated still have persistent infection.

### Findings

The takeaway message from this ground-breaking study is that LD may persist, is hard to treat and difficult to diagnose when negative lab tests do not accurately reflect actual infection.

The significance of the findings cannot be overstated. The study contradicts the foundation of the IDSA guidelines. Drs. Monica Embers, Stephen Barthold, Mario Phillip and colleagues found that the bacterium that cause LD, *Borrelia burgdorferi* (*Bb*), persists in infected monkeys despite

treatment. Its findings further suggest diagnostic limitations based on the EM rash as well as the inappropriateness of IDSA short-term treatment protocols.

The findings discount both the effectiveness of the IDSA 28-day treatment protocol for treating early-disseminated LD and that of the 90-day treatment protocol for treating late-disseminated LD. Since the presence of *Bb* was confirmed by the study, researchers concluded that the C6 antibody test gives false negative results; it is not sensitive enough to detect active disease in those who have been infected for more than a few months or those who have persistent infection despite treatment.

The study concludes: "Reliable procedures to determine that infection has been cleared from Lyme patients have not been established." Since the Embers study suggests that antibody lab tests fail to detect LD roughly 50% of the time, the IDSA testing requirement will leave many patients undiagnosed and untreated.

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Visit [lymedisease.org](http://lymedisease.org) to read the original LPW series of posts on the Embers study.

*LYME POLICY WONK is posted regularly on [lymedisease.org](http://lymedisease.org) by Lorraine Johnson, executive director of LymeDisease.org. You may contact her at [ljohnson@lymedisease.org](mailto:ljohnson@lymedisease.org).*

# Evidence of persistence

## Flawed testing for Bb infection puts patients at risk

By Raphael Stricker, MD, and Lorraine Johnson, JD, MBA

Current laboratory tests widely used for Lyme disease rely on indirect measures of infection based on the immune system's antibody response to *Borrelia burgdorferi*, the bacterium that causes Lyme disease. Antibody tests are highly insensitive and miss a whopping 43% of Lyme cases. In addition, these tests can only determine past exposure to the bacteria, not active infection. They also cannot determine whether the infection has been eradicated.

By relying only on these flawed tests, doctors may believe the patient has been cured when this is not always the case. Researchers conducting extensive tissue biopsies of animals, a technique too invasive for clinical practice, have demonstrated disease persistence. Persistence of the bacteria in humans after only short-term treatment has also been shown through tissue biopsies of the brain, liver, spleen, skin, eye, bladder, and lymph nodes in humans.

Evidence for persistent <i>B. burgdorferi</i> infection following at least 2-4 weeks of treatment for Lyme disease in humans*			
Study Reference	Study Origin	Persistence Shown By	Sample Source
Weber (1988)	Europe	Histology	Brain, liver
Schmidli (1988)	Europe	Culture	Synovial fluid
Cimmino (1989)	Europe	Histology	Spleen
Preac-Mursic (1989)	Europe	Culture	Skin, CSF
Pfister (1991)	Europe	Culture	CSF
Strle (1993)	Europe	Culture	Skin
Preac-Mursic (1993)	Europe	Culture	Iris
Hauptl (1993)	Europe	Culture	Ligament
Strle (1996)	Europe	Culture	Skin
Preac-Mursic (1996)	Europe	Culture	Skin, CSF
Oksi (1996)	Europe	Culture/PCR	CSF/ Brain, synovial fluid
Priem (1998)	Europe	PCR	Synovial fluid
Oksi (1999)	Europe	Culture, PCR	Blood
Breier (2001)	Europe	Culture	Skin
Hunfeld (2005)	Europe	Culture	Skin
Hudson (1998)	Australia	Culture, PCR	Skin
Steere (1988)	USA	Histology	Synovial
Kirsch (1988)	USA	Histology	Lymph node
Liegner (1993)	USA	Histology/PCR	Skin/ Blood
Battafarano (1993)	USA	Histology, PCR	Synovial fluid
Chancellor (1993)	USA	Histology	Bladder
Nocton (1994)	USA	PCR	Synovial fluid
Shadick (1994)	USA	Histology	Brain
Masters (1994)	USA	Culture	Blood
Lawrence (1995)	USA	PCR	CSF
Bayer (1996)	USA	PCR	Urine
Nocton (1996)	USA	PCR	CSF

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# Embers Study Contradicts IDSA Guidelines

Among many reasons the IDSA guidelines should be revised is the famous monkey trial

By Lorraine Johnson, JD, MBA

## Mandatory Antibody Lab Tests

### IDSA

Clinical findings are sufficient for the diagnosis of erythema migrans (EM), but insufficient alone for diagnosis of extracutaneous manifestations of LD. Diagnostic testing performed in laboratories with excellent quality-control procedures is required for confirmation of extracutaneous LD.

### Embers

The C6 antibody test failed to detect LD in 50% of monkeys with persistent infection over time despite direct evidence of the bacteria. This means the test is not sensitive enough to be required for diagnosis.

## Treatment of Early-Disseminated LD

### IDSA

Doxycycline, amoxicillin, and cefuroxime axetil are effective for the treatment of early LD. Most patients respond promptly and completely. Some individuals have persistent subjective complaints, despite receiving therapy that otherwise appears curative. Less than 10% of individuals do not respond to antibiotic therapy, as evidenced by the presence of objective clinical manifestations, and rarely is re-treatment required.

### Embers

All infected monkeys treated with this protocol failed to clear the infection. Early disseminated was defined as four months after inoculation. This means short-term protocols are expected to fail in monkeys with early disseminated LD.

## Bb Persistence

### IDSA

There is no convincing biologic evidence for the existence of symptomatic chronic *Bb* infection among patients after receipt of recommended treatment regimens for LD.

### Embers

Embers found direct evidence of persistence in all monkeys treated with 28 days of antibiotics and in eight out of 11

treated with 90-day Klemperer protocol. This means *Bb* persistence is the norm in monkeys.

## Effectiveness of Antibiotic Therapy

### IDSA

Antibiotic therapy has not proven useful and is not recommended for patients with chronic (six months) subjective symptoms after recommended treatment regimens for LD.

### Embers

Three of 11 infected monkeys cleared the infection using the 90-day Klemperer protocol. This means that 90 days of antibiotics worked in about 25% of the monkeys. It suggests that rather than being ineffective, the course of antibiotics used may be insufficient.

## Recommended Treatment Modalities

### IDSA

Because of a lack of biologic plausibility, lack of efficacy, absence of supporting data, or the potential for harm to the patient, the following are not recommended for treatment of patients with any manifestation of LD: combinations of antimicrobials, pulsed-dosing, long-term antibiotic therapy.

### Embers

The use of variable and pulse-dosing regimens of antibiotics may improve efficacy and warrants testing. This means that non-standard approaches may improve efficacy. Note that 90 days was better than 28 in the Embers study.

## Mechanisms of Persistence

### IDSA

LD lacks characteristics of other infections that justify longer treatment courses, such as infections in immunodeficient hosts; infections in which a pathogen is inhibited but not killed by antimicrobial therapy or in which available antimicrobials are minimally active *in vitro*; infections caused by an intracellular pathogen, those involving a biofilm, a heart valve, or clinical site in which there is ischemia, a foreign body, a sequestrum, or frank pus. The cystic

forms of *Bb* seen under certain growth conditions *in vitro* have not been shown to have any clinical significance.

### Embers

The nature of the persistent organisms and the acquisition of tolerance to antibiotics are questions that need to be addressed. The *Bb* spirochete is known to invade collagenous tissue as a possible mechanism of immune evasion. The fact that organisms can persist in the presence of antibiotics such as penicillin and cephalosporins (ceftriaxone) that interfere with cell wall synthesis appears to stem from their ability to enter a dormant, non-dividing state, thus avoiding the need for cell wall synthesis to continue growth. A persister phenotype may be responsible for the recalcitrance of persisting spirochetes evident by previous studies with mice and dogs, and by those presented in this report. This means there are lots of plausible mechanisms for persistence.

## Decline of Antibody Levels

### IDSA

Additional compelling evidence against the hypothesis that persistent symptoms are the result of persistent infection is the fact that the concentrations of antibodies against *Bb* in many patients diminish to undetectable levels. The panel is unaware of any chronic infection in which antibody titers diminish despite persistence of the causative organism.

### Embers

In all of the infected animals, the C6 antibody index rose steeply within the first 5–8 weeks post-inoculation (PI). Thereafter, the responses fit into three patterns, depending on whether the animals were or were not treated with antibiotics. In the treated group, the response declined steadily in all animals during treatment and reached background levels at the endpoint. In contrast, the responses of the untreated group remained either largely unchanged (5 out of 12 animals), or returned to background levels (7 out of 12 animals) but not in parallel with the kinetics of the treated group's decline in specific antibodies.

# ILADS Treatment Guidelines Revised

For clinical management of tick bites, erythema migrans rashes and persistent disease

By Daniel J Cameron, MD, Lorraine B Johnson, JD, MBA and Elizabeth L Maloney, MD

Evidence-based guidelines for the management of patients with Lyme disease were developed by the International Lyme and Associated Diseases Society (ILADS).<sup>1</sup>

The guidelines address three clinical questions: the usefulness of antibiotic prophylaxis for known tick bites; the effectiveness of erythema migrans

Evaluation system. ILADS guidelines are not intended to be the sole source of guidance in managing Lyme disease, and they should not be viewed as a substitute for clinical judgment nor used to establish treatment protocols.

Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values [1] (*See end references\_Ed.*). The International Lyme and Asso-

ciated Diseases Society (ILADS) anticipates performing GRADE assessments on additional topics related to the diagnosis and treatment of tick-borne diseases in the future.

The GRADE scheme classifies the quality of the evidence as high, moderate, low or very low. The quality of evidence from randomized controlled trials (RCTs) is initially rated as high, but may be downgraded based on five limitations: study bias, publication bias, indirectness (generalizability), imprecision and inconsistency. Evidence quality from observational studies is generally low, but may be upgraded based on a large effect or dose-response gradient [6]. Rather than labeling recommendations as strong or weak, these guidelines use the terms “recommendation” or “strong recommendation” for or against a medical intervention. The GRADE scheme itself is a continually evolving system. These guidelines attempt to incorporate the current state of GRADE.

Although Lyme disease is not rare, the treatment of Lyme disease has not attracted pharmaceutical interest, and the evidence base for treating Lyme disease is best described as sparse, conflicting and emerging. For example, Hayes and Mead of the CDC performed a systematic review of the evidence regarding the treatment of late neurologic Lyme disease and their GRADE-based evaluation rated the quality of the evidence as very low [7]. The ILADS guidelines working group reached a similar conclusion after assessing the research evidence pertaining to its three clinical questions, rating the evidence quality as very low. The low quality of evidence seen in Lyme disease is consistent with the evidence base for the field as a whole. Indeed, the majority of recommendations in infectious disease medicine generally are based on low-quality evidence [8].



Betty Maloney, MD, a co-author of the revised ILADS treatment guidelines, summarized the evidence-based approach for attendees at the 2014 conference in Washington, DC. Dan Cameron, MD, (right), president of ILADS, is the Guidelines' author for correspondence.

treatment; and the role of antibiotic retreatment in patients with persistent manifestations of Lyme disease. Healthcare providers who evaluate and manage patients with Lyme disease are the intended users of the new ILADS guidelines, which replace those issued in 2004. These clinical practice guidelines are intended to assist clinicians by presenting evidence-based treatment recommendations, which follow the Grading of Recommendations Assessment, Development and

and Evaluation (GRADE) system as its basis for evidence assessment and the development of recommendations to ensure a transparent and trustworthy guideline process [2–5].

These guidelines address three fundamental treatment questions: the usefulness of antibiotic prophylaxis for known tick bites, the effectiveness of erythema migrans (EM) treatment and the role of antibiotic retreatment in patients with persistent manifestations of

<sup>1</sup> Expert Rev. Anti Infect. Ther. 12(9), 1103–1135 (2014)



When high-quality evidence is not available, guideline panels are faced with making recommendations based on low or very low quality evidence. Although evidence alone is never sufficient to determine guideline recommendations [2], when evidence is weak, the values of those on the panel, including differing specialty perspectives, may carry more weight [8]. One of the goals of the GRADE scheme is to make transparent the value judgments underlying recommendations.

When the evidence base is of low or very low quality, guideline panels should be circumspect about making strong recommendations to avoid encouraging uniform practices that are not in the patient's best interest and to ensure that research regarding benefits and risks is not suppressed [8]. Guidelines panels should also make the role of their values and those of patients in recommendations explicit and should promote informing and empowering patients to engage in shared decision-making [8].

This panel has placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary [9].

In addition, this panel believes the goals of medical care in Lyme disease

are to prevent the illness whenever possible and to cure the illness when it occurs. When this is not possible, the panel believes the emphasis for treatment should be on reducing patient morbidity. Therefore, the panel placed a high value on reducing patient risks for developing the chronic form

treating the treatable [10]. To this end, the panel valued primary prevention (by effectively treating a tick bite), secondary prevention (by treating an EM rash sufficiently so as to restore health and prevent disease progression), and tertiary prevention (by treating patients whose illness may be responsive to additional therapy, thereby reducing the morbidity associated with the chronic forms of the disease).

ILADS is mindful of the role of patient preferences and values in GRADE as well as the IOM's call for patient-centered care that is responsive to the needs, values and expressed preferences of individual patients [11]. Patient-centered care focuses on achieving treatment outcomes that patients value [11], including the restoration of health, prevention of health deterioration and the provision of treatments that have the potential to improve quality of life (QoL). To

facilitate the development of treatment plans addressing the unique circumstances and values of individual patients, patient-centered care encourages shared medical decision-making.

Shared decision-making takes into account the best scientific evidence



California Lyme Disease Association

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**LDA News**

**Bestselling Author Amy Tan Supports LymeAid4Kids Fund**

**Children without insurance will benefit**

Jackson, October 27, 2003—The Lyme Disease Association (LDA), a national non-profit organization dedicated to Lyme disease education, prevention, research, and patient support, announced the creation of LymeAid4Kids, a fund administered through the LDA and designed to be used by families with no insurance who need to have their children properly evaluated for possible Lyme disease.

Internationally acclaimed author Amy Tan, whose books *The Joy Luck Club*

See LymeAid4Kids on page 31

**ILADS Publishes New Treatment Guidelines**

**Evidence-based world-wide standards**

Bethesda, Maryland - The International Lyme and Associated Diseases Society (ILADS) has published new guidelines for diagnosing and treating Lyme disease, to help physicians combat the fastest growing vector-borne disease in the United States. The guidelines are necessary to address the high rate of treatment failures and relapses seen using standardized short-term treatment protocols. The guidelines, which are evidence-based and peer-reviewed, recommend that the treatment be individualized based on the clinical course of the patient.

In addition, the guidelines emphasize that diagnosis must be made clinically, with laboratory tests playing a supportive role. The ticks that carry Lyme disease can also carry a number of other serious diseases, and the guidelines also stress the importance of diagnosing and treating any coinfections.

ILADS criticized guidelines calling for a standardized short-term treatment as ineffective and premature. "Treatment response is highly variable," said ILADS president Dr. Steven Phillips of Connecticut.

See Guidelines on page 35

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**Inside...**

**LDA reps meet with Health & Human Services**

**page 32**

**Hundreds Attend Connecticut Hearing**

by Paula Capasso

Hartford - On Thursday, January 29, hundreds of patients, physicians, scientists and government officials packed into an overflowing room at the Legislative office building in Hartford, Connecticut, to participate in a hearing convened by Connecticut Attorney General Richard Blumenthal and Public Health Commissioner Robert Galvin, MD, in response to thousands of calls letters and petitions voicing concerns about the difficulties surrounding the diagnosis, treatment and reporting of Lyme disease.

Lyme disease was first recognized

See Hearing on page 24

available, clinical expertise, and the role of patient's values and preferences in deciding among available treatment options [12,13]. Despite the terminology, decision-making is not truly shared between clinician and patient; the responsibility for choosing between options remains with the clinician.

To effectively engage in shared decision-making, patients need to understand the implications of their choices. Physicians should not assume that patients share their values in making risk/benefit determinations. Studies have demonstrated that patients and physicians may have very different assessments of preferences and risk tolerance [8]. In addition, there is considerable variation among individual patients in their tolerance for risk and in what they regard as a valuable benefit. Patients may also tolerate more risk when they have severe presentations of disease or when there are no other treatment options available [14].

In the GRADE system, recommendations take into account not only the quality of the evidence, but also the balance between benefits and harms and patient values and preferences [5]. In instances where a GRADE evaluation concludes that the evidence quality is low or very low or that there are trade-offs between risks and benefits that depend on the values of the individual, the GRADE system recommends that recommendations should identify a range of therapeutic options and acknowledge that different choices may be appropriate for different patients.

In assessing the balance between the risks and benefits of antibiotic treatments for Lyme disease, the panel weighed the burden of disease, the magnitude and relative importance of patient-centered outcomes as well as treatment-associated risks and the risks attendant on not treating. The panel acknowledged that the health-related and economic consequences of chronic disease are enormous for individuals, families, communities, healthcare systems and the nation, im-

pacting the well-being of individuals, family functioning and economic productivity [15–18]. Therefore, the panel recommends that patients be informed of the risks and benefits of treating and not treating, including the risks of continuing to suffer significant morbidity or permitting a serious systemic infection to progress.

The panel assessed risks and benefits of treatment on a generalized basis. In addition, the panel recognizes that there is a need for clinicians, in the context of shared medical decision-making, to engage in a risk–benefit assessment that reflects the individual values of the particular patient.

Guidelines for the diagnosis and treatment of Lyme disease are conflicting. Supplementary material can be found online at [informahealthcare.com/suppl/10.1586/14787210.2014.940900](http://informahealthcare.com/suppl/10.1586/14787210.2014.940900). The IOM recently highlighted the conflicting Lyme guidelines of ILADS and the Infectious Diseases Society of America (IDSA) and noted that the National Guidelines Clearinghouse has identified at least 25 different conditions in which conflicting guidelines exist [19]. According to the IOM, conflicting guidelines most often arise when evidence is weak, organizations use different assessment schemes, or guideline developers place different values on the benefits and harms of interventions [20].

The adoption of GRADE by ILADS is, in part, an effort to use the same assessment scheme as the IDSA, although it should be noted that the IDSA's Lyme disease guidelines listed on the National Guidelines Clearinghouse were originally published in 2006 and do not reflect the organization's adoption of GRADE for guideline revisions after 2008. Additionally, the use of GRADE is one element of ILADS' compliance with the eight standards identified by the IOM as being integral to creating trustworthy treatment guidelines.

The ILADS guidelines were developed in phases. A working group identified three questions to address,

conducted a literature search and subsequent assessment of the evidence quality and evaluated the role of patient preferences and values for each question. A preliminary draft of the guidelines was sent to the full guidelines panel and, subsequently, outside reviewers for review and comment, with the document being further refined. The panel and working group members were required to disclose potential financial conflicts of interest. The full panel, which consisted of the board of directors of ILADS, determined that fee for service payments are inherent in the provision of health care and did not disqualify experienced clinicians from serving on the guideline panel nor did serving on the boards of non-profit organizations related to Lyme disease. Financial relationships exceeding \$10,000 per year that were not intrinsic to medical practice were viewed as potential conflicts; no panel or working group members held such financial conflicts of interest.

### Scope of problem

The burden of Lyme disease for individuals and society remains high. Despite the availability of numerous preventative measures [21,22], the incidence of acute Lyme disease is significant. The CDC currently estimates that the annual number of new cases of Lyme disease in the U.S. exceeds 300,000 [23]; how these individual patients fare is an important consideration, and ILADS is primarily interested in preventing and reducing the morbidity associated with chronic disease. Although some prospective studies found long-term outcomes were good, many had significant limitations [24–26]. There is substantial evidence of varying quality demonstrating that the severity [16–18,27–29], duration [16,18,27,29,30] and cost [15,31] of persistent manifestations of Lyme disease can be profound. While the etiology of these manifestations is uncertain, their impact is clear. Two retrospective cohorts [27,30], two case series [32,33], a meta-analysis [34], two

prospective European studies, and four NIH-sponsored clinical trials [16–18] describe significant long-term consequences of Lyme disease. Findings include:

- Thirty-four percent of a population-based, retrospective cohort were ill an average of 6.2 years after antibiotic treatment [27];
- Sixty-two percent of a retrospective evaluation of 215 Lyme disease patients from Westchester County, NY, remained ill an average of 3.2 years after antibiotic treatment [30];
- A meta-analysis of 504 patients treated for Lyme disease found this group had more fatigue, musculoskeletal pain and neurocognitive difficulties than 530 controls [34]. Additionally, it demonstrated that persistent Lyme disease symptoms were a distinct set of symptoms, which differed from those of fibromyalgia, chronic fatigue syndrome and depression [34];
- Among 23 European pediatric patients with objective findings of Lyme neuroborreliosis sequelae, daily activities or school performance were negatively impacted in 10 (43%) [28];
- A European study of adults treated for neuroborreliosis found that at 30 months post-treatment, 16% were cognitively impaired [29];
- On entrance, patients enrolling in the four NIH-sponsored clinical trials on antibiotic retreatment had experienced poor long-term outcomes from their prior therapy. Participants in the two trials by Klempner *et al.* had persistent symptoms, which were sufficiently severe as to interfere with daily functioning [18];
- Using a combined total of 22 standardized measures of QoL, fatigue, pain and cognition [16–18], the investigators of the four NIH-sponsored retreatment trials documented that the patients' QoL was consistently worse than

that of control populations [16–18] and equivalent to that of patients with congestive heart failure [18]; pain levels were similar to those of post-surgical patients, and fatigue was on par with that seen in multiple sclerosis [16,18]. TABLE 1 compares the QoL scores of the NIH Lyme disease participants at the time of their study enrollment to those of patients with other chronic diseases, including diabetes, heart disease, depression, osteoarthritis, rheumatoid arthritis, lupus, fibromyalgia and epilepsy [35–40].

### Executive summary of treatment recommendations

With the goal of fostering evidence-based, patient-centered care for patients with Lyme disease, the panel performed a deliberate GRADE assessment of the pertinent trial evidence regarding three fundamental treatment questions and reviewed the risks and benefits of antibiotic therapies used in the treatment of Lyme disease. The panel also considered the ramifications of withholding antibiotic treatments or using non-curative regimens and acknowledged that either may result in a significant disease burden. Following the completion of these activities, the panel drew several conclusions regarding the treatment of Lyme disease.

Based on these conclusions, the panel formulated treatment recommendations reflecting ILADS values and patient preferences. Recommendations for the individual clinical questions are summarized here. A detailed discussion of each question, including the complete GRADE analysis, the risk-benefit evaluation, ILADS statement of values and the subsequent individual treatment recommendations, in full, follows this summary.

**QUESTION 1: DOES A SINGLE 200 MG DOSE OF DOXYCYCLINE FOLLOWING A TICK BITE PROVIDE EFFECTIVE PROPHYLAXIS FOR LYME DISEASE?**

### Organizational values

The panel placed a high value on preventing disease, thereby avoiding both the unnecessary progression from a potentially preventable infection to one that is chronic and associated with significant morbidity and costs. The panel placed a high value on not causing the abrogation of the immune response. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary.

#### Recommendation 1a

Clinicians should not use a single 200 mg dose of doxycycline for Lyme disease prophylaxis

**Recommendation:** very low-quality evidence.

**Role of patient preferences:** low. The relative trade-offs between risks and benefits are clear enough that most patients will place a high value on avoiding a seronegative state and its attendant delays in diagnosis and treatment.

#### Recommendation 1b

Clinicians should promptly offer antibiotic prophylaxis for known *Ixodes* tick bites in which there is evidence of tick feeding, regardless of the degree of tick engorgement or the infection rate in the local tick population. The preferred regimen is 100–200 mg of doxycycline, twice daily for 20 days. Other treatment options may be appropriate on an individualized basis

**Recommendation:** very low-quality evidence.

**Role of patient preferences:** moderate. Most patients will place a high value on preventing chronic illness. However, some patients will value avoiding unnecessary antibiotics and prefer to not treat a tick bite prophylactically. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

### Recommendation 1c

During the initial visit, clinicians should educate patients regarding the prevention of future tick bites, the potential manifestations of both early and late Lyme disease and the manifestations of the other tick-borne diseases that may have been contracted as a result of the recent bite. Patients receiving antibiotic prophylaxis should also be given information describing the symptoms and signs of a *Clostridium difficile* infection and the preventative effect of probiotics. Patients should be encouraged to immediately report the occurrence of any and all tick-borne disease manifestations and manifestations suggestive of a *C. difficile* infection

**Recommendation:** very low-quality evidence.

**Role of patient preferences:** low. The benefits of educating patients about potential disease manifestations clearly outweigh any attendant risks associated with education.

**QUESTION 2: SHOULD THE TREATMENT OF AN EM RASH BE RESTRICTED TO 20 OR FEWER DAYS OF ORAL AZITHROMYCIN, CEFUROXIME, DOXYCYCLINE AND PHENOXYMETHYL-PENICILLIN/AMOXICILLIN?**

### Organizational values

The panel placed a high value on avoiding both the unnecessary progression from a potentially curable infection to one that is chronic and the morbidity and costs associated with chronic disease. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary.

### Recommendation 2a

Treatment regimens of 20 or fewer days of phenoxymethyl-penicillin, amoxicillin, cefuroxime or doxycycline and 10 or fewer days of azithromycin

are not recommended for patients with EM rashes because failure rates in the clinical trials were unacceptably high. Failure to fully eradicate the infection may result in the development of a chronic form of Lyme disease, exposing patients to its attendant morbidity and costs, which can be quite significant.

**Recommendation:** very low-quality evidence.

**Role of patient preferences:** moderate. Although many patients will value avoiding the risk of treatment failure over a potentially modest increase in the risk of significant adverse events that may be associated with longer treatment durations, others may prefer to avoid the additional risks of longer treatment. Clinicians should inform patients that the combined failure rate for the individual agents investigated in the previously discussed EM trials were judged by this panel to be unacceptably high when antibiotic treatment was restricted to 20 or fewer days (provide the appropriate value for each); the evidence supporting the use of longer treatment durations is limited and of low quality [41–43] and increases in antibiotic duration may increase the risk of antibiotic-associated adverse events, although the risks associated with oral antibiotics are low and some of this risk can be mitigated by the concomitant use of probiotics [44,45]. Treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

### Recommendation 2b

Clinicians should prescribe amoxicillin, cefuroxime or doxycycline as first-line agents for the treatment of EM. Azithromycin is also an acceptable agent, particularly in Europe, where trials demonstrated it either outperformed or was as effective as the other first-line agents [46–49]. Initial antibiotic therapy should employ 4–6 weeks of amoxicillin 1500–2000 mg daily in divided doses, cefuroxime 500 mg twice daily or doxycycline 100 mg twice daily or a minimum of 21 days

of azithromycin 250–500 mg daily. Pediatric dosing for the individual agents is as follows: amoxicillin 50 mg/kg/day in three divided doses, with a maximal daily dose of 1500 mg; cefuroxime 20–30 mg/kg/day in two divided doses, with a maximal daily dose of 1000 mg and azithromycin 10 mg/kg on day 1 then 5–10 mg/kg daily, with a maximal daily dose of 500 mg. For children 8 years and older, doxycycline is an additional option. Doxycycline is dosed at 4 mg/kg/day in two divided doses, with a maximal daily dose of 200 mg. Higher daily doses of the individual agents may be appropriate in adolescents.

Selection of the antibiotic agent and dose for an individual patient should take several factors into account. In the absence of contraindications, doxycycline is preferred when concomitant *Anaplasma* or *Ehrlichia* infections are possibilities. Other considerations include the duration [27,32,50] and severity [50–53] of symptoms, medication tolerability, patient age, pregnancy status, co-morbidities, recent or current corticosteroid use [54,55] cost, the need for lifestyle adjustments to accommodate certain antibiotics and patient preferences. Variations in patient-specific details and the limitations of the evidence imply that clinicians may, in a variety of circumstances, need to select therapeutic regimens utilizing higher doses, longer durations or combinations of first-line agents.

**Recommendation:** very low-quality evidence.

**Role of patient preferences:** moderate. See recommendation 2a.

### Recommendation 2c

Clinicians should provide ongoing assessments to detect evidence of disease persistence, progression or relapse or the presence of other tick-borne diseases. Lacking a test of cure, ongoing assessments are crucial for determining if treatment has been clinically effective. The first assessment should immediately follow the completion of therapy and subsequent eval-

uations should occur on an as-needed basis.

**Recommendation:** very low-quality evidence.

**Role of patient preferences:** low. The benefits of monitoring the response to treatment clearly outweigh any attendant risks associated with monitoring.

### Recommendation 2d

Clinicians should continue antibiotic therapy for patients who have not fully recovered by the completion of active therapy. Ongoing symptoms at the completion of active therapy were associated with an increased risk of long-term failure in some trials and therefore clinicians should not assume that time alone will resolve symptoms. There is a wide range of options, and choices must be individualized, based on the strength of the patient's initial response.

Strong-to-moderate responses favor extending the duration of therapy of the initial agent; modest responses may prompt an increase in the dose of the original antibiotic or a switch to a different first-line agent or tetracycline. Minimal or absent responses suggest a need for a combination of first-line agents, which includes at least one that is able to effectively reach intracellular compartments; injectable penicillin G benzathine (Bicillin LA) or intravenous (iv.) ceftriaxone are other options. Disease progression or recurrence suggests that the iv. antibiotics or injectable penicillin G benzathine, as discussed previously, may be required. For patients requiring antibiotic therapy beyond the initial treatment period, subsequent decisions regarding the modification or discontinuation of treatment should be based on the therapeutic response and treatment goals. Additionally, minimal or absent responses and disease progression require a re-evaluation of the original diagnosis (see remarks following Recommendation 2f).

**Recommendation:** very low-quality evidence.

**Role of patient preferences:** moderate. While most patients will place a high value on the potential of regaining their pre-morbid health status and preventing chronic illness by continuing treatment, a substantial portion may also value avoiding unnecessary antibiotics. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

### Recommendation 2e

Clinicians should retreat patients who were successfully treated initially but subsequently relapse or have evidence of disease progression. Therapeutic options include repeating the initial agent, changing to another oral agent or instituting injectable penicillin G benzathine or iv. ceftriaxone therapy. Choices must be individualized and based on several factors, including the initial response to treatment; the time to relapse or progression; the current disease severity and the level of QoL impairments.

Prior to instituting additional antibiotic therapy, the original diagnosis should be reassessed and clinicians should evaluate patients for other potential causes that would result in the apparent relapse or progression of symptoms and/or findings (see remarks following Recommendation 2f). The presence of other tick-borne diseases, in particular, should be investigated if that had not already been done.

Following a long period of disease latency, minimal manifestations causing little deterioration in the patient's QoL favor continued observation or repeating therapy with the initial agent; mild manifestations or QoL impairments may prompt a switch to a different first-line agent, tetracycline or the use of a combination of first-line agents. Disease relapse or progression with mild manifestations or QoL impairments occurring within a few months of treatment suggests a need for longer regimens using either tetracycline, a combination of oral first-line agents, injectable penicillin G ben-

zathine or iv. ceftriaxone. Regardless of the duration of disease latency, when disease manifestations or QoL impairments are significant or rapidly progressive, injectable penicillin G benzathine or iv. ceftriaxone may be required. Subsequent decisions regarding the modification or discontinuation of a patient's treatment should be based on individual therapeutic response and preferences

**Recommendation:** very low-quality evidence.

**Role of patient preferences:** high. While most patients will place a high value on the potential of regaining their pre-morbid health status and improving their QoL and preventing chronic disease through continued antibiotic treatment, a substantial portion will also value avoiding potentially unnecessary antibiotics. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

### Recommendation 2f

Clinicians should educate patients regarding the potential manifestations of Lyme disease, carefully explaining that disease latency can be prolonged. Education should also include information on preventing future bites, the manifestations of the other tick-borne diseases that they may have contracted as well as the symptoms and signs of a *C. difficile* infection and the preventative effect of probiotics. Patients should be encouraged to immediately report the occurrence of any recurrent or newly developing manifestation of Lyme disease as well as those suggestive of other tick-borne diseases or a *C. difficile* infection. Clinicians should emphasize that the need to report manifestations of tick-borne diseases never expires.

**Recommendation:** very low-quality evidence.

**Role of patient preferences:** low. The benefits of educating patients about potential disease manifestations clearly outweigh any attendant risks associated

with education.

**QUESTION 3. SHOULD PATIENTS WITH PERSISTENT MANIFESTATIONS OF LYME DISEASE BE RETREATED WITH ANTIBIOTICS?**

**Organizational values**

The panel placed a high value on reducing the morbidity associated with chronic Lyme disease and improving the patient's QoL as well as on the need for individualized risk/benefit assessment and informed shared decision-making. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong compelling evidence to the contrary.

**Recommendation 3a**

Clinicians should discuss antibiotic retreatment with all patients who have persistent manifestations of Lyme disease. These discussions should provide patient-specific risk-benefit assessments for each treatment option and include information regarding *C. difficile* infection and the preventative effect of probiotics (although none of the subjects in the retreatment trials developed *C. difficile* infection).

**Strong recommendation:** very low-quality evidence. Note: In GRADE, a strong recommendation may be made in the face of very low-quality evidence when the risk-benefit analysis favors a particular intervention such that most patients would make the same choice.

**Role of patient preferences:** low. The benefits of educating patients about the potential benefits of retreatment and the risks associated with various treatment options, including not treating, clearly outweigh any attendant risks associated with education.

**Recommendation 3b**

While continued observation alone is an option for patients with few manifestations, minimal QoL impairments and no evidence of disease progression,

in the panel's judgment, antibiotic retreatment will prove to be appropriate for the majority of patients who remain ill. Prior to instituting antibiotic retreatment, the original Lyme disease diagnosis should be reassessed and clinicians should evaluate the patient for other potential causes of persistent disease manifestations. The presence of other tick-borne illnesses should be investigated if that had not already been done. Additionally, clinicians and their patients should jointly define what constitutes an adequate therapeutic trial for this particular set of circumstances.

When antibiotic retreatment is undertaken, clinicians should initiate treatment with 4-6 weeks of the selected antibiotic; this time span is well within the treatment duration parameters of the retreatment trials. Variations in patient-specific details and the limitations of the evidence imply that the proposed duration is a starting point and clinicians may, in a variety of circumstances, need to select therapeutic regimens of longer duration.

Treatment options are extensive and choices must be individualized. Each of these options would benefit from further study followed by a GRADE assessment of the evidence and consideration of associated risks and benefits, but until this information is available, clinicians may act on the currently available evidence.

In choosing between regimens, clinicians should consider the patient's responsiveness to previous treatment for Lyme disease, whether the illness is progressing and the rate of this progression; whether untreated co-infections are present; whether the patient has impaired immune system functioning or has received immunosuppressant corticosteroids and whether other co-morbidities or conditions would impact antibiotic selection or efficacy. Clinicians should also weigh the extent to which the illness interferes with the patient's QoL, including their ability to fully participate in work, school, social and fam-

ily-related activities and the strength of their initial response against the risks associated with the various therapeutic options. Antibiotic selection should also consider medication tolerability, cost, the need for lifestyle adjustments to accommodate the medication and patient preferences.

For patients with mild impairments who had a strong-to-moderate response to the initial antibiotic, repeat use of that agent is favored. Patients with moderate impairments or only a modest response to the initial antibiotic may benefit from switching to a different agent or combination of agents. For patients with significant impairments and/or a minimal or absent therapeutic response, a combination of oral antibiotics, injectable penicillin G benzathine or iv. ceftriaxone (with the latter two used alone or in combination with other agents) is preferred. For patients who experienced disease progression despite earlier therapy, treatment with injectable penicillin G benzathine or iv. ceftriaxone, alone or in combination with other antibiotics, is advisable. Additionally, minimal or absent responses and disease progression require a re-evaluation of the original diagnosis.

**Recommendation:** very low-quality evidence.

**Role of patient preferences:** high. The heterogeneous nature of the patient population seen in clinical practice, particularly with regard to variations in disease severity, QoL impairments and aversion to treatment-related risk is likely to affect the risk-benefit assessment. Although many patients will value the opportunity to improve their individual QoL through antibiotic treatment over the risk of adverse events, others may prefer to avoid the risks associated with treatment. Hence, treatment options, including their associated risks and benefits, should be discussed with the patient in the context of shared medical decision-making.

**Recommendation 3c**

Clinicians should re-assess pa-

**Table 1. Long-term consequences (or impairments) of Lyme disease.**

Clinical trials		Lyme disease cases mean (SD)	Healthy controls mean (SD)	Impairments in other illnesses – (mean)	Ref.
<i>QoL PCS – range 1–100 (the lower the score, the worse the QoL)<sup>†</sup></i>					
PCS	Klempner et al., seropositive	33.1 (9.9)	50 (10)	Diabetes (42), heart disease (39), depression (45), osteoarthritis	[18,202]
PCS	Klempner et al., seropositive	35.8 (8.8)	50 (10)	(39) and rheumatoid arthritis	[18]
PCS	Cameron recurrent	39.6 (9.7)	50 (10)	(42)	[87]
PCS	Fallon et al.	37.1 (8.6)	55.9 (3.6)		[16,38]
<i>QoL MCS – range 1–100 (the lower the score, the worse the QoL)<sup>‡</sup></i>					
MCS	Klempner et al., seropositive	43.4 (11.6)	50 (10)	Diabetes (48), heart disease (49), depression (37), osteoarthritis	[18]
MCS	Klempner et al., seropositive	46.7 (9.7)	50 (10)	(49) and rheumatoid arthritis	[18]
MCS	Cameron recurrent	35.9 (14.6)	50 (10)	(48)	[87]
MCS	Fallon et al.	39.2 (11.6)	56.2 (2.9) <sup>‡</sup>		[16,38]
<i>Fatigue – FSS – range 0–7, severe fatigue (&gt;4.0)<sup>§</sup></i>					
FSS	Krupp et al., post-treatment	5.7 (1.4)	2.1 (0.5)	ALS (4.35), multiple sclerosis (5.1)	[16,17]
FSS	Fallon et al.	5.2 (1.5)	2.1 (0.5)		[16,203,204]
<i>FIQ – range 0–100 [205] (the higher the score, the greater the impairment)<sup>¶</sup></i>					
FIQ	Klempner et al., seropositive	58.4 (19.7)	14 and 21.9	Fibromyalgia (58–78)	[18,35,36,39,206]
FIQ	Klempner et al., seropositive	47.9 (15.2)	14 and 21.9		[18,206]
<i>Pain – MPQ range 0–78 [207] and VAS range 0–10 (the higher the scores, the greater the pain) [208]</i>					
MPQ	Fallon et al.	11.6 (1.5)	1.1 (2.5)	Widespread pain after breast cancer surgery (7.0)	[16,40]
VAS	Fallon et al.	5.2 (3.1)	0.1 (0.2)	Fibromyalgia (6.48)	[16,35]
<i>Neurocognitive dysfunction index<sup>††</sup></i>					
Index	Fallon et al.	-0.49 (0.63)	0.55 (0.40)		[16]

<sup>†</sup>The PCS on the SF-36 measure of QoL is a measure of physical health, role physical, bodily pain and general health [209].

<sup>‡</sup>The MCS on the SF-36 measure of QoL is a measure of mental health, emotional role functioning, social functioning and vitality [209].

<sup>§</sup>The FSS assesses the impact of fatigue on everyday functioning [210].

<sup>¶</sup>The FIQ is a measure of functional disability, ability to have a job, pain intensity, sleep function, stiffness, anxiety, depression and the overall sense of wellbeing<sup>¶</sup> adopted by Burckhardt et al. for fibromyalgia [211] and subsequently used in Lyme disease [16,212].

<sup>\*\*</sup>The MPQ estimates the sensory and affective elements of pain, both qualitatively and quantitatively [213].

<sup>††</sup>An index based on motor, psychomotor, attention, total memory, Buschke, Benton, working memory, fluency, IQ by Barona, IQ by NAART-R, immediate memory and delayed memory; higher values indicate better cognitive functioning. Additional outcomes described in the NIH-sponsored retreatment trials include cognitive, role functioning and pain on MOS abnormalities [18], psychopathology [16] and a OspA measure of spinal fluid [17].

ALS: Amyotrophic lateral sclerosis; FIQ: Fibromyalgia impact questionnaire; FSS: Fatigue severity scale; MCS: Mental component score; MPQ: McGill Pain Questionnaire; MOS: Medical outcome scale; PCS: Physical component score; SD: Standard deviation; VAS: Visual analog scale; QoL: Quality of life.

tients immediately following the completion of the initial course of retreatment to evaluate the effectiveness of retreatment and the need for therapeutic adjustments. Reassessment may need to be done much earlier and with greater scrutiny in patients with severe disease or when the therapeutic intervention carries substantial risk.

For patients who improve yet continue to have persistent manifestations and continuing QoL im-

pairments following 4–6 weeks of antibiotic retreatment, decisions regarding the continuation, modification or discontinuation of treatment should be based on several factors. In addition to those listed in Recommendation 3b, the decision to continue treatment may depend on the length of time between the initial and subsequent retreatment, the strength of the patient's response to retreatment, the severity of the patient's current impairments, whether diag-

nostic tests, symptoms or treatment response suggest ongoing infection, and whether the patient relapses when treatment is withdrawn.

In cases where the patient does not improve after 4–6 weeks of antibiotic retreatment, clinicians should reassess the clinical diagnosis as well as the anticipated benefit. They should also confirm that other potential causes of persistent manifestations have been adequately investigated prior to con-

tinuing antibiotic retreatment. Decisions regarding the continuation, modification or discontinuation of treatment should consider the factors noted above as well as the definition of an adequate therapeutic trial.

Whenever retreatment is continued, the timing of subsequent follow-up visits should be based on the level of the therapeutic response, the severity of ongoing disease, the duration of current therapy and the need to monitor for adverse events.

**Recommendation:** very low-quality evidence.

**Role of patient preferences:** high. See Recommendation 3b.

*Editor's Note: The ILADS guidelines working group was led by Daniel Cameron, MD, MPH; Lorraine Johnson, JD, MBA; and Betty Maloney, MD. Contributions to the development of these guidelines were made by the entire ILADS board of directors and outside reviewers.*

1 D. Cameron. International Lyme and Associated Diseases Society, PO Box 341461, Bethesda MD, 20827-1461, USA

2 L. Johnson. LymeDisease.org, PO Box 1352, Chico, CA 95927, USA

3 B. Maloney. Partnership for Healing and Health Ltd, PO Box 84, Wyoming, MN 55092

\* Author for correspondence: 914.666.4665 contact@danielcameronmd.com

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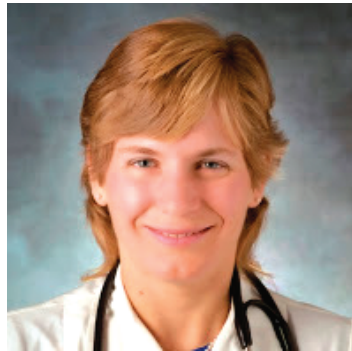


# A Single Vision

Teresa Royer MacKnight, DO 1953 – 2010

ILADS founder didn't live to see her dream reach fruition

By Beatrice Szantyr, MD



Terri was a doer and a dreamer. She had a keen, inquisitive intellect. And she had passion – for people, for life. Her patients and her colleagues respected and loved her.

When Terri became ill, she worked hard to figure out what was wrong and how to make it right. Like so many who have struggled with tick-borne illnesses, she encountered physicians who began by caring—but who gave up when Terri did not get well.

Terri had the vision for creating ILADS and served briefly as its president, till her illness made it impossible to continue. Although her life gradually became small, she envisioned a medical society that allowed health care professionals to exchange clinical experience about the complexities of Lyme. Perhaps it could protect clinicians who dared to reach beyond the incomplete Lyme treatment. Sharing medical information might allow more patients to receive early, comprehensive treatment.

ILADS ultimately exists to bind together a community of healers, caregivers, researchers, advocates, and scientists in order that we may serve those who seek their care with us. Terri set the path we have chosen to reach that goal, based on education, honest inquiry, sound science, and compassion.

Terri's memorial video may be viewed at [youtube.com/watch?v=t1Inr026LZk](https://www.youtube.com/watch?v=t1Inr026LZk)

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*Editor's Note: This Executive Summary of the 2014 ILADS Lyme treatment guidelines reprinted by permission of the International Lyme and Associated Diseases Society (ILADS). The guidelines were published in Expert Review of Anti-Infective Therapy 12(9), 1103-1135 (2014).*

# ILADS Conference 2014

## LLMDs riveted to cutting-edge science during their DC sessions

By Pamela Cocks, MPH, MLS

ILADS is blossoming with strong dedicated leadership and increasingly engaged members, reports current president Dan Cameron, MD. The momentum is encouraging. The 2014 conference registered over 700 attendees, while membership exceeds 550 professionals. Ray Stricker, MD, ILADS past-president, was struck by the diversity of medical specialties caring for TBD patients, something reminiscent of the early AIDS epidemic he saw in San Francisco. When the ID docs were clueless, primary care providers stepped in with multi-specialty organizations like the American Academy of HIV Medicine, the spiritual twin of ILADS.

### Fundamentals

Attendees were exposed to a sea of knowledge about tick-borne illness. Plenty of case histories illustrated the complications of diagnosis and treatment. Capturing the struggle that so many LLMDs experience as well as continuing denial by mainstream medicine, Dan Kinderlehrer, MD, borrowed wisdom from Schopenhauer: "Truth is eventually revealed as obvious all along."

Retired from practice, Joe Burrascano, Jr., MD, remains a remarkable resource, having earned his stripes on the front lines over many years. Describing the history of *Borrelia*, he stressed there is no formula for diagnosis. Even a layperson can appreciate the difficulty interpreting signs and behaviors of a complicated bacterium that can become a multi-system disease. Understanding the biology of the bug and its companion co-infections is critical to unraveling the mystery of chronicity. Richard Horowitz, MD, joined Burrascano to present an advanced discussion of managing the complex Lyme patient. Dan Kinderlehrer, MD, Wayne Anderson, ND, Neil Nathan, MD, and Kristine Gedroic, MD, carried the session on integrative medicine.

Several Q & A panels addressed telling topics like autism, the role of herbals, treatment during pregnancy, mitochondrial damage, sexual transmission and case reporting.

### Diagnostic tests

Dr. Stricker moderated a terrific session on laboratory advances. Some older tests were validated while newer ones got attention. Dr. Burrascano highlighted the promising Advanced Lab culture test. Jyotsna Shah showed that the IGeneX Western blot has 97% sensitivity – remarkably good news. Other intriguing work involves PCR (Sin Hang Lee) and cytokines (Brian Fallon and Gottfried Kellerman). One nanotube technique (Charlie Johnson, Jr.) was truly space age.

There was plenty of buzz and concern over the proposed FDA regulations to limit LDTs (lab-developed tests).

### The brain and behavior

One break out session explored the issue of TBD encephalopathy - damage to the brain from the infection. As the spirochete invades the brain causing inflammation, patients can exhibit such neuropsychiatric symptoms as diminished cognitive function, inability to concentrate, reversed sleep-wake cycle, nightmares, anxiety,



LymeDisease.org's informational table at ILADS 2014 conference in October in Washington, D.C. Jo Anne Vidal (left), membership, and Dorothy Leland, VP of Education and Outreach.

subtle personality changes, lethargy, depression. Understanding the psychopharmacology of TBD is important to managing chronic Lyme. Lesions appearing on a SPECT scan must be differentiated from other syndromes, however. With proper diagnosis a patient can explain her illness to family, friends and colleagues, thus improving social acceptance. Clinical psychologist Sheila Statlender, PhD, is encouraged to see a growing willingness to discuss this once taboo topic.

### Revised treatment guidelines

The Society's recently published guidelines are an impressive project, reflecting rigorously evaluated evidence and a focus on patient-centered care. Calling them a milestone achievement, Dr. Stricker believes these guidelines now set the standard and serve to emphasize how biased and antiquated the IDSA guidelines are. Incorporating standards endorsed by the Institute of Medicine, they rely on science rather than the opinion of conflicted third parties and insurance companies. Betty Maloney, MD, one of the authors, explained the framework for evaluating existing evidence — all the evidence — and the profound respect ILADS has for the value of clinical judgment.

### Honoring Charles Ray Jones, MD

Attendees celebrated Dr. Jones at a well-attended dinner honoring his dedicated care of pediatric Lyme patients. Sheila Statlender, PhD, co-chair of the event with Ken Liegner, MD, spoke for everyone who felt the honor was well deserved. Like so many, Sheila is forever grateful to Dr. Jones for having treated her children. A video message from Senator Richard Blumenthal (CT) highlighted the evening, the substance of which was printed in a special certificate. Making his way to the podium, Jones warmly thanked ILADS for the honor and reiterated his love of the kids he treats and his plan to continue doing so.

*Pam Cocks, whose two children have Lyme disease, serves as managing editor of The Lyme Times.*

# Xenodiagnosis

The search for reliable diagnostics may return to the tick

By Betty Maloney, MD

Evidence for persistent *B. burgdorferi* infection continues to mount, and the human xenodiagnostic trial<sup>1</sup> provides the latest addition. This article highlights important aspects of the trial and, this being Lyme disease, some curiosities about how investigators presented their findings.

It's important to understand the connection between xenodiagnosis and why it may be useful in Lyme disease as well as how investigators presented their findings.

## Premise

Xenodiagnosis is based on the relationship between vectors (the carriers) and the pathogens (disease agents) they transmit. Pathogens depend on vectors to move between hosts, and vector-pathogen pairs evolve together. This allows signaling mechanisms to develop such that pathogens in one host move towards their vector's "call," become ingested and, ultimately, are transmitted to a new host when the vector next feeds. As depicted in the diagram, xenodiagnosis uses a vector (a tick) to "probe" a host (a mouse) suspected of being infected and, once feeding is completed, the vector is examined by PCR for evidence of the pathogen.

In humans, post-treatment serologic tests for Lyme disease are diagnostically worthless because neither positive nor negative results can be taken at face value. Results may be negative because an ineffective course of antibiotics failed to clear the infection but kept the immune system from producing a full antibody response to *Bb*. In patients who have been treated and feel well, positive results may simply reflect the old infection and not an ongoing one. This explains the interest in xenodiagnosis. The saliva of black-legged ticks contains chemicals that attract *Bb* to a bite site. Knowing that xenodiagnosis successfully demonstrated persistent infection in animal models, it was logical to investigate whether it could identify persistent Lyme infection in humans.

1 Marques A, Telford SR 3rd, Turk SP, et al. "Xenodiagnosis to detect *Borrelia burgdorferi* infection: a first-in-human study." *Clin Infect Dis*. 2014 Apr;58(7):937-45

## Study design

Officially titled "Searching for Persistence of Infection in Lyme Disease," the study sought to determine whether xenodiagnosis can be used to successfully investigate the presence of Lyme bacteria. The primary outcome measure specifically focused on determining whether xenodiagnosis could detect the continued presence of *Bb* in patients with persistent, post-treatment manifestations of Lyme. Assessing human xenodiagnosis safety was the secondary outcome measure.

## Findings

The study included 36 patients separated into five categories; outcomes for all groups are listed in the table. Each had 25-30 *Bb*-free ticks placed on their skin

Subject type	Subjects	Untestable ticks	Outcome
Current EM, on treatment	1	0	+ PCR
Post-treatment EM	5	1	No + PCR
Post-treatment, well, high C6 index	10	3	No + PCR
Post-treatment, ill	10	2	+ PCR in 1 of 8
Healthy controls	10	5	No + PCR

that fed until they naturally detached. If xenodiagnosis works, the patient with a current EM should be positive (he was) and the healthy controls should be negative (they were). Researchers found two other subjects PCR+ but thought the results represented contamination and were therefore labeled indeterminate.

Given that the xenodiagnostic test was appropriately positive and negative in the subjects and the healthy controls respectively, the positive result in a persistently ill post-treatment subject is highly significant evidence of persistent infection. In fact, the study's record had declared prior to the trial's start that: "evidence that *Bb* can be recovered by xenodiagnosis after antibiotic therapy in subjects with continued symptoms would change the current paradigm for potential mechanisms of disease and provide researchers and clinicians a tool for identifying patients with persistent infection." (Emphasis added)

## Results

Although one might think this resolves the question of persistent infection in humans, when it comes to Lyme disease it appears that the ground rules are subject to change. The study details (*clinicaltrials.gov*) state that the primary endpoint was to "determine whether xenodiagnosis can detect the continued presence of *Bb* in patients with Lyme disease after antibiotic therapy" and list safety as the secondary outcome measure. Instead, the authors claimed, "The primary goals of this study were to develop procedures for xenodiagnostic testing of patients with Lyme disease and to determine the safety of tick xenodiagnosis in humans." This allowed them to shift their discussion away from their most important finding — a persistent *Bb* infection in a post-treatment patient with ongoing manifestations of Lyme disease — and towards the more mundane safety finding.

The authors went to great lengths to discount the significance of their own findings. Although neither of the positive xenodiagnostic specimens produced *Bb*-positive cultures or allowed for the transmission of *Bb* to immunodeficient mice, the authors only mentioned those findings in relationship to the post-treatment ill patient. They rightfully questioned whether the recovered DNA was actual evidence of *Bb* viability but the discussion on this point seemed unbalanced. The authors hypothesized that the ticks simply acquired DNA remnants from dead *Bb* (which just happened to be in the vicinity of the bite site), and offered results from a Lyme arthritis study as scientific support. However, there are significant differences between the current and previous studies. Although the arthritis study found joint fluid specimens remained PCR+ for up to 11 months post-treatment, the post-treatment patient in the xenodi-

*Continued on next page*

# NorVect Convenes in Oslo

## First of its kind on vector-borne diseases in Scandinavia

As Lyme disease and other tick-borne infections are on the rise in Scandinavia, Norwegian patients are taking things into their own hands. In May 2014, a patient-founded organization called NorVect – the Nordic Network for Vector-borne Diseases – brought together leading Lyme doctors and researchers in Oslo, Norway. Key presenters included Joseph Burrascano, MD, Richard Horowitz, MD, Edward Breitschwerdt, DVM, Alan MacDonald, MD, and Eva Sapi, PhD. Burrascano called it an historic event bringing together giants in the field. According to NorVect. co-founder Siw Hansson, Lyme patients in Norway have difficulty obtaining proper care. She told the Huffington Post, “The only Lyme treatment center in Norway was shut down by the health authorities last year, the doctor lost his license and patients need to go abroad for treatment. There are doctors that wish to treat patients longer but choose not to do so because they fear they will lose their jobs.”

NorVect - founded and run by patients - hopes to help change that, as it works for open and constructive dialogue between patients, their families, health practitioners, authorities and politicians. A second Oslo conference is planned for May 2015. For more information, see [www.norvect.no](http://www.norvect.no).

### NIH Trials , from page 6

response; those patients who had more joint involvement or more neurologic abnormalities on physical exam were more likely to show benefit from antibiotic re-treatment. Hippocrates would be proud to see that the clinical exam trumped the laboratory test in predicting treatment response.

#### Persistent infection?

These human antibiotic trials cannot answer the question of whether patients have persistent infection, as treatment response could occur for a variety of reasons. The mouse models, however, certainly support the rationale for intermittent antibiotic retreatment for those with persistent or relapsing symptoms. Small amounts of *Borrelia* may persist and later reactivate many months later, once again causing local inflammation.

There is an urgent need in our medical armamentarium for a blood marker that will tell us quickly and accurately whether

or not active infection is present in a patient with persistent symptoms. When such a test is identified, the guesswork that plagues patients and clinicians will be eliminated.

#### Conclusion

As part of their assessment of the NIH trials, the authors wrote the following summary statement (abstracted):

Based on the evidence cited, one cannot conclude that repeated antibiotic therapy is ineffective in improving certain symptoms associated with post-treatment Lyme disease (PTLDS) syndrome. Nor can it be concluded that repeated antibiotic therapy is robustly effective. One can conclude that approximately 60% of patients with fatigue may experience meaningful but partial clinical improvement in fatigue with antibiotic retreatment. Guidelines for Lyme disease need to clarify that controlled trials have revealed conflicting results, with some studies demonstrating efficacy

and others showing no benefit to repeated treatment.

Specifically, the chronic Lyme trials lead to the following recommendation ...: “IV ceftriaxone therapy is moderately efficacious for patients with chronic (>6 months) subjective fatigue after recommended antibiotic treatment regimens, but the risk associated with IV antibiotic therapy requires careful discussion with the patient of the cost-benefit ratio. Sustained improvement from IV ceftriaxone therapy for other PTLDS symptoms such as physical dysfunction and pain is uncertain, with positive results suggested by one study but not by others.

*For those interested in reading the complete assessment of the NIH clinical trials by Fallon and his research team, please refer to the on-line manuscript in Open Neurology (Fallon et al, 2012). Brian Fallon is the director of the Lyme and Tick-Borne Diseases Research Center at Columbia University, NYC.*

### Xenodiagnosis, from page 25

agnosis study produced PCR+ specimens twice, first at ~14 months post-diagnosis and again at 22 months. Furthermore, because joints are immune-protected sites, the ability of immune scavenger cells to remove such debris in a timely fashion is hampered, and the study's findings are not surprising. In contrast, it is hard to imagine nonviable borrelial DNA lingering in the skin of an immune-competent host for 22 months.

#### Conclusions

In their final grasp for straws, the authors suggest that the PCR+ in the persistently ill post-treatment patient may not reflect *Bb* persistence but rather patient noncompliance with previous antibiotic therapy, inadequate blood levels of the prescribed antibiotics, or re-infection.

Despite the investigators' apparent bias against their own positive findings, the

study can be summarized this way: the human xenodiagnostic trial offers convincing evidence that *Bb* is able to persist in humans who have been treated for Lyme disease yet have ongoing manifestations of the infection.

The accumulated evidence demonstrating persistent infection continues to rise; hopefully, it will soon gain widespread acceptance.



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# Borrelia Biofilm

## What have we learned about the companion structures surrounding Bb?

By Eva Sapi, PhD, and David Luecke, MA

*Borrelia* is a clever and resourceful pathogen. It employs a variety of mechanisms to counteract eradication by its host, adopting alternate morphologies in response to changing and unfavorable environmental conditions [1-7] including antimicrobial agents [1-7]. In addition to its familiar corkscrew-shaped spirochete form,

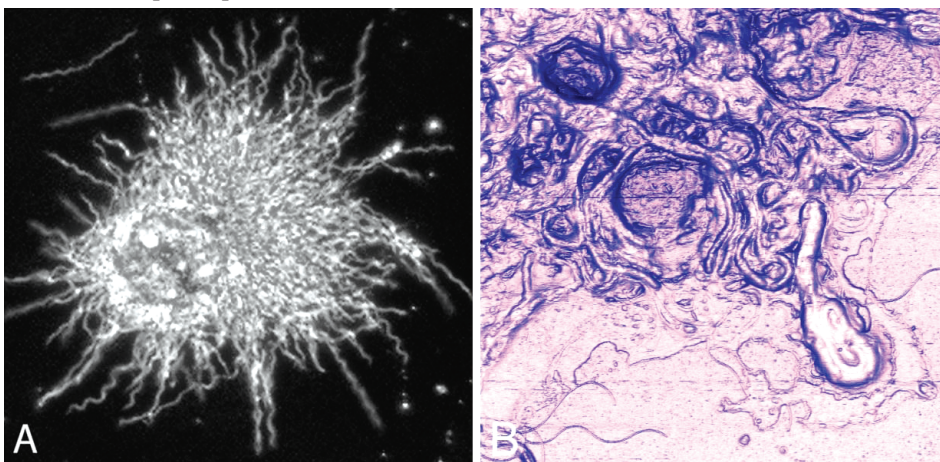
*Borrelia burgdorferi* (*Bb*) can transform from motile spirochetes into cystic, granular or cell wall deficient forms. Our University of New Haven research group recently published that this bacterium has an additional yet uncharacterized form called biofilm [8].

What is biofilm? A biofilm is a complex aggregation of microorganisms growing on a solid substrate [4-5]. Unlike the more familiar “planktonic” lifestyle in which bacteria float or swim freely, biofilms surround the bacteria with a complex polymeric matrix, better known as “slime.” Within biofilms, bacteria have characteristics distinct from those of free-swimming bacteria of the same species, including a significantly increased tolerance to antimicrobial therapies (up to 1000 fold), making them very difficult to eradicate [9-12].

Our UNH group studied *Bb* for several hallmark features of biofilm, including structural rearrangements and secretion of the slime. Our studies revealed that *Borrelia* aggregates have alginate-rich protective layers with extracellular DNA and calcium on the surface, which are well-

known biofilm specific components for other bacterial species [12]. We also found substantial evidence that *Bb* is capable of forming biofilm *in vitro*.

In previously published antibiotic studies [13], we reported that biofilm formation dramatically increases *Borrelia*'s resistance to antibiotics, consistent with the general literature on biofilms [14].



**Panel A** Dark field image of a small developing *in vitro* biofilm (Panel A); spirochetes at the edge of the biofilm can be easily identified but not the other alternative forms. In AFM image of a similar film (Panel B), alternative forms become readily apparent.

**Panel B** is an atomic force microscopy image of a *Bb* B31 biofilm using NanoSurf atomic force microscope in contact mode.

Taken together, these observations could play a significant role in *Borrelia*'s survival in diverse environmental conditions by providing refuge to individual cells.

We still need to understand the varied components and development of these structures. To perform these studies, we will use atomic force microscopy (AFM), a microscopic technique capable of scanning live biofilm in nanoscale [17-18]. Because *Borrelia* spirochetes are at the limit of what light microscopy can resolve, AFM will provide an important advantage over that conventional technique. In patient samples, light microscopy pictures always have some ambiguity that helps perpetuate the mythical perception of chronic Lyme.

Alternative forms of *Borrelia*, such as cystic/granular and cell-wall-deficient (CWD), are finally getting recognition for their importance in Lyme disease.

Because of their small size and uncharacteristic shape, these forms are difficult to see *in vitro* or *in vivo* and difficult to confidently identify as *Borrelia* (Figure 1A). It is even worse *in vivo*, where they are basically optically invisible, frustrating since we suspect that alternative forms may be the prevalent morphology in chronic infection. With its enhanced resolving

power, AFM allows observation and characterization of these alternative forms (Figure 1B).

Last year LymeDisease.org raised funds for our new AFM (Nanosurf) that is most suitable for this biofilm research. Figure 2 (opposite page) shows our first image of *Borrelia* biofilm using the new AFM.

Our next research question is whether we can find these structures *in vivo*, and whether they are relevant to the survival strategies for *Borrelia* in infected tissues. For these studies

we have collected tissues from biopsy sections of *Borrelia* lymphocytoma and *Erythema Chronicum Migrans* (*bull's-eye rash*) as well as multiple organ sites from experimental mouse models.

Results from our future studies will help CLD patients by identifying alternative structures of *Borrelia* including different components in infected tissues. If we can prove that *Borrelia* is indeed capable of forming a biofilm *in vivo*, a structure with known antibiotic resistance, it will change the way we think about Lyme disease, especially in patients where it seems to be persistent despite long-term antibiotic treatment. If we can understand how *Borrelia* survives treatment, it will provide novel therapeutic targets and the hope of eradicating infection in these patients.

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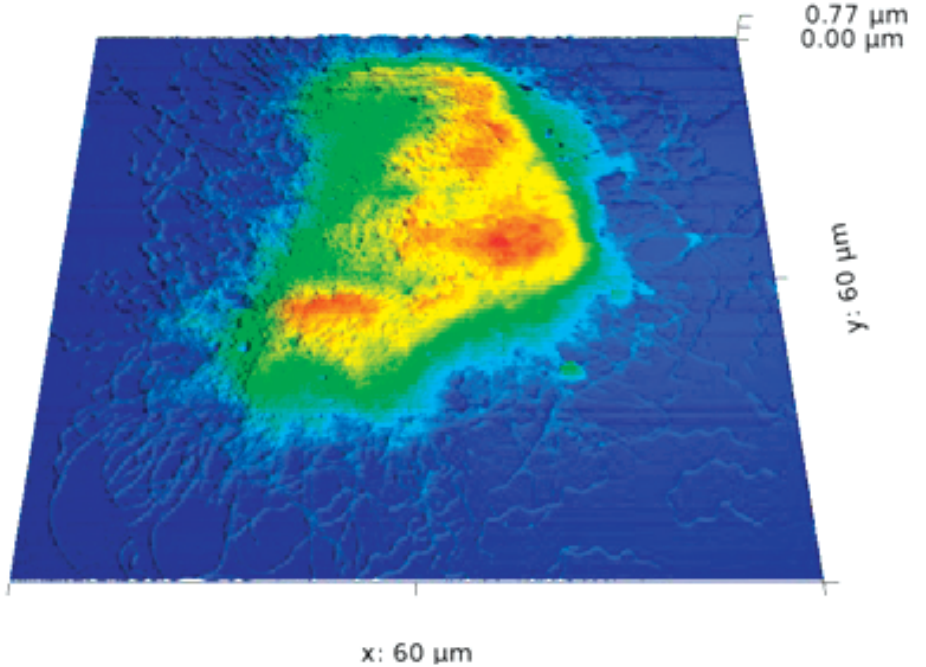


Figure 2 is an atomic force microscopy image of a Bb B31 biofilm using a NanoSurf atomic force microscope in contact mode.

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*Eva Sapi and David Luecke are members of the Lyme Disease Research Group, Department of Biology and Environmental Sciences, University of New Haven, West Haven, Connecticut.*

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# The Complications of Co-infections

Blood-sucking parasites transmit a world of disease into the lives of Lyme patients

By Lorraine Johnson, JD, MBA

Ticks are the number one vector of disease in the U.S. and second only to mosquitoes worldwide. Ticks frequently take blood meals from small rodents like rats, squirrels and mice that are carrying diseases. Diseases picked up from these blood meals may then be passed on to their next meal ticket ... which could be you. So how many pathogens can a tick transmit? A recent study<sup>1</sup> from China provides some answers.

Researchers collected local ticks and allowed them to feed on laboratory rats that had been bred in captivity and were free of disease. Afterward, they examined the ticks and the rats for bacteria believed to cause disease. Findings? The ticks contained 373 types of bacteria and had transmitted 237 to the rats. The

Disease	First Reported	Characteristic Symptoms	Diagnostic Tests
Babesiosis	1888	No	Yes
Ehrlichiosis	1986	No	Yes
Anaplasmosis	1994	No	Yes
Lyme disease (EM)	1912	Yes	Yes
Lyme disease (whole syndrome)	1977	No	Yes
STARI	1997	No	No
Tick-borne Encephalitis	1937	Yes	Yes
Rocky Mountain Spotted Fever	1896	Yes	Yes
Tick-borne Relapsing Fever	1904	Yes	Yes
Rickettsiosis	1999	No	No
B. miyamotoi	2011	No	No
Heartland virus	2014	No	No

Data derived primarily from a recent study by Dr. Ellen Tijssen Klasen and colleagues

authors concluded there is “unambiguous evidence that there are as yet unidentified pathogens associated with ticks [which] increases the risk of multiple infections in humans, [leading] to more severe clinical manifestations.”

Since the discovery of the Lyme bacteria *Borrelia burgdorferi* in 1981, researchers have identified more than 15 additional tick-borne bacteria. For instance, it wasn't until 2011 that *Borrelia miyamotoi* was first identified and recognized as a cause of disease by the CDC. Heartland virus was first identified by the CDC in 2014.

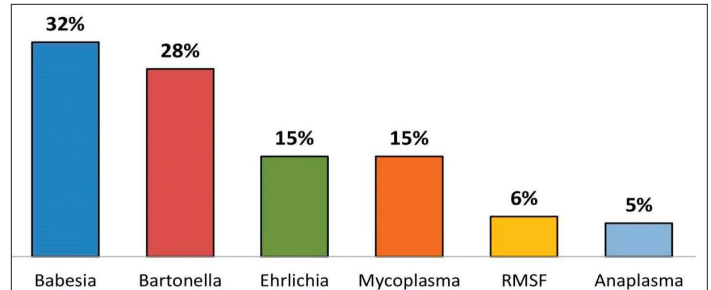
A single bite can transmit multiple tick-borne diseases or a victim may be co-infected through multiple tick bites from multiple ticks. According to a study<sup>2</sup> of patients in Connecticut and Minnesota, 20% of patients with Lyme disease also showed evidence of a co-infection. LDO's own recently published survey<sup>3</sup> of over 3,000 patients with chronic Lyme found over 50% had at least one co-infection and 30% had two or more co-infections.

The most common co-infections in the LDO study were *Babesia* (32%), *Bartonella* (28%), and *Ehrlichia* (15%) while a study by Dr.

Janet Sperling in Canada found that the most common were *Bartonella* (36%), *Babesia* (19%), and *Anaplasma* (13%).

All reported tick-borne diseases have increased significantly over time according to the Institute of Medicine<sup>5</sup>. Between 1992 and 2006, the incidence of Lyme disease increased 101%. Between 2000 and 2008, the incidence of Rocky Mountain Spotted Fever

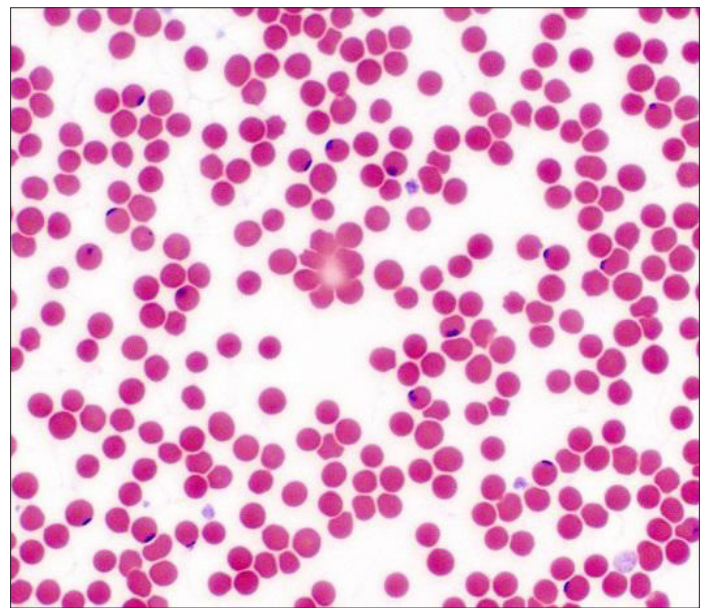
## Co-infections



Rates of co-infections in over 3,000 patients surveyed with chronic Lyme disease<sup>4</sup>.

(RMSF) shot up over 400%. Between 2000 and 2007, the incidence of Anaplasmosis rose by 275%, while the incidence of Ehrlichiosis increased by more than 100%.

Many tick-borne diseases do not have distinctive symptoms, and for some pathogens diagnostic tests do not even exist. The chart below lists selected co-infections, the date they were discovered, whether they have characteristic symptoms, and whether there is a diagnostic test yet available.



*Babesia*

Many co-infections threaten more than just the tick host. For example, *Babesia* can be passed from mother to unborn child as

Continued on page 34



# TBD Epidemiology

## California ticks carry a plethora of disease agents to unsuspecting Lyme patients

By Robert S. Lane, PhD

My career-long study of ticks, tick-borne disease agents and their wildlife partners were spurred in 1974 when, as a newly-hired public health biologist with the California Department of Health Services, I was asked to lead an investigation aimed at determining the then unknown tick vector(s) and vertebrate hosts of Rocky Mountain spotted fever (RMSF).

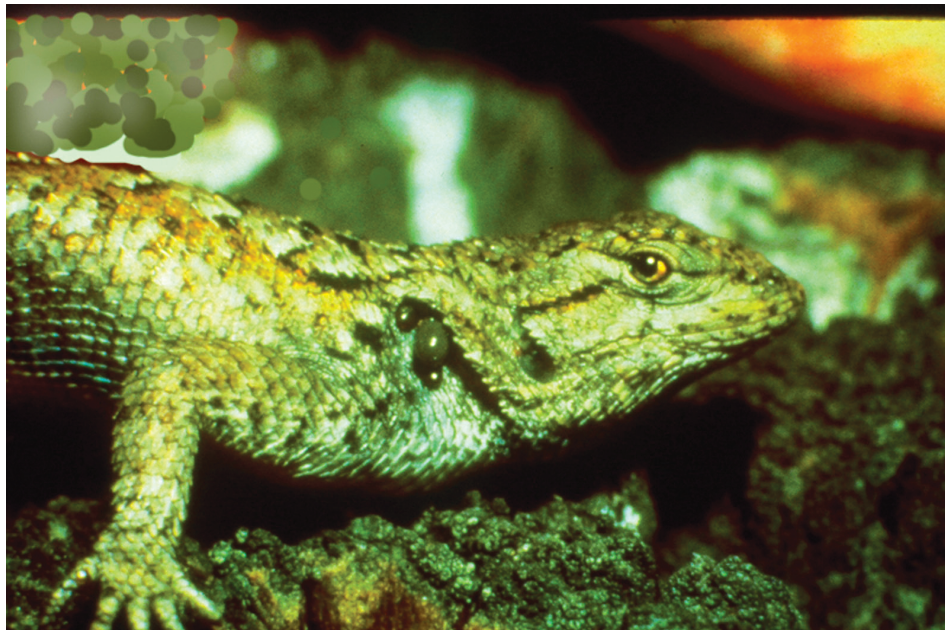
In collaboration with colleagues in the Vector Biology and Control Section and the Viral and Rickettsial Disease Laboratory, along with researchers at the U.S. Public Health Service, Rocky Mountain Laboratories in Hamilton, Montana, several known or novel rickettsiae were isolated and characterized from human or non-human biting ticks, and a few small mammals were implicated as hosts.

The Pacific Coast tick (*Dermacentor occidentalis*), a human-biter, was reconfirmed as the primary carrier of an unclassified spotted fever group rickettsia, designated 364D, and incriminated as causing a mild form of RMSF. Recent molecular studies by other researchers have reconfirmed some of our earlier tick/rickettsial-survey findings and, in 2010, Marc Shapiro and co-workers reported in the journal *Clinical Infectious Diseases* that the unclassified 364D rickettsia actually causes an eschar-associated illness. [Ed. note: An eschar is a dry, dark scab or scar.], So keep an eye on that “emerging” disease, too.

We have investigated other tick-borne diseases as well: Colorado tick fever, human babesiosis, human granulocytic anaplasmosis, relapsing fever-group agents, tick paralysis, tularemia, and particularly Lyme disease (LD). After Dr. Willy Burgdorfer and colleagues published their epochal discovery of the LD spirochete (subsequently named *Borrelia burgdorferi* in his honor) in black-legged ticks from Shelter Island, New York, in 1982, Willy invited me to join him in the inaugural tick-LD spirochete survey in western North America. This collaboration led to the discovery that the western

black-legged tick (*Ixodes pacificus*) is the primary carrier of *B. burgdorferi* in the Far West. Willy generously taught me laboratory techniques essential for investigating tick-pathogen-host interrelationships, which enabled me to establish my own LD research program at U.C. Berkeley in 1984. Most of the ecological/

habitats, particularly dense woodlands. In both Alameda and Mendocino counties, more than a handful of named and one or more uncharacterized *Borrelia* spp. were detected in host-seeking *Ixodes* spp. ticks. The described species included *B. miyamotoi*, a relapsing-fever group spirochete implicated recently as a human



The western fence lizard, a widespread and abundant host of sub-adult western black-legged ticks, is immune to infection with Lyme-group spirochetes. In northwestern California, this reptile may host as many as 90% of the sub-adult ticks in some chaparral or woodland habitats.

epidemiological research was conducted in northwestern California because this region is a hotbed of LD activity. The University of California Hopland Research and Extension Center became the hub for these studies.

### What have we learned?

For starters, the diversity of the tick vectors, vertebrate hosts and Lyme-group spirochetes mirror the remarkable biodiversity for which California is legendary. Moreover, the environmental conditions, the key tick/wildlife players and the epidemiology of LD differ markedly from those in the eastern U.S. Besides *I. pacificus*, several other *Ixodes* spp. ticks, a number of rodents and, perhaps secondarily, ground-foraging birds, interact to maintain Lyme-group spirochetes in certain permissive

pathogen in Russia and the northeastern U.S. Obviously, the latter findings beg the question – do any of them, other than *B. burgdorferi*, occasionally cause clinical illness in California?

Risk factors for tick-exposure or LD were found to include, among others, woodcutting, sitting atop logs or against tree trunks, gathering firewood and duration of tick attachment for the nymphs; contact with low vegetation bordering the uphill (versus the downhill) margins of hillside hiking trails and the time-of-day that one ventures outdoors for the adult ticks; and habitat type for both nymphs and adult ticks.

By contrast, the immune systems of the western fence lizard and southern alligator lizard, mega-hosts of sub-adult western

*Continued on page 34*

# Where Are the Studies?

*Pathology studies must focus on patients with relapsing symptoms*

By Tom Grier

The first time I took a hard look at Lyme disease from a scientific perspective was in



Tom Grier

1990. I was searching for answers to why I had been misdiagnosed with multiple sclerosis. Looking back nearly 25 years, I have more perspective and an aerial view of just how convoluted the science and politics of Lyme disease research has been over the past two decades. I bore witness to how medical science doesn't always choose a direction that emphasizes either a cure or a treatment for patients who repeatedly relapse and fail to fully recover from this complicated disease.

In the early years of Lyme research – 1982 – it was discovered that the cause of human Lyme disease was from a spirochete related to tick-borne relapsing fevers. It was only natural to do epidemiological studies to know where Lyme disease was, how prevalent it was, and how it was spreading. It was distressing that the number of those studies done year after year seemed endless, while the studies that looked at the pathogenesis of the human disease process were being ignored.

Over the past two decades, while sci-

entists conducted thousands of studies of the deer population, ticks, mice and rodents, they were only conducting a few significant human treatment studies. Virtually none of the studies went beyond serological testing. Very few human studies actually biopsied patient tissue using bacterial staining and culture. To date, absolutely no taxpayer dollars have ever funded an autopsy study to look for the bacteria surviving in human tissues post-antibiotic treatment, nor funded a pathology-based study to investigate the high incidence of multiple sclerosis among Lyme patients.

Almost all significant research done on syphilis over the past 100 years has been based on human pathology and brain autopsies. Considering that Lyme disease – like syphilis – is caused by a spirochete capable of entering the brain and heart, and that the annual incidence of Lyme is nearly six times that of the annual incidence of syphilis, it seems only sensible that we would put the same effort into Lyme disease pathology studies as was done for syphilis. So where are the studies?

Many scientists have become frustrated with this lack of interest by the U.S. in microbiology and human tissue studies. Some scientists tried to do independent university studies that were underfunded and lacked cooperation from the medical community. Yet these few independent pathology studies have yielded provocative results that demand national brain autopsy studies.

We can count on one hand the national taxpayer-funded human Lyme pathology studies. If we include live pathology-based animal and *in vitro* studies, we still have so few that most Lyme veterans can name them from memory. As a world leader in medicine, America has not only fallen behind, but has allowed its influence to curtail the advancement of Lyme disease research in other countries. We have embedded CDC Epidemic Intelligence Service (EIS) agents in other countries and marketed U.S. patented serology tests created and based on a single strain of *Borrelia* that isn't even found in nature.

## Lyme research to date

Here are some significant Lyme studies funded by the U.S. taxpayer with a synopsis of their results and significance.

Persistence of *Bb* following antibiotic treatment in mice. Hodzic E, Feng S, Holden K, Freet KJ, and Barthold SW. *Antimicrob Agents Chemother.* 2008 May; 52(5): 1728–1736.

Infected mice treated with a month of ceftriaxone remained PCR positive and transferred live bacteria to uninfected ticks able to infect other mice.

Persistence of *Bb* in Rhesus macaques following antibiotic treatment of disseminated infection. Embers ME, Barthold SW, et al. January 2012.

Following aggressive antibiotic treatment several monkeys remained infected and could transfer the infection to uninfected ticks. Immune stains of tissues confirmed the presence of *Borrelia* spirochetes in the myocardium. Although the Embers-Barthold study met its scientific criteria and was completed, it was not allowed to be published for over a decade. The parallel Klempner NIH human study ended early but was nevertheless published with incomplete data, making bold, broad, absolute conclusions that were not supported by the evidence.

Invasion of human neuronal and glial cells by an infectious strain of *Bb*. Livingston JA, Gilmore Jr, RD. 2006, pps 1-9.

This is perhaps the best microbiology study ever done by the CDC on the pathogenesis of *Bb*. Using *in vitro* (in the laboratory) cultures, they showed that Lyme spirochetes attached to living human brain cells. Indeed, the pathogen had an attraction to and penetrated brain cells and could live unencumbered for over a week. The beautiful three-dimensional photographs clearly showed both neuron invasion and glial cell invasion occurred rapidly and repeatedly. *Borrelia* was selective in the cells it targeted, and by targeting and penetrating blood vessel cells (endothelial cells), it was capable of penetrating all tissues. Why did the CDC bury this study and offer no further support to

*Continued on page 34*

# Neuropathology

## A short history of neural *Borreliosis* research

By Alan B. MacDonald, MD

During 1981-1982, studies were underway to write new chapters on the nature of tick-borne *Borrelia* infection in the human host. Dr. Jorge Benach and Dr. Edward Bosler collected ticks from Shelter Island, NY, seeking to explain outbreaks of Rocky Mountain spotted fever. Dr. Willy Burgdorfer dissected the ticks and discovered *Borrelia* spirochetes associated with Lyme disease. Careful purification of the causative agent was accomplished by

Dr. Alan Barbour at the Rocky Mountain Lab, the National Institutes of Health, and the Centers for Disease Control.

### Microscopic tissue studies

Infectious disease pathologists recognized that microscopic studies of human diseased tissues could solidify the links between Lyme antibodies in human blood to Lyme spirochetes in human tissue. Pathologists require special training to diagnose human diseases, and pathologists with advanced skills in infectious disease

are a distinct minority among all practicing pathologists.

Dr. Paul Duray was the essential pathologist team member of Dr. Allen Steere's Lyme group at Yale University. Steere had written on clinical aspects of Lyme, including arthritis, meningitis and dermatitis. Although later he wrote about "the expanding spectrum of Lyme disease," at this time his notion was that Lyme was restricted to relatively superficial areas of the infected host and that such superficial diseases could be eradicated easily with several weeks of antibiotics. Duray overturned these superficial notions, proving that Lyme could cause serious illness in tissues deep inside the human body.

### Syphilis and Lyme

As a young pathologist at a Southampton, NY, hospital, I was intrigued by the similarities between human syphilis and Lyme. Based on the medical literature, I hypothesized that manifestations of syphilis might have a parallel disease presentation in Lyme patients. I began a study of Lyme borreliosis with a prospective autopsy series seeking histologic microscopic evidence for Lyme spirochetes in human material.

I began a series of autopsies on miscarried human fetuses delivered at the hospital. With elaborate microscopic studies and corresponding clinical microbiology cultures of autopsy fetal tissue, I documented that *Borrelia* infection was the cause of fetal death in a series of cases. Initial microscopic techniques included the use of special silver stains to render the spirochetes in tissue visible under the microscope, and concurrent microbiology culture of human liver and brain from the miscarriages producing positive cultures of *Borrelia*.

### Vienna symposium

In 1985 I presented my findings at the 2<sup>nd</sup> International Symposium on Lyme Disease and related disorders in Vienna, Austria. In 10 minutes at the podium, I presented 100 slides showing only spirochetes recovered from fetal autopsy tissue. The audience was incredulous, but the dis-

*Continued on page 35*



## Co-infections, from page 30

well as by transfusion. A recent CDC article<sup>6</sup> reveals that the percentage of ticks in Maine infected with *Babesia* increased from 29% in 1995 to 60% in 2011. A similar study<sup>7</sup> in New York showed that the *Babesia* co-infection rate was twice as high as previously thought. This increase in infection rates puts residents, babies and the blood supply at greater risk.

We may be seeing just the tip of the iceberg. As the Chinese study indicates, ticks carry a staggering number of pathogens, many of which have not yet been identified. So what's keeping Lyme patients sick? Maybe it's not just this or that, but a toxic stew of pathogens - identified or not - keeping them down.

Lorraine Johnson, JD, MBA, serves as executive director of *LymeDisease.org*.

## Epidemiology, from page 31

black-legged ticks in some habitats, are lethal to LD spirochetes present in the midguts of attached nymphs. This explains at least in part why so few adult ticks are infected with *Borrelia* spp. ( $\approx 1$  to 2%) in northwestern California and, therefore, are less likely to transmit spirochetes to people as compared with nymphs ( $\approx 5$  to 15%).

Disease ecology never is as simple as it may appear. Recent research carried out in Marin County woodlands suggests that paradoxically the western fence lizard may increase one's risk of exposure to the nymphs by maintaining higher tick densities locally.

In Mendocino County, about one-quarter of the residents of a small rural community tested positive for LD spirochetes, though only a single "hot" strain amid 12 *B. burgdorferi* strains detected in nymphs countywide infected 95% of the residents. The cumulative frequency of LD in that community during the late 1980s

## Studies, from page 32

Livengood and Gilmore for more studies *in vivo* (in the living) using what they had learned *in vitro*?

Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. Klempner, MS, Hu LT, Evans J, et al. *N Engl J Med* 2001; 345:85-92 July 12, 2001.

This study has been debated and reviewed in such depth that its flaws can fill an entire book. My disagreement is that they did not meet their own standards for enrollment and completion yet they published with incomplete data based on a flawed study design. The data collected do not fully support their bold and absolute conclusions that longer antibiotic treatments do not benefit patients with persistent symptoms.

The biggest red flag is that seven other non-government studies with larger patient populations all showed significant relapse rates in patients after discontinuation of antibiotics. The relapse rates ranged from 22% to 58%. One state-funded public health study on Nantucket Island had over 100 patients followed for over five years. Without that kind of extended follow-up in the Klempner study, it is hard to draw useful conclusions.

## Conclusion

The complete lack of significant pathology-based studies after

## Resources

Johnson L, Wilcox S, Mankoff J and Stricker RB (2014). Severity of chronic Lyme disease compared to other chronic conditions: a quality of life survey. *PeerJ*, DOI 10.7717/peerj.322. (Open access)

## (Endnotes)

- 1 [www.sciencedirect.com/science/article/pii/S1877959X14001332](http://www.sciencedirect.com/science/article/pii/S1877959X14001332)
- 2 [www.ct.gov/caes/lib/caes/documents/special\\_features/tickhandbook](http://www.ct.gov/caes/lib/caes/documents/special_features/tickhandbook)
- 3 <https://peerj.com/articles/322/>
- 4 <https://doi.org/10.7717/peerj.322>
- 5 [http://books.nap.edu/openbook.php?record\\_id=13134&page=222](http://books.nap.edu/openbook.php?record_id=13134&page=222)
- 6 <http://www.cdc.gov/nczod/diseases/zoonotic/borrelia/lyme/0938-t1&sa=D&sntz=1&usg=AFQjCNGJcBbV5pjMmybevVvBqxaT7ZsYaw>
- 7 [www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0099348](http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0099348)

was comparable to some high-risk communities in the north-eastern U.S. The message is clear: in ecologically diverse California, LD, though reportedly of low prevalence statewide, can be highly prevalent locally or regionally.

None of the foregoing discoveries would have been possible without the enormous contributions made by the many members of my research team and other colleagues, or without the generous financial assistance of various funding agencies and donors. In concluding, I would like to pay special tribute to Phyllis Mervine and her confreres in honor of the 25th anniversary of the highly informative *Lyme Times*, and for their other beneficent ministrations on behalf of the Lyme community.

*Bob Lane is professor emeritus at the University of California Berkeley,*

more than two decades means that taxpayer-supported medical institutions are purposely avoiding designing and funding such studies. The implementation of a National Brain Autopsy Study has never been debated. Instead, the CDC focus remains on funding studies that potentially yield profitable patents on Lyme tests and projects with little patient benefit.

Instead of better science to determine persistence post-treatment, we have obfuscation and pork-barrel politics. Research monies paid by taxes are consistently allocated to the same organizations that have repeatedly failed to look at bacterial persistence in tissues post antibiotics.

As long as this continues, no real progress will be made to help patients with relapsing symptoms. Since the U.S. has failed in their leadership, I appeal to the world community.

In the beginning of the 20th century, the Pasteur Institute was the premier expert on spirochetes and *Borrelia* organisms. From my heart I truly wish the Pasteur Institute would once more take the lead in *Borrelia* research. I sincerely feel the American medical system has become a bloated bureaucracy that has lost its purpose and vision to do truly meaningful Lyme disease research that benefits infected patients.

*Tom Grier, a regular contributor to The Lyme Times, has been a Lyme patient advocate for over 20 years.*

coveries were not taken seriously. Among the concerns raised:

- The tissues did not demonstrate an expected microscopic cellular inflammatory response (a lack of inflammation repeatedly corroborated in subsequent needle autopsy pathology studies from international investigators).
- I was not a member of a medical school faculty.
- I had grown *Borrelia* spirochetes from deep anatomic sites.
- I was reporting fatal outcomes for Lyme infection.

At the same 1985 conference, Dr. Andrew Pachner delivered a lecture on Lyme in the nervous system of humans. At the conclusion, he recited the categories "primary, secondary, and tertiary neuroborreliosis." I was aware that nervous system disease in syphilis was subdivided into primary, secondary, and tertiary forms.

When Pachner uttered the words "tertiary neuroborreliosis," I recognized the idea for a research project. Dementia was one of the most feared forms of tertiary syphilis. Reasoning that tertiary neuroborreliosis was now open for study, I hypothesized that dementia in tertiary neuroborreliosis might be fertile territory for pathology investigation. Further, the most prevalent dementia of our time, Alzheimer's, might be the Lyme *Borrelia* "equivalent" of syphilitic dementia (general paresis of the insane).

### Borrelia and Alzheimer's

Back at the Southampton hospital I secured institutional permission to undertake a study of Alzheimer's autopsy brain specimens to search for microscopic evidence of *Borrelia* in diseased brain tissues. I became an affiliated research investigator under Glenner, director of the Alzheimer brain bank, University of California San Diego School of Medicine. In short order I received four fresh frozen autopsy Alzheimer brains from via Federal Express.

I applied the exact autopsy techniques previously perfected in my studies of fetal *Borrelia* infection due to miscarriage. I placed freshly thawed cubes of hippocampus in BSK culture medium. I took sections from the hippocampus of Alzheimer's brains and used special silver staining techniques perfected for the sole purpose of demonstrating spirochetes in tissue. These stains disclosed that spirochetes were present in the hippocampus of all four brains.

With the best available *Borrelia*-specific antibodies developed by Barbour (H5332 and H9724), I stained slides from the hippocampus sections of the brain specimens. I developed a special fingerprint contact impression of fresh thawed Alzheimer's hippocampus tissue and stained these "touch preparations" with silver stains and Barbour's *Borrelia*-specific antibodies.

These studies confirmed the presence of *Borrelia* in autopsy hippocampus from Alzheimer disease fresh frozen autopsy brains. To confirm the diagnosis of Alzheimer's by conventional criteria, I applied Alzheimer's specific silver staining methods to demonstrate the requisite neurofibrillary tangles and amyloid plaques. As further quality control, I sent glass slides from each of the four cases to the Armed Forces Institute of Pathology in Washington, D.C., for confirmation of Alzheimer's by board certified neuropathology specialists. Four of four cases were confirmed by outside consultation

using strict criteria for pathologic diagnosis of Alzheimer's.

### JAMA rejection

Immediately, I reported my results to the Journal of the American Medical Association (JAMA). By sheer coincidence, the editor in chief was George D. Lundberg, MD, a pathologist, to whom I sent a handwritten letter describing the events leading to the discovery of *Borrelia* spirochetes in Alzheimer's brain tissue. As is customary, JAMA solicited the opinion of outside reviewers whose identities were concealed.

One reviewer wrote, "These results, if true, would be of enormous importance; however, the appearance of the spirochetes in photomicrographs resembles the appearance of *Borrelia* spirochetes in culture... I do not know how to reconcile this..." This reviewer had not paid attention to the text of my manuscript, which detailed the successful cultivation of *Borrelia* spirochetes from cultures of Alzheimer's hippocampus tissue. I had successfully stained the cultivated spirochetes with Barbour's antibodies, producing positive results that were photographed and included in my manuscript.

JAMA's letter of rejection included their concern about possible repercussions by the public and medical community. Appended to the letter was a portion of a rejected reviewers letter explaining concern and reservations about the resemblance of my images of cultured spirochetes to images of *Borrelia* spirochetes grown in the laboratory from the B31 reference strain. Undeterred, I negotiated a compromise with JAMA to publish my findings in a briefer form, namely a letter to the editor, including a summary of two cases with pictures of cultured pure *Borrelia* and pictures of positive reactions with Barbour's specific antibodies. We agreed to substitute the word "dementia" for "Alzheimer's." The letter to the editor was published as "*Borrelia* in the brains of patients dying with dementia."

In 1987 I published a second case entitled "Concurrent neurocortical borreliosis and Alzheimer's disease" [*Human Pathology* v18,no 7]. In 1988 the New York Academy of sciences invited me to participate in a symposium entitled "Lyme disease and related disorders." The concept of cystic *Borrelia* forms was introduced to the world for the first time based on the identification in slides from a case of Alzheimer's, which all showed spiral *Borrelia* spirochetes reactive with antibody H5332.

All three of my papers were generally ignored until 1993 when Dr. Judith Miklossey independently began her work in neuropathology. She has begun to establish links between chronic spirochetal infection of the human brain and the subsequent development of Alzheimer's. She continues her work confirming that Alzheimer's disease and *Borrelia* infection of the human brain do indeed occur together.

I am continuing Alzheimer's/*Borrelia* research using specimens from the Harvard University brain bank and *Borrelia*-specific molecular Beacon DNA probes, which uniquely bind to *Borrelia* DNA and have no reaction with human or microbial DNA.

*Alan MacDonald, MD, a pathologist by training, was the first to publish evidence of various forms of Bb. He is currently a research associate with Dr. Eva Sapi at the U. of New Haven's Borrelia Research Lab.*

# Patient-Powered Research

Why the patient voice is critical to our national research agenda

By Lorraine Johnson, JD, MBA

Why is it important to have patients at the center of research studies?

Traditionally, research has been researcher-centered rather than patient-centered. Researcher-centered research pursues questions and curiosities of researchers that may have little relevance to patient care. While this research may advance the pet theory of a researcher or generate additional funding to support their theory, it may not improve patient care. It may, in fact, not even be research that patients think is important. And it may not apply to patients seen in clinical practice.

The Patient Centered Research Institute (PCORI) is a government funding organization that seeks to put patients at the center of research. Patient-powered research (PPR) is intended to be part of a learning healthcare system – one that learns from its mistakes. If they suggest a therapy, they look to see if, in fact, it works; if not, they go back to the drawing board.

PPR involves patients in framing the question, selecting the patient population,

determining the treatment approach to be studied, and interpreting and disseminating the results. Examples of organizations that pioneered PPR include the Dr. Susan Love Research Foundation's Army of Women.

As the authors of a recent article in Health Affairs explain:

Too much clinical research has been funded, conducted and published without attention to the ultimate relevance of the research questions or usefulness of the study findings to healthcare decision makers — namely, patients, caregivers, clinicians, payers and policy makers. Much clinical research has missed the mark.

When we look back over the past 10 years of research in Lyme disease, too much research funding has been given to answer questions that help support research paradigms of research. For example, how many projects do we need to fund to help Gary Wormser, MD, advance his theory that Lyme disease does not persist and that patients should not be treated? How about a research project that seeks to improve patient quality of life? To help patients get

back to work or school?

And as for a learning healthcare system in Lyme disease, it doesn't exist. When patients remain ill, the response has been "so what, too bad, learn to cope." Why not ask the obvious questions that patients care about? If 30 days of treatment doesn't work, what does? If 90 days of treatment doesn't work, what does? Or do these treatments work with certain patients, but not others? For these questions even to be asked, patients need a voice in selecting what type of research matters.

Right now, Lyme disease research remains in the age of the dinosaurs. Patient-powered research could change that. Count me in!

## References

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*Lorraine Johnson serves as a patient representative on PCORI. She is the executive director of LymeDisease.org and posts regularly on Lyme Policy Wonk at lymedisease.org. Contact her at lbjohnson@lymedisease.org. On Twitter, she's @lymepolicywonk.*

Congratulations  
to *The Lyme Times* and *LymeDisease.org*  
for 25 years of advocacy on behalf of Lyme patients

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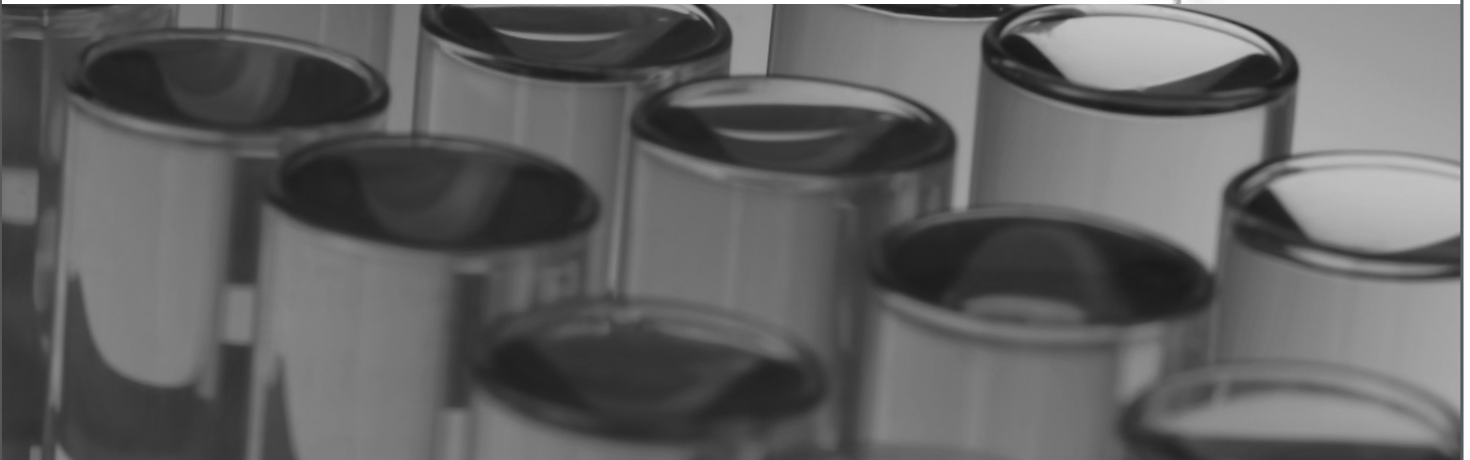


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# THE FDA WANTS TO REGULATE LYME LAB TESTS.

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## WHY IS THIS IMPORTANT?

The types of lab tests the FDA is considering regulating include tests manufactured by the specialty labs that patients and doctors rely on for accurate tick-borne disease diagnosis.

**Current FDA-approved tests are shown to miss more than 50% of Lyme disease cases.**

## WE NEED YOUR VOICE TO MAKE A DIFFERENCE!

The results of the survey will be used to assess patients views on Lyme lab tests and to inform our conversations with the FDA regarding its proposed regulation of Lyme disease testing.