Lyme retreatment guidance may be flawed

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A new statistical review calls into question studies that have been taken as proof that antibiotic retreatment for chronic Lyme disease is futile. That misunderstanding has led to medical guidance that discourages retreatment and insurance coverage for it. Instead, the authors of the review suggest, the proper reading of the studies and their data is that they prove nothing.

Deer ticks, Lyme disease, and medical guidance
Accepted medical practice discourages antibiotic retreatment in cases where Lyme disease symptoms persist. A new review of studies behind current medical advice says those studies prove nothing. *Credit: Centers for Disease Control*

PROVIDENCE, R.I. [Brown University] — Most doctors treat Lyme disease with antibiotics for two to four weeks after diagnosis, but if symptoms persist after that, medical guidelines recommend against antibiotic retreatment. That recommendation may not be warranted. A newly published statistical review of the four studies upon which those guidelines are based reports flaws in design, analysis, and interpretation that call into question the strength of the evidence against retreatment.

Allison DeLong, a biostatistician at Brown University's Center for Statistical Sciences and lead author of the study published online Aug. 19, 2012, in *Contemporary Clinical Trials*, said the four studies do not prove that retreatment does not work. That questionable interpretation, however, has led doctors to forgo treatment and insurance companies to withhold reimbursement.

"The goal of the paper is to clarify what was actually found from these clinical trials and what could be said and what couldn't be said," DeLong said. "A lack of evidence should not be used to deny treatment when the studies have serious flaws."

Evidence in the trials is most often inconclusive, she and three co-authors found. Two studies even found some statistically significant benefits from antibiotics.

DeLong has been curious about Lyme disease retreatment for more than a decade since a friend of hers seemed to benefit from therapy. Her friend paid for the treatment out-of-pocket. Statisticians would call that anecdote an "n of 1," but the example stuck with DeLong as more people, including journalists, began to question whether retreatment really was ineffective.

In 2009 and 2010, DeLong and her colleagues decided to look into the matter with full statistical rigor. Their analysis started by scanning the medical literature for any randomized clinical trials offering evidence of the efficacy of antibiotic retreatment for Lyme disease. Careful review of more than 100 studies ultimately whittled the field down to the four studies on which the Infectious Diseases Society of America and the American Academy of Neurology are based their guidelines.

The most influential studies were conducted by Klempner et al., and published together in the *New England Journal of Medicine* in 2001. The multicenter trials enrolled chronic Lyme sufferers with positive or negative blood serum results for Immunoglobulin G, an antibody that might indicate active infection. In each of the IgG positive and negative groups, patients either received IV antibiotics followed by oral antibiotics or IV placebo followed by oral placebo. Their symptoms were measured along the way using a subjective set of health quality-of-life measures called the SF-36.

Although Klempner et al. found no significant benefit to retreatment, findings from subsequent SF-36 studies in chronic illnesses provide evidence that the Klempner study was looking for unrealistically large differences.

"The trials, as designed, called for treatment effects considerably larger than the minimum clinically important differences (MCID) identified in other chronic illnesses, suggesting that the sample sizes were inadequate and the trials were very likely underpowered to detect the true underlying MCIDs," DeLong and her co-authors wrote in the journal.

Klempner's statistics showed that treatment might or might not have been effective given the broad range of a statistical measure known as the confidence interval, DeLong said.

In another of the four trials conducted by Krupp et al., researchers found that retreatment produced a significant benefit for fatigue, but the authors of the study mistakenly discounted that result, DeLong said.

The authors became concerned that their results were tainted by too many subjects realizing that they were receiving real treatment instead of the placebo. The measure of fatigue is subjective and could be influenced by that realization. But DeLong found that the subjects weren't likely to have realized anything. Here's why: If the members of each group have a blindly optimistic seven in 10 chance of believing that they received real medicine, then the people who really were would be right seven out of 10 times and the people receiving the placebo would only be right 3 out of 10 times. The people receiving the medicine would seem like they had discovered their status, but in reality they were only making a lucky, optimistic guess.

While the Krupp study was adequately powered to measure a significant benefit from fatigue, it had less power to measure the two other treatment effects it considered: improvements in cognitive processing and clearance of a potential Lyme disease biomarker, DeLong said.

The last of the four studies, by Fallon et al., had a very small sample size. It found hints of some benefits from retreatment but nothing definitive either positively or negatively.

Ultimately, DeLong said, the best evidence to support or refute antibiotic retreatment will come when scientists develop a definitive test for active Lyme disease infection. In the interim, it is possible that chronic Lyme disease patients harbor an ongoing infection that antibiotics could treat.

"The interpretation of the trials goes too far," she said. "You can't say it's been shown that retreatment is not beneficial. You can't then jump to the conclusion that this shows there is no persistence of infection."

In addition to DeLong, the paper's other authors are statistics graduate student Barbara Blossom of Colorado State University (Brown A.B., 1993), Dr. Elizabeth Maloney of Wyoming, Minn., and Dr. Steven Phillips of Greenwich Hospital in Connecticut.

Editors: Brown University has a fiber link television studio available for domestic and international live and taped interviews, and maintains an ISDN line for radio interviews. For more information, call (401) 863-2476.

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Antibiotic retreatment of Lyme disease in patients with persistent symptoms: a biostatistical review of randomized, placebo-controlled, clinical trials.

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Abstract

INTRODUCTION:

Lyme disease (Lyme borreliosis) is caused by the tick-borne spirochete Borrelia burgdorferi. Long-term persistent illness following antibiotic treatment is not uncommon, particularly when treatment is delayed. Current treatment guidelines for persistent disease primarily rely on findings from four randomized, controlled trials (RCTs), strongly advising against retreatment.

METHODS:

We performed a biostatistical review of all published RCTs evaluating antibiotic retreatment, focusing on trial design, analysis and conclusions.

RESULTS:

Four RCTs met the inclusion criteria; all examined the efficacy of intravenous ceftriaxone versus placebo at approximately 3 or 6 months. Design assumptions for the primary outcomes in the two Klempner trials and two outcomes in the Krupp trial were unrealistic and the trials were likely underpowered to detect clinically meaningful treatment effects. The Klempner trials were analyzed using inefficient statistical methods. The Krupp RCT was well-designed and analyzed for fatigue, finding statistically significant and clinically meaningful improvement. Fallon corroborated this finding. Fallon also found improvement in cognitive functioning, a primary outcome, at 12 weeks which was not sustained at 24 weeks; improvements in physical functioning and pain were demonstrated at week 24 as an interaction effect between treatment and baseline symptom severity with the drug effect increasing with higher baseline impairment.

DISCUSSION:

This biostatistical review reveals that retreatment can be beneficial. Primary outcomes originally reported as statistically insignificant were likely underpowered. The positive treatment effects of ceftriaxone are encouraging and consistent with continued infection, a hypothesis deserving additional study. Additional studies of persistent infection and antibiotic treatment are warranted.

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Lyme Disease: Antibiotics fuel debate

Written by Mary Beth Pfeiffer Poughkeepsie Journal
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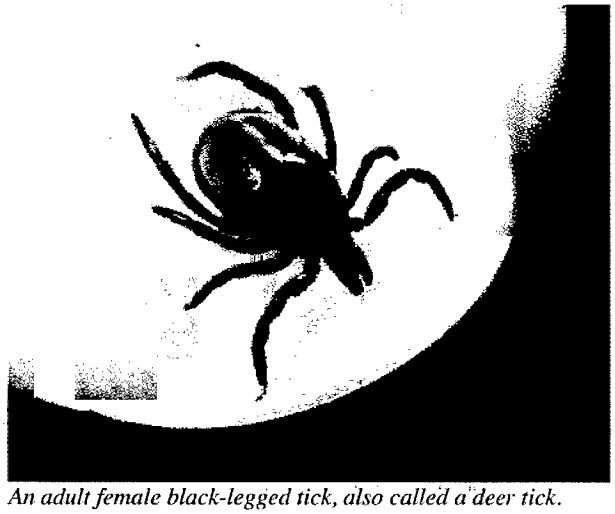

An adult female black-legged tick, also called a deer tick.

ABOUT THIS Series

This is part 2 in a Poughkeepsie Journal series on Lyme disease. In three months of research, the Journal spoke to scientists, physicians and patients and studied scientific and statistical reports.

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Go to www.poughkeepsiejournal.com to read scientific studies on Lyme disease and to view video interviews with Lyme patients. To read part 1 of the series, click on the Journal's watchdog reports page.
The Poughkeepsie Journal will host a
live chat about Lyme disease with
Mary Beth Pfeiffer, projects writer, on
Facebook at 7 p.m. Thursday. Join us at www.poughkeepsiejournal.com/ facebook

Enemy No. 1 in the war on Lyme disease is a tiny tick that has put the mid-Hudson Valley at the epicenter of a global health threat.

But the prime target of some is not an army of arachnids, as ticks are known. Instead, in this bull's-eye is a handful of doctors — doctors who dispense long-term antibiotics for the illness. At least five, including two in Dutchess County, are under investigation by state licensing officials, the Poughkeepsie Journal has exclusively learned.

While officials contend they do not investigate physicians "simply because 'traditional' treatment protocols (two to four weeks of antibiotics) are not followed," the medications are at the heart of a vitriolic and far-reaching debate over how best to care for advanced Lyme disease, according to interviews with scientists, physicians, patients and their advocates.

The disagreement has marked the disease as a political and scientific quagmire, these people said. Most importantly, it has hampered access to care for Lyme sufferers — in both early and later stages of the disease.

"I had been struggling since 2009 to get diagnosed with Lyme," said Dina Rosado, 44, of Highland, who suffered seizures, vision loss, pain and anxiety before receiving intravenous antibiotics from the 12th doctor she saw. "The word Lyme is taboo to a lot of doctors. They don't want to touch it."

The story told by Rosado, who was sometimes bedridden and estimates she is 70 percent better after months of intravenous and oral antibiotics, echoed that of other long-term Lyme patients who said they saw six, 10, even 14 doctors before getting a diagnosis.

They were told, variously, they did not have Lyme, they suffered multiple sclerosis, fibromyalgia or rheumatoid arthritis, or, even had a mental disorder.

"Just because they are treating you like you're not sick doesn't mean you're not sick," said Antonia McVicker, 26, who contracted the disease while living in Ulster County and had two of 10 doctors refer her for psychiatric care. "It's the only medical issue where you have half the doctors against the patient."

Such physicians would argue that these patients merely found a doctor willing to name their malady Lyme and treat it with antibiotics. But the patients' experiences, coupled with some key scientific research that chronic Lyme believers say has been ignored, suggest they may be on to something.

"I think there is evidence that repeated antibiotic therapy can be helpful," said Brian A. Fallon, a psychiatry professor and director of the Lyme and Tick-borne Diseases Research Center at Columbia University Medical Center in New York City. "We don't know enough about therapeutic approaches that are helpful ... to start accusing doctors of doing the wrong thing when studies have not been done."

Jill Auerbach, a Lyme patient and chairwoman of the Hudson Valley Lyme Disease Association, argues that doctors should err on the side of treatment: "Do you leave these ill patients untreated and send them away when there is still no scientific consensus?"

The mid-Hudson Valley has the nation's highest rates of Lyme disease, a health threat complicated by emerging evidence of other infections carried by ticks. More than 26,000 cases of Lyme disease were reported in Dutchess and Ulster counties from 1992 to 2011, with estimates that tens of thousands more have gone unreported. Dutchess had the most cases of any county nationwide from 2002 to 2006, the latest statistics show.

Because it has such high disease numbers, the valley has some of the most experienced Lyme physicians, who often receive cases from far-flung states. As such, a national debate about so-called chronic Lyme disease is playing out, almost literally, in our backyards, with patients — and doctors — square in the middle.

"Just about every physician in the state who cares for people with chronic Lyme is currently under investigation," said a local physician among five over whom the state quietly opened investigations in the past 18 months. "It's very threatening."

No doctor would publicly acknowledge ongoing investigations — on the advice of attorneys, for fear of alienating state monitors and because such probes are a sensitive issue for any physician.

Dueling sides

At the root of Lyme patients' struggle for care is a contentious debate over how best to diagnose Lyme disease, the reliability of laboratory tests and the precise definition of chronic Lyme.

On one side is the prevailing medical wisdom, codified in guidelines of the Infectious Diseases Society of America, a 9,000-member physician organization, that the Lyme bacteria are killed off by 14- to 28-day courses of antibiotics. The guidelines, adopted by the U.S. Centers for Disease Control and Prevention, are based largely on a 2001 study that found no meaningful improvement and no active infection in 129 chronically ill Lyme patients after 90 days of antibiotic re-treatment.

The patients' severe, lingering symptoms, from arthritis to neurological impairment, were real, the study concluded, but were not due to live Lyme bacteria. Most physicians follow the guidelines closely, in particular as nonconforming doctors have been targeted for discipline.

On the other side, however, are doctors and patients who maintain they have seen improvement, in sometimes dire cases, after longer, often repeated, courses of oral and intravenous antibiotics. Their view is bolstered by animal studies showing that the bacteria, a spirochete like syphilis, survived initial antibiotic treatment in dogs, mice and monkeys, suggesting the need for more treatment. Additionally, two small studies showed short-lived improvement with antibiotics in people who had already been treated once.

The debate over chronic Lyme disease — what the CDC calls "post-treatment Lyme disease syndrome," affecting 10 percent to 20 percent of patients — reflects two polar viewpoints on Lyme: On one hand, it is a disease that is difficult to catch and easy to cure; on the other, it is a long-term threat that withstands medicine's best pharmaceutical defense.

A key player in this fray is the state Office of Professional Medical Conduct, which oversees physicians and is obliged to investigate all complaints against them. Statistics show half of 8,501 complaints filed for all reasons in 2010 came from the public, and a small number, 3 percent, were filed by insurance companies, which are feared and viewed with suspicion by doctors who treat chronic Lyme disease.

"Physicians who care for patients with chronic Lyme disease are often 'red-flagged' by insurance companies" for incurring big costs, said Dr. Kenneth Liegner, a Pawling Lyme specialist, at a May conference at Skidmore College in Saratoga Springs. They "risk being subjected to sanctioning and 'de-selection' if they participate with insurance companies."

Hence, many don't, requiring considerable upfront payment — from $650 to $1,800 — that limits care to those who can afford it. Treatments are also costly: about $750 a month for drugs and supplies alone, some covered by insurance, plus $1,000 to $3,000 to insert an arm catheter that feeds drugs to the heart.

While costs are hefty, there is no evidence that insurers have reported Lyme doctors — complaints are confidential — and two companies declined requests to comment. One physician said state licensing officials began a probe just after a claim for antibiotic treatment was questioned by an insurer. At the same time, the licensing office itself was found to have contacted patients of a Dutchess County physician several years ago to encourage them to file complaints, two sources with direct knowledge told the Journal.

State officials could not say how many doctors have been censured; three probes are known. In 1999, a Lyme physician's license was revoked after charges of "gross negligence" and ordering excessive treatment. (The revocation was reversed in 2010.) In 2002, a physician was found negligent and was sentenced to two years of licensing probation. Both practiced on Long Island. In 2007, a Dutchess doctor settled undisclosed "nondisciplinary" charges and faced no suspension.

Jeffrey Hammond, a spokesman for the licensing board, part of the state Health Department, said in an email, "OPMC does not investigate physicians because they use long-term antibiotics to treat Lyme disease. Generally speaking, OPMC has disciplined physicians for negligence in the treatment of the Lyme disease."

But for licensing officials, treatment outside the official guidelines may be the same thing, observers believe.

"If every question (by state overseers) is how you treat Lyme disease, you are against these long-term treatments," said Assemblyman Joel Miller, a Poughkeepsie Republican involved in the issue since the 1990s and who has been in contact with physicians under investigation.

'Witch hunt' alleged

Unlike Massachusetts, Connecticut, Rhode Island and New Hampshire, New York does not have a law to protect physicians who treat Lyme disease with long-term antibiotics. But in 2005, under pressure from state legislators

such as Miller, the medical-conduct office issued a memorandum on Lyme treatments "that are not universally accepted."

"It is contrary to the policy and practice of the office ... to identify, investigate or charge a physician ... solely on that practitioner's recommendation or provision of such a treatment modality," it stated.

Miller said the memo is not being followed and called the new probes a "witch hunt." Miller, U.S. Rep. Christopher Gibson and Assemblyman Richard Gottfried, D-Manhattan, have discussed the probes with the state health commissioner or licensing director, both of whom declined an interview through a spokesman.

Physicians who treat chronic Lyme say that medicine is sometimes an art as much as a science that calls for practitioners to try things in the service of healing. Some use oral or intravenous antibiotics or a combination, sometimes "pulsing" drugs in a week-on, week-off rotation. Some add alternative therapies and vitamins.

"Ultimately, you have to use your clinical judgment as a physician," said Dr. Daniel Cameron of Mount Kisco, Westchester County. He said he frequently finds long-term oral antibiotics successful and prescribes intravenous drugs if needed.

At an outpatient clinic at Vassar Brothers Medical Center, about a quarter of patients receiving intravenous medications are under treatment for Lyme disease, many for longer periods than the guidelines suggest. The guidelines, essentially treatment recommendations, do not preclude such care.

"I've watched people come in who couldn't walk," said Carmela Legari, the infusion center supervisor. "You can watch the symptoms slowly dissipate."

Such observations may be common in chronic Lyme circles, skeptics say, but are not science.

"If you are saying something works," said Dr. Phillip Baker, executive director of the American Lyme Disease Foundation, "it's incumbent on you to provide evidence that it works." (Typical of the debate, there are several warring organizations, with Baker's on one side and the Lyme Disease Association on the other.)

The drawbacks to antibiotic treatment are potentially serious side effects. One patient had a life-threatening pulmonary embolism and another had intestinal bleeding, studies show, while the intravenous line has led to infection. But Lyme-treating physicians argue that antibiotics have been used for long periods for other diseases such as tuberculosis and say they limit intravenous use to a small fraction of cases.

The question is how much and how long for Lyme. Patients interviewed varied from repeated two-month courses to up to a year of intravenous treatment, with varying results, and up to three years of oral medications.

Dr. Steven J. Bock, a family doctor and alternative practitioner in Rhinebeck, said he has treated 7,500 Lyme patients; he initially resisted the idea of antibiotics as an adherent of complementary medicine like acupuncture and herbs, which he also uses.

"When someone has been sick with a lot of multiple symptoms," he said, "and then they go on antibiotics longer than the usual but they turn out on the other end 95 percent better — that to me is a clinical success."

He acknowledged that some respond better than others.

Dr. Kari Bovenzi, one of few pediatricians who treat advanced cases of Lyme disease, believes longer antibiotic courses are necessary to beat back the hearty Lyme spirochete.

"There is something about this bacteria ... it is a survivor," said the Albany physician, who began treating Lyme after her own bout in 2009. "It took lots of antibiotics and other treatments for me to feel I could think again."

Dr. Richard Horowitz of Hyde Park, who has treated more than 12,000 Lyme patients, the majority from outside Dutchess, said the naysayers are wrong.

"They are basically saying Lyme is easily diagnosed, easily treated and (those with lingering problems) are dealing with an auto-immune reaction," said Horowitz, who lectured on Lyme in China recently at the request of the Chinese government. "Unfortunately, that's not true."

"Re-treatment (with antibiotics) does help patients," he said. "There's not even a doubt that re-treatment helps."

Horowitz believes that many Lyme cases go undetected because of unreliable testing; others resist treatment because of co-infections from other bugs carried by ticks, such as babesia.

Evidence missing

While so-called Lyme-literate physicians may have substantial success, their evidence is mostly anecdotal. At the same time, their diagnoses are often clinical, based on symptoms rather than blood tests, which they say are conflicting and imprecise.

"I have seen many, many patients referred and treated for chronic Lyme disease and for chronic co-infections," said Dr. Gary Wormser, an infectious disease physician at New York Medical College in Westchester County who has published widely on tick-borne diseases. "Almost invariably the patients have never had any evidence of ever having had Lyme disease or a co-infection."

Wormser, more than anyone, is the voice and face of efforts to portray the Lyme bacteria as easily killed off with antibiotics, while maintaining that remaining symptoms are from other causes. Wormser led the Infectious Diseases Society panel that wrote the Lyme guidelines that are so controversial today.

"There's no evidence in North America of persistence of the spirochete after treatment," he said. "We've published on it and we've looked."

Anyone prescribed prolonged antibiotics for Lyme or a co-infection, he wrote in capital letters in an email, should get a second opinion from "A MAINSTREAM MEDICAL PRACTITIONER."

At a congressional hearing on Lyme disease in July, called to explore its global implications, Stephen Barthold, a professor of veterinary medicine at the University of California at Davis, testified that animal studies are clear.

"Experimental studies, using a broad spectrum of animal species (mice, dogs, monkeys) and a variety of antibiotics, have all shown a failure to completely cure the animals" of Lyme infection, he testified. Barthold, who has studied Lyme disease for 25 years, detected the presence of Lyme spirochetes using unconventional methods not used on humans. These included letting uninfected ticks bite animals to see if they became infected and, after euthanasia, harvesting samples of tissue where Lyme is suspected to hide.

"These surviving spirochetes are not simply 'DNA debris' as some contend, but are rather persisting, but non-cultivable, spirochetes," he told members of Congress, who are considering legislation to form a Tick-Borne Disease Advisory Committee that would coordinate federal response and, it is hoped, resolve the conflict over chronic Lyme disease.

Wormser said the studies "are being over-interpreted" and the animals weren't given antibiotic doses comparable

to humans, which Barthold disputed.

Guidelines survive

While both sides agree that more research needs to be done, the society's guidelines, which ascribe many lingering Lyme symptoms "to the aches and pains of daily living," hold fast. They survived a 2008 investigation by then Connecticut Attorney General Richard Blumenthal, who said the disease panel "blocked appointment of scientists and physicians with divergent views on chronic Lyme" and had members with financial interests in "drug companies, Lyme disease diagnostic tests, patents and consulting arrangements with insurance companies."

Blumenthal's report led to a second panel and hearing where, among others, a Brown University statistical analysis was presented on four human Lyme studies. An author, Allison DeLong, said the primary study on which the guidelines were based suffered from "substantial statistical problems that prevent its use in formulating treatment guidelines." Other studies, which challenged the guidelines, had "no problems with their statistics or interpretation," she testified.

Nonetheless, the panel upheld the guidelines in 2009 as "the highest-quality medical/scientific evidence" — while noting they were not intended to be "rigid dicta, inflexible rules, or requirements of practice."

As the debate has played out in science journals and Internet chatter, advocates, patients and Lyme-treating physicians said it has had an unfortunate upshot: It has scared off doctors from prescribing antibiotics for Lyme disease.

"Doctors are not treating at the first sign," said Mary Belliveau, a retired nurse who runs a Lyme disease support group in Rhinebeck. "They say, 'Wait to see if symptoms develop.'"

Pam Weintraub, a former Westchester resident and journalist who wrote a book called "Cure Unknown" on her family's years-long Lyme struggle, said doctors are "intimidated from even looking for Lyme disease." Why? "Fear that they would be investigated."

Gibson, who with Smith and Blumenthal is sponsoring the legislation to form a federal advisory committee on Lyme disease, said New York needs to change priorities.

"The focus should not be going after doctors," he said. "Some (patients) are getting treated. But the issue is there aren't enough doctors that are treating them." He said the guidelines should be changed and doctors made "privy to some of the successful protocols."

Lyme patients, meantime, believe it shouldn't be so difficult to get the antibiotics they believe have helped them.

"I thought I was dying, and then all of sudden you start to gradually feel better," said Doreen Peone, 51, of Saugerties, who was on intravenous treatment for a year.

"No one will ever know what Lyme pain is like," she added, "until they experience it."

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WHY IS CHRONIC LYME DISEASE CHRONIC?

Several factors may account for persistent symptoms. These include low grade persistent infection which either causes damage directly or indirectly through the inflammatory and toxic effects of an activated immune response, permanent damage as may occur in brain injured patients, or a Lyme-triggered autoimmune reaction.

The persistent infection hypothesis is based on several lines of evidence. Clinical case reports and large clinical series indicate that some patients benefit from longer and repeated courses of antibiotic therapy. Published reports indicate that, even after antibiotic therapy, persistence of the spirochete Borrelia burgdorferi may be demonstrated by either culture or demonstration of Bb DNA by PCR analysis in animals (mice, dogs) and humans. While positive cultures despite antibiotic treatment were reported early in European Lyme disease, in the United States there is only one reported case of confirmed Bb growth by culture after treatment (Liegner et al). The mechanisms of persistence and immune evasion are thought to include sequestration in intracellular or other immunologically privileged sites, antigenic variation, decreased expression of surface antigens in vivo, capture of the host-cell's own membrane forming a virtual immunoprotective cloak, and/or early down-regulation of the immune response. Much in vitro evidence now exists to demonstrate that Bb can lodge intracellularly in human endothelial cells, astrocytes, fibroblasts, and macrophages. Bb in vitro has been shown to enter B Lymphocytes and to exit drawing with it the outer surface membrane of the lymphocyte. Bb in vitro can modify its shape into potentially cyst-like forms; these forms however at present are of uncertain significance. These findings suggest that failure to eradicate Bb completely by antibiotic therapy may be due to intracellular localization in vivo, the selection of resistant strains, or sequestration in sites (such as the central nervous system) where antibiotic penetration may be less adequate.

The post-infectious inflammatory hypothesis also is supported by several lines of evidence. For example, patients with Lyme arthritis who carry the HLA-DR4 or DR2 allele are more vulnerable to developing a chronic antibiotic-resistant arthritis. Indirect evidence exists to support molecular mimicry as at least one possible explanation for persistent symptoms. For example, the flagellin protein

(on the tail of the spirochete) can generate antibodies that cross-react with myelin basic protein, thereby contributing to axonal dysfunction. Finally, remnants of pieces of the spirochete may result in a persistent activation of the immune system, causing the production of interleukin-6, tumor necrosis factor, and nitric oxide. These cytokines produce fatigue and malaise, two of the more prominent symptoms experienced by patients with chronic Lyme disease.

It is reasonable to assume that some patients suffer from persistent infection whereas others suffer from immune-mediated post-infectious damage. Until more is known about the factors which identify who may respond to repeated treatment and who is unlikely to respond, clinical decisions will be based on physician preference rather than objective data. Longer vs shorter duration placebo-controlled antibiotic trials need to be conducted with long-term blinded follow-up using objective markers. Until then, the optimal treatment of the patient with chronic Lyme Disease will be unknown. At this point in medical history, decisions about the treatment of the patient with chronic Lyme disease need to be individually shaped by the clinician's experience, the patient's clinical profile and history of antibiotic responsiveness, and the emerging medical literature.