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Chronic Lyme Disease: Why Is This Still Controversial?

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Abstract

While it is clear that a cohort of patients treated for acute Lyme disease continue to have persistent symptoms, the etiology of these symptoms remains controversial despite clear evidence that multiple mechanisms may be responsible for their etiopathogenesis. These include persistent infection with *Borrelia burgdorferi*; the existence of coinfections; chronic systemic inflammation associated with dysregulation of the immune system, autoimmunity, and excessive mast cell activation; and dysregulation of the autonomic nervous system. Rather than rely on flawed IDSA guidelines, it is incumbent on physicians to seriously investigate the underlying mechanisms of chronic symptoms in these patients.

Keywords: Lyme disease; *Borrelia burgdorferi*; Coinfections; Post treatment lyme disease syndrome; IDSA guidelines

Introduction

Lyme disease is the most common vector-borne disease in the United States. The chronology of textbook acute Lyme disease is well established: *Ixodes* tick attachment, Erythema Migrans (EM) rash, flu-like syndrome and, if left untreated, early disseminated infection that can progress to late-stage Lyme disease. The consensus of the medical community is that, if diagnosed in a timely fashion and treated with an appropriate course of antibiotics, there is the likelihood of a cure.

However, it is now well accepted that 10-20% of patients treated for acute Lyme disease will subsequently develop chronic symptoms [1,2]. These patients have now been classified as suffering from Post Treatment Lyme Disease Syndrome (PTLDS). The actual prevalence of individuals who develop chronic symptoms following treatment for acute Lyme disease may be far greater than 10-20%. Shadick, et al., noted that 13 of 38 patients (33%) diagnosed and treated for acute Lyme disease remained significantly symptomatic for over six years after treatment [3]. Asch, et al., reported that 114 of 215 patients (53%) continued to complain of fatigue, joint pains, cardiac and neurological symptoms for over three years after treatment for acute Lyme disease [4].

According to the Infectious Disease Society of America (IDSA), if patients are treated with appropriate antibiotics for up to fourteen days, there is no evidence that infection persists in an otherwise immunocompetent host. They state that "There is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease" [5].

The IDSA guidelines do not explain why some patients previously diagnosed with Lyme disease and treated with antibiotics continue to be symptomatic.

Literature Review

A review of the medical literature was performed regarding the pathophysiology of *Borrelia burgdorferi (B.burgdorferi),* evidence of persistent infection, methods of immune suppression and evasion and antibiotic resistance, and the prevalence of tick-borne coinfections. Additionally, an analysis of the IDSA guidelines in reference to Lyme disease was performed.

What are the numbers?

Lyme borreliosis is a worldwide epidemic. A report in 2022 estimates that 14.5% of the world's population has or has been infected with *B.burgdorferi* [6]. In the United States, the Centers for Disease Control and Prevention (CDC) reports that nearly 500,000 new cases of Lyme disease have occurred annually from 2010 to 2018 [7]. However, the CDC surveillance criteria are quite restrictive, and the CDC clarifies that these criteria are not appropriate for clinical diagnosis in a doctor's office [8]. When clinical criteria are used to make a diagnosis, it is estimated that there are more than 1,000,000 new cases of Lyme disease in the United States every year [9,10]. In fact, when directly comparing clinical diagnosis with the CDC surveillance criteria recommendation for two-tier testing, investigators found that the CDC criteria would identify only 22% of subjects, suggesting over 2,000,000 new cases of Lyme disease occur annually in the U.S [11]. Even if the conservative estimate that only 10-20% of these patients will develop chronic symptoms is used, there are hundreds of thousands of patients who will become chronically ill from Lyme disease every year. This does not include those who were never diagnosed with acute Lyme disease, perhaps never witnessed a tick bite or a rash, and simply developed chronic symptoms of unknown etiology. The number of these chronically infected ill individuals is unknown.

What is the basis of the IDSA recommendations?

The IDSA base their conclusion of insufficient evidence for persistent infection on four retreatment trials where an additional course of antibiotics did not demonstrate appreciable improvement of patient symptoms. Two of these trials were performed by the same research team, and are referred to collectively as "the Klempner study" [12]. The first Klempner trial treated seventy-one patients who were seropositive for *B.burgdorferi* and had chronic symptoms after previous treatment for Lyme disease. The second Klempner trial was comprised of fifty-one patients with the same history who were seronegative. Patients in both studies were treated with one gram of IV ceftriaxone daily for one month followed by oral doxycycline 100 mg twice daily for two months. The researchers assessed outcome using the SF-36 questionnaire, a patient-reported survey which measures both mental and physical health, and found no change in clinical symptoms after the two months of treatment.

Fallon, et al., conducted a different study consisting of thirty-seven patients who had previously been treated for Lyme disease, were still symptomatic, and had persistent IgG positivity on Western Blot [13]. Patients were treated with two grams of IV ceftriaxone daily for ten weeks, and at twelve weeks reported significant improvement in fatigue, pain, cognition, and physical functioning. However, at twenty-four weeks, fatigue and cognitive issues relapsed, although pain and physical functioning maintained their improvement.

Krupp, et al., and colleagues conducted a study of fifty-five patients with ongoing symptoms following treatment for Lyme disease [14]. All were administered IV ceftriaxone 2 gm daily for one month; after four weeks patients reported significant improvement in fatigue but not in cognition.

Do these four studies support the IDSA conclusions? The Klempner studies have so many flaws that some claim they were designed to fail. First, the antibiotic doses and the duration of treatment are considered insufficient by many; doctors who specialize in the treatment of chronic tick-borne infections typically recommend twice those doses and for a longer duration [15]. Furthermore, it turns out that 30 percent of patients had already failed IV antibiotic treatment for at least thirty days (a median of seventy-one days in the seropositive group and fifty-four days in the seronegative group), meaning there was significant selection bias to include subjects who had already failed to respond to retreatment [16,17]. And finally, while many patients with Lyme disease are concurrently infected with other tick-borne infections, there was no testing or treatment for co-infections.

Regarding the Fallon study, the IDSA cites it as not providing evidence for benefit of retreatment in patients who continue to have symptoms following treatment for Lyme disease. However, Fallon documented significant improvement when patients were assessed twelve weeks after completing a retreatment regimen. The IDSA has highlighted the fact that improvement was not fully sustained at twenty-four weeks (when patients had been off treatment for fourteen weeks) and thereby concluded that additional treatment is ineffectve. The alternative interpretation is that patients would do even better with longer durations of treatment. While this study also did not consider the existence of co-infections, the positive response to antimicrobial treatment provides strong evidence for persistent infection.

Similar conclusions can be drawn from the Krupp study. Again, the IDSA claims that this study proves that retreatment with antibiotics is ineffective, when in fact the clinical improvement in fatigue after only one month of treatment offers supportive evidence of the effectiveness of retreatment and persistent infection.

DeLong, et al., performed a bio-statistical review of these four trials and concluded that ceftriaxone treatment produced clinically meaningful improvements in fatigue and cognitive functioning, and that patients with serious baseline pain and poor physical functioning after conventional Lyme disease treatment are likely to experience significant and sustained improvement from more prolonged retreatment [16]. The bottom line is that the results of these four retreatment trials do not support the IDSA position that a short course of antibiotics successfully eradicates infection with *B.burgdorferi*, and two of the studies are consistent with persistent infection in patients previously treated with antibiotics. There are no studies that have documented that two weeks of antibiotics cures all cases of acute (or late-stage) Lyme disease.

What is the quality of the IDSA guidelines?

Khan, et al., reviewed all the guidelines issued or endorsed by the IDSA from March 1994 to June 2009 [18]. They determined that "The IDSA guideline recommendations are primarily based on low-quality evidence derived from nonrandomized studies or from expert opinion." Lee and Vielemeyer analyzed forty-one IDSA guidelines released from January 1994 to May 2010 [19]. They concluded that "More than half of the current recommendations of the IDSA are based on level III evidence [expert opinion] only. Until more data from well-designed controlled clinical trials become available, physicians should remain cautious when using current guidelines as the sole source guiding patient care decisions."

In 2013, Lenzer, et al., published their concerns regarding the integrity of practice guidelines [20]. They stated that ". . . widespread financial conflicts of interest among the authors and sponsors of clinical practice guidelines have turned many guidelines into marketing tools of industry. Financial conflicts are pervasive, under-reported, influential in marketing, and uncurbed over time." They concluded that "Biased guidelines can cause grave harm to patients, while creating a dilemma for doctors who may face professional or legal consequences when they choose not to follow guidelines they distrust. Such guidelines fail to place patients' needs foremost, and instead protect livelihoods and preserve ideologies."

Johnson and Stricker analyzed the IDSA guidelines regarding Lyme disease and described multiple flaws and weaknesses [21]. These included conflicts of financial interest among key panel members regarding Lyme disease patients, diagnostic tests, vaccine development, and insurance consulting fees [22]; and found that 38 of the 71 guideline recommendations (47%) were based on Level III evidence (expert opinion without data), which is considered the weakest level of evidence [23].

As more research comes to light, the evidence is mounting that the IDSA Lyme guidelines are flawed both in their development and in their recommendations.

What is the evidence for persistent infection?

The medical literature is replete with both human and animal studies that have demonstrated persistent infection with *B.burgdorferi* despite aggressive and prolonged antimicrobial treatment. Some of these studies are dependent on PCR evidence of persistence, which has been challenged on the basis that fragments of DNA may persist in

the absence of active microbial infection. However, some of these studies have confirmed live spirochetes as well as response to retreatment.

Oksi, et al., reported on 165 patients who had experienced *Ixodes* tick attachments and EM rashes and were serologically positive for Lyme disease. Following antimicrobial therapy, 136 of the patients were retested and 14 were PCR positive for *B.burgdorferi*, of which twelve had clinically relapsed. Three of these patients had positive blood cultures for *B.burgdorferi*, and all responded to retreatment. "We conclude that the treatment of Lyme borreliosis with appropriate antibiotics for even more than three months may not always eradicate the spirochete."

Chancellor, et al., described seven patients with neurologic and urologic issues associated with Lyme disease [25]. All were treated with IV ceftriaxone, but four of the seven relapsed and were re-treated with IV ceftriaxone. One patient who continued to have symptoms had *B.burgdorferi* present in a bladder biopsy.

Middelveen, et al., studied twelve patients with Lyme disease symptoms who had been treated or were being treated with antibiotics [26]. Cultures of blood, urogenital secretions, or skin demonstrated *B.burgdorferi* in all twelve patients; the control group all had negative cultures.

Steere, et al., reported that six out of twelve patients treated for Lyme arthritis continued to have spirochetes in their joints [27].

There are multiple case reports of people who were treated aggressively for Lyme disease but continued to have evidence of persistent infection. For example, a twenty-four-year-old woman developed an EM rash after camping in Pennsylvania, then developed arthritis years later [28]. Despite multiple antibiotic trials and multiple arthroscopic and open synovectomies, Lyme spirochetes were demonstrated by PCR and silver stain in the synovial fluid and in the synovium. The patient always responded to antibiotics but relapsed when antimicrobial therapy was discontinued.

Multiple animal studies have demonstrated persistent infection in animals despite aggressive treatment with antibiotics. These include mice, rats, hamsters, guinea pigs, gerbils, dogs, and nonhuman primates, including baboons and rhesus macaques [29]. Embers, et al., infected rhesus macaque monkeys with *B.burgdorferi*, and twenty-seven weeks later treated them with antibiotics analogous to the Klempner trial—IV ceftriaxone followed by oral doxycycline [30]. On necropsy, 75 percent demonstrated persistent infection using culture, immunofluorescence, and PCR techniques. In a separate trial of the same study, the researchers infected monkeys and treated them at the early stages with four weeks of oral doxycycline. Persistent infection was demonstrated by xenodiagnosis: Uninfected ticks allowed to feed on these monkeys then exhibited *B.burgdorferi* in their midguts.

In a follow-up study, Embers exposed monkeys to ticks carrying *B.burgdorferi* and four months later treated them with doxycycline orally for twenty-eight days at a dose proportional to that used in humans [31]. Living *B.burgdorferi* spirochetes were found in multiple organs after treatment. "It is apparent from these data that *B.burgdorferi* bacteria, which have had time to adapt to their host, have the ability to escape immune recognition, tolerate the antibiotic doxycycline, and invade vital organs such as the brain and the heart."

Hodzic, et al., injected mice with *B.burgdorferi* and treated them with ceftriaxone injections for thirty days [29]. At twelve months, all the mice were positive for persistent infection based on xenodiagnosis —positive PCR for *B.burgdorferi* in ticks that fed off the mice.

This is a sampling of the hundreds of articles in the medical literature that demonstrate persistent infection with the Lyme spirochete following treatment with antibiotics [32]. Dr. Keith Berndtson extensively reviewed the evidence of persistent infection and documented that the Lyme spirochete can ". . . remain infective in humans and animals despite aggressive antibiotic challenge" [33].

How does *B. burgdorferi* evade the immune system and resist antibiotics?

In Berndtson's article he reviewed the mechanisms by which *Borrelia* spirochetes evade immune defenses and survive treatment with antibiotics [33]. The following bulleted list is taken directly from Berndtson's article:

- Exploit tick salivary proteins to delay early host immune responses.
- Deceive alternative complement pathways by masking surface antigens.
- Usurp the host's plasminogen activating system.
- Continuously vary its surface antigens to frustrate humoral immune responses.
- Translocate using uniquely agile motility skills.
- Use chemotactic and niche-seeking traits to evade host immune traffic.
- Engage in quorum sensing and in biofilm-like behavior.
- Upgrade its genetic code through Horizontal Gene Transfer (HGT).
- Assume atypical morphologies that differ from its spirochetal form.
- Potentially form persister cells able to tolerate antibiotic challenge (thus far unproven).

In his article, Berndtson provided extensive explanation and references for the above issues, and there is updated evidence for the presence of persister cells [34-36]. While there is ongoing evidence of persistence, the mechanism of chronic symptoms is not well defined. These patients have evidence of immune dysfunction and autoimmunity with chronic systemic inflammation, dysfunction of the autonomic nervous system, and mast cell activation with release of cytokines [37-40]. This is not dissimilar to patients suffering from long COVID, who exhibit similar symptoms to chronic Lyme disease [41].

However, the elephant in the room is the presence of coinfections. The *Ixodes* tick harbors a microbial menagerie: In addition to *B.burgdorferi*, these include *Babesia* spp., *Bartonella* spp., *Anaplasma phagocytophilum,* the Spotted Fever group of *Rickettsia*, *B.miyamotoi*, and Powassan virus [42]. Surveys of ticks from multiple continents have demonstrated that "Coinfection of ticks is the rule not the exception" [43-50]. The presence of multiple infections constitutes a bigger challenge to a competent immune response, especially in the presence of microbes that are capable of suppressing immune function and evading immune surveillance. In addition some of the microbial coinfections require different antibiotics.

Discussion and Conclusion

It is clear that patients infected with *B.burgdorferi* who were never diagnosed or treated for acute Lyme disease have a persistent infection. However, the existence of persistent infection in patients treated for acute Lyme disease and who continue to be symptomatic

remains controversial. In their acknowledgment of chronic symptoms following treatment of acute Lyme disease with two to four weeks of antibiotics, the CDC states that "…5-10% can have prolonged symptoms of fatigue, body aches, or difficulty thinking following treatment. "The cause of these symptoms is currently unknown" [51].

In fact, there is clear evidence that persistence of chronic symptoms may be due to multiple mechanisms:

- Persistent infection with *B.burgdorferi* as demonstrated by multiple studies in animals and humans that have documented live spirochetes following antibiotic therapy and improvement in symptoms in retreatment studies. Immune suppression and immune evasion by *B.burgdorferi* is well documented.
- Persistent infection with one or more coinfections that have never been treated.
- Systemic inflammation associated with immune dysregulation, autoimmunity, and excessive mast cell activation.
- Dysregulation of the autonomic nervous system.
- All of the above.

Western medicine adheres to the principle of Evidence-Based Medicine (EBM) as the standard of care. According to Dr. David Sackett, considered the father of EBM, "EBM is the integration of clinical expertise, patient values, and the best research evidence into the decision making process for patient care." Clinical expertise refers to the clinician's cumulated experience, education and clinical skills. The patient brings to the encounter his or her own personal and unique concerns, expectations, and values" [52].

As the medical community has adopted EBM, Sackett's emphasis on "clinical expertise and patient values" has been lost. Rather than rely on flawed guidelines, it is incumbent on physicians to validate patients' symptoms and utilize their expertise to thorougly investigate their underlying etiology. Further clinically relevant research is sorely needed to delineate better diagnostic and treatment modalities.

Disclosure

Portions of this article are excerpted from the author's book Recovery from Lyme Disease: The Integrative Medicine Guide to Diagnosing and Treating Tick-Borne Illness (Skyhorse, 2021).

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