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Controversies in Persistent (Chronic) Lyme Disease

ABSTRACT

The Centers for Disease Control and Prevention estimates that more than 300 000 new cases of Lyme disease occur each year in the United States and that 10% to 20% of these patients will remain symptomatic despite receiving appropriate antibiotic therapy. Many elements of the disease are poorly understood and have generated considerable controversy. This paper discusses the medical controversies related to posttreatment manifestations and their potential impact on infusion nurses.

Key words: antibiotic therapy, *Borrelia burgdorferi*, chronic Lyme disease, controversy, diagnosis, infusion nurses, persistent Lyme disease, post-Lyme disease syndrome

Lyme disease is an increasingly important public health concern. It is the most common vector-borne illness in the United States, with the Centers for Disease Control and Prevention (CDC) estimating that the annual incidence in the United States exceeds 300 000 cases.[1,2] The CDC also estimates that 10% to 20% of patients appropriately treated for the infection will remain symptomatic for an unspecified and variable period of time.[1] Patients contract *Borrelia burgdorferi*, the bacterial agent of Lyme disease, via bites from infected black-legged (deer) ticks. Ongoing expansion of the ticks' range increases the likelihood that case numbers will continue to rise.[3]

Lyme disease is multistaged and frequently produces a multisystemic illness. In early (acute) Lyme disease, the infection is localized to the skin. Symptoms and signs usually begin within 2 to 30 days of a bite. The expanding *erythema migrans* rash (EM) is the hallmark manifestation of this stage. Its appearance varies. The most common form is solid colored and oval shaped; less than 20% of all EM rashes have the classic "bull's eye" pattern.[4,5] A summary of 15 years of CDC surveillance cases found that an EM was noted in 70% of reported cases.[6] The rash expands and fades over weeks. Although it will resolve without treatment, antibiotics hasten resolution. Bacterial dissemination to other body sites defines late disease. This stage of the infection often involves several tissue types or systems, giving rise to a wide variety of nonspecific disease manifestations. Dissemination can occur soon after the bite, yet the symptoms and signs of late disease may not appear for weeks, months, or years.[7-9] It is not unusual for patients to initially present with late-stage disease.

Both early and late Lyme disease are treated with antibiotics. Generally speaking, treatment is more likely to be successful for early disease than for late disease.[10] However, treatment outcomes are highly variable, and an individual's response is impossible to predict with certainty.

CONTROVERSY 1: ESTABLISHING TERMINOLOGY FOR THE CONDITION

Distinguishing patients with persistent posttreatment manifestations of Lyme disease from patients who have a history of Lyme disease, yet are symptomatic from other causes, is a difficult and imprecise clinical activity. The lack of universally understood terminology contributes to the problem and hampers serious efforts to investigate the condition.

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The semantics here are important and deserve careful consideration. In the early literature, "chronic" frequently appeared in association with Lyme disease.[8,11] The connotation was neutral; the term simply denoted that the illness could be long-standing, without imparting responsibility to any particular disease mechanism.

The term's usage diverged over time. Some researchers and clinicians applied the term to all cases in which symptoms had been present for several months or longer, regardless of treatment status. That usage asserted that chronic infection with *B burgdorferi* was the most likely pathophysiologic mechanism of ongoing disease.[12] Dismissing the possibility of chronic infection, the Infectious Diseases Society of America (IDSA) attached negative connotations to the term *chronic Lyme* and discouraged its use.[13] Those who continued to employ the phrase, which now included physicians, affected patients, and their advocates, were stigmatized, and the patients' ongoing manifestations were frequently dismissed.[14,15] Not surprisingly, patients who identified themselves as having chronic Lyme to physicians often reported being marginalized medically.[16,17]

Post-Lyme disease syndrome (PLDS) was endorsed by the IDSA and CDC as an alternative term to describe patients who have ongoing posttreatment symptoms but no objective findings.[10,18] However, this label is rejected by many because it implies that the initial bacterial infection has been cleared and that ongoing manifestations are the result of other pathophysiologic mechanisms.[19,20] Given that there are no "tests of cure" for Lyme disease (tests able to prove bacterial eradication) or biomarkers that can identify the presence of PLDS, this assumption lacks proof.[19-21]

Given the varying terminology, this article uses the term *persistent Lyme disease* to describe patients who remain ill following commonly prescribed, stage-specific, antibiotic treatment.

CONTROVERSY 2: VALIDITY OF PERSISTENT MANIFESTATIONS BEING ATTRIBUTABLE TO LYME DISEASE

Many patients report ongoing symptoms following treatment for Lyme disease, yet physicians disagree over the nature of these symptoms.[10,20] Some physicians discount the likelihood that posttreatment symptoms are directly related to the earlier Lyme infection.[10,14,22] This sentiment is expressed in articles with titles such as "Dispelling the Chronic Lyme Disease Myth"[22] and in the often-stated phrase, "I don't believe in chronic Lyme." Instead, the suggestion is that patients are simply reporting symptoms commonly seen in the general population or those of a secondary condition such as fibromyalgia or chronic fatigue syndrome.[10,14]

Other physicians hold that such symptoms are most likely directly attributable to the previous infection and represent treatment failure.[20] This group notes that most of the reported posttreatment symptoms began before treatment and that the original Lyme diagnoses were, in part, based on their very existence.[20]

The bulk of the evidence to date generally supports the second group of physicians. Clinical researchers have repeatedly documented persistent posttreatment symptoms and/or findings and concluded that this was evidence of treatment failure. In 1983, Steere et al noted that 50% of their patients experienced symptoms following treatment.[23] During the 3 decades that followed, prospective studies on different disease stages consistently documented posttreatment signs and symptoms, which the researchers attributed to the prior infection.[24-30] Several community-based, follow-up studies also demonstrated high rates of persistent manifestations.[31-33]

While complete recovery is more likely for patients with early rather than late disease, common antibiotic regimens for either stage are not highly efficacious. A careful analysis of 9 randomized, comparative trials for EM reported that outcomes were not as positive as originally reported.[20] This patient-centered, evidence-based analysis found that 10 to 20 days of therapy with first-line agents failed to restore 16% to 48% of patients to their pre-Lyme health status.[20] Similarly, a well-designed observational trial reported that 33% of patients treated with 3 weeks of doxycycline experienced disease manifestations during the 3- to 6-month posttreatment interval.[34]

Although few well-designed US studies investigated the treatment of late neurologic disease, those that did documented high rates of persistent disease. One study of patients who had either peripheral neuropathy, encephalopathy, or both found that treatment with 14 days of intravenous (IV) ceftriaxone produced improvement in 63%, improvement followed by relapse in 22%, and no change in 15%.[8] In a second study by the same researcher, 18 encephalopathy patients were treated with 30 days of ceftriaxone.[30] Although the outcomes were generally better, only 39% considered themselves back to their pre-Lyme baseline—that is, normal.

Studies demonstrate that symptoms commonly reported by persistent Lyme disease patients occur more frequently in that group than in matched controls or an age-matched subset of the general population.[31,32,35] For example, 41% of the subjects in Asch and colleagues' study[31] (average age was 38.9 years) reported having arthritis. This is 5 times higher than the rate of arthritis (7.8%) in the general US population ages 18 to 44 years.[36]

Recent evidence does not support suggestions that persistent posttreatment fatigue is attributable to newly developed chronic fatigue syndrome or that posttreatment pain represents the onset of fibromyalgia. Distinct

differences in cerebral spinal fluid proteins of patients with persistent Lyme disease and those with chronic fatigue syndrome have been demonstrated.[37] A longitudinal study of culture-positive EM patients found that only 1% developed definite fibromyalgia, which is lower than the incidence in the general population.[38] Whether or not some persistent symptoms are due to Lyme-induced immune dysregulation is unknown.

In sum, the extensive evidence demonstrating the presence of posttreatment manifestations and the fact that they are present at rates in excess of those seen in appropriately matched groups should shift the debate from whether one "believes" in chronic Lyme to whom should be treated and in what manner.

CONTROVERSY 3: SIGNIFICANCE OF PERSISTENT LYME DISEASE

While characterized by some as "the aches and pains of daily living,"[10(p1115)] there is growing recognition of the potential significance of persistent Lyme disease. Evidence from 4 National Institutes of Health (NIH)-sponsored retreatment trials, well-conducted patient surveys, and a large medical claims database demonstrates that the physical, social, and economic costs of persistent Lyme disease for individuals can be substantial and are an economic burden for the country as a whole.[16,39-43]

The NIH retreatment trials documented significant impairments in study subjects.[39-41] Given the various entrance criteria, it was generally expected that subjects would have demonstrable impairments in the specific areas under investigation. For example, subjects in Krupp and colleagues' trial were required to have severe fatigue, and subjects in Klempner and colleagues' trials were required to have symptoms that "interfered with their functioning."[40(p85),41] Although the entrance criteria for Fallon and colleagues' encephalopathy trial did not require that subjects have any baseline physical impairments, 73% of the enrollees had abnormalities on sensory exam, and 38% had motor deficits.[39] As a group, the subjects reported significant physical impairments. Their pain levels were similar to postsurgical patients, their fatigue was on par with that experienced by patients with multiple sclerosis, and their physical functioning was comparable to patients with congestive heart failure.[39] Although it is important to recognize that the subjects in the NIH trials had significant impairments, their outcomes are not reflective of the persistent Lyme disease patient group as a whole.

Interestingly, surveys of patients with persistent Lyme disease documented similar impairments. One published survey openly recruited patients who had been diagnosed and treated for Lyme disease yet had ongoing manifestations of Lyme disease for 6 months or more post treatment.[42] To participate, the respondents must have had an initial Lyme disease diagnosis that was based on either the presence of an EM rash or extracutaneous manifestations of Lyme disease coupled with positive 2-tier testing. The 1087 respondents reported significant impairments. Seventy-two percent rated their health as fair or poor compared with 16% of a general population of similar age. They averaged 20 days of poor physical and 15 days of poor mental health per month. Thirty-nine percent had stopped working, and an additional 28% had reduced their work hours. Thirty-nine percent had spent at least $5000 out of pocket for Lyme-related expenses. This self-selected group, like the NIH subjects, is not representative of the entire persistent Lyme disease patient population. However, the respondents provide a glimpse of what life is like for many.

A retrospective study using an expansive medical insurance claims database identified 52 795 individuals diagnosed and treated for Lyme disease who met the study's strict criteria.[43] Comparing health care costs within this group, total costs over a 12-month posttreatment period were $3800 higher for patients who had 1 or more posttreatment Lyme disease symptoms than for those who had none. The magnitude of the sample size and conservative study design make the findings particularly compelling.

Taken together, the trial, survey, and database evidence clearly identify that the health and financial costs associated with persistent Lyme disease are significant and should not be casually dismissed.

CONTROVERSY 4: THE ROLE OF SEROLOGIC TESTING IN PERSISTENT LYME DISEASE

Some physicians use serology to rule persistent Lyme disease in or out, but others disagree with that strategy.[44]

The evidence demonstrates that none of the clinically available serologic tests for Lyme disease can determine whether or not a patient has an ongoing *B burgdorferi* infection.[44] Serologic tests, enzyme-linked immunosorbent assays (ELISAs), and Western blots are designed to diagnose untreated Lyme disease.[21,45] Lyme serology does not identify the bacterium itself; instead, the tests look for antibodies to various *B burgdorferi* antigens. Elevated levels indicate exposure to *B burgdorferi* and, in the appropriate setting, can support a clinical diagnosis of Lyme disease. Although antibody levels wane over time, some individuals who have recovered fully will continue to have measurable antibody levels for years.[21,44] Thus, positive serology in patients who have been treated for Lyme disease is not necessarily indicative of ongoing infection.[21,44]

Similarly, negative results are not indicative of cure.[44] In a typical antibody response, the initial antibodies are in the immunoglobulin M (IgM) class.[21] As the immune response matures, antibody production shifts away from IgM antibodies to immunoglobulin G (IgG) antibodies. Many patients treated for Lyme disease do not develop a measurable IgG response following antibiotic therapy.[27,46] Failure to seroconvert has been associated with a higher risk of treatment failure—that is, having persistent manifestations.[27] Additionally, an antibiotic trial in Lyme-infected monkeys found that C6 ELISA antibodies were appropriately elevated in early disease but were later undetectable in all treated animals, including those that remained actively infected.[47]

Lyme serology is also uninformative with regard to the other potential mechanisms of persistent Lyme disease.

CONTROVERSY 5: THE UNCERTAIN PATHOPHYSIOLOGY OF PERSISTENT LYME DISEASE

The pathophysiologic mechanism(s) responsible for persistent Lyme disease have not been fully elucidated. Several potential mechanisms have been suggested, but the supporting evidence for most is quite limited.[10,20] Potential mechanisms include (1) the presence of other untreated infections, (2) a postinfectious state, (3) permanent or temporary tissue damage, (4) secondary conditions triggered by the initial infection and persisting despite bacterial eradication, (5) immune dysfunction due to autoantibodies or unregulated inflammation, and (6) persistent *B burgdorferi* infection. It is possible that multiple mechanisms are operating in a given patient. Evidence in support of 1 mechanism does not disprove the others.

Many physicians acknowledge all of these potential mechanisms, except persistent infection.[10,14,18] Others maintain that persistent infection is a demonstrated cause of persistent Lyme disease, yet recognize that the other mechanisms may play a role.[19,20]

The volume of evidence supporting persistent infection is substantial. Persistent infection has been demonstrated in patients with Lyme disease by polymerase chain reaction (PCR) and culture.[48-58] An NIH-sponsored xenodiagnostic study in humans documented that uninfected ticks acquired *B burgdorferi* deoxyribonucleic acid (DNA) from feeding on a persistently symptomatic patient who had been treated for Lyme disease more than 1 year earlier.[59] This finding is significant. The immune system typically clears bacterial debris quickly; therefore, the presence of *B burgdorferi* DNA strongly supports that the infection was ongoing. Animal studies have corroborated the human findings, documenting bacterial persistence by culture, PCR, and histopathologic testing of posttreatment necropsy specimens and by xenodiagnosis.[47,60,61]

CONTROVERSY 6: MANAGEMENT OPTIONS—POTENTIAL BENEFIT OF ANTIBIOTIC RETREATMENT

It is a widely held belief, one encouraged by the CDC and IDSA, that antibiotic retreatment does not improve patient outcomes and is excessively risky.[10,18] The alternative position is that retreatment can be beneficial and appropriate in select patients.[20,62]

A careful examination of the evidence supports the selective use of antibiotic retreatment for persistent Lyme disease. The 4 NIH-sponsored clinical trials specifically investigated whether patients with persistent Lyme disease improved with antibiotic retreatment.[39-41] Those who assert that retreatment is not beneficial correctly note that the trials by Klempner et al found no benefit from antibiotic retreatment.[40] However, this assertion overlooks the trials' poor design, which biased them toward finding no treatment effect.[19,62] In light of these flaws, Klempner and colleagues' trials should not be cited as evidence sources on this topic. In contrast, both Krupp and colleagues' and Fallon and colleagues' trials demonstrated that retreatment with ceftriaxone was beneficial for patients with severe fatigue.[39,40] Fallon et al also found that retreatment decreased pain and improved physical functioning in the patients most affected by these quality-of-life impairments.[39] Because several patients had serious adverse events, neither author group recommended ceftriaxone therapy on a generalized basis.[39,41] However, both recommended additional studies to seek out antibiotics that were effective, safer, and less expensive.[39,41] In addition, as Fallon et al pointed out in their 2012 review of the NIH trials, repeat antibiotic therapy, including additional ceftriaxone therapy, may be justifiable on a case-by-case basis for patients with severe quality-of-life impairments.[62]

With regard to the safety of IV ceftriaxone, the NIH-sponsored retreatment trials provided approximately 8110 days of antibiotic or placebo treatment to 221 subjects via an indwelling device.[39-41] There were 13 significant adverse events, yielding 0.86 adverse events per 1000 intravascular device days, or a 5.9% risk per patient.[39-41]

Trials for early and late disease also demonstrated that retreatment may be beneficial.[20] Unfortunately, these findings have received little attention and likely are unknown to most physicians. In several of the EM trials conducted in the United States, researchers retreated subjects who were thought to have failed therapy and frequently reported that the subsequent outcomes were favorable.[24-28] A patient in the previously mentioned encephalopathy trial relapsed at

8 months but recovered following retreatment with ceftriaxone.[30]

Basic science research, observational studies, and clinical experience have demonstrated that a wide variety of antibiotics may be useful for persistent Lyme disease.[20] While IV antibiotics continue to be used in advanced cases, many protocols now use combinations of oral antibiotics to avoid the risks associated with IV therapy, such as catheter-related infections, phlebitis, and thromboembolism.[20]

It appears that the usefulness of nonantibiotic therapies is widely recognized.[10,14,20] Patients with antibiotic-refractory arthritis may benefit from synovectomy.[63,64] IV immunoglobulin has been useful for cases of autoimmune polyneuropathy secondary to Lyme disease, and gabapentin has demonstrated effectiveness for reducing Lyme-induced neuropathic pain.[65,66] In theory, immune modulators may be useful if symptoms are due to immune dysfunction. However, ongoing infection would need to be decisively ruled out because dampening the immune response risks allowing quiescent *B burgdorferi* to flourish again. Thus, although palliative therapies offer many symptom-specific benefits, health care professionals must bear in mind that the use of such therapies should not preclude efforts to identify and treat the underlying cause(s) of persistent Lyme disease.

IMPACT OF CONTROVERSIES ON INFUSION NURSES

The science of persistent Lyme disease is uncertain and evolving. Despite this, many physicians have firm opinions regarding persistent Lyme disease that conflict with the reasoned opinions of their colleagues. Because IV antibiotics are often used to treat patients with persistent Lyme disease, infusion nurses and the patients under their care may be swept up in this highly contentious debate.

Yet, this also means that infusion nurses are well positioned to help ensure that therapeutic choices are patient centered and consistent with the practice of evidence-based medicine. Although they lack the power to prescribe, infusion nurses can influence treatment decisions by providing information and advocating for the patient's right to shared decision making. Although patient advocacy under these circumstances may be uncomfortable for some, it is a professional duty.[67]

To function as a reliable information source, infusion nurses need to stay abreast of advances in the field and willingly communicate their knowledge to patients, physicians, and colleagues. By providing materials and references regarding the basic science and trial evidence, as well as areas of scientific uncertainty, infusion nurses can help physicians and patients recognize potential therapeutic options. Nurses working with patients in the community can bring written information with them on home visits and bookmark appropriate online resources on the patient's home computer. Nurses working in infusion centers can provide patients with the same written information and list of online resources when they arrive for care. Although these nurses may find it easier to educate colleagues than community-based nurses, both groups have a professional responsibility to do so.[68] Infusion nurses may choose to use this paper and selected references from it in that capacity.

The scientific uncertainty and wide range of therapeutic regimens and modalities used to treat patients with persistent Lyme disease highlight the need for physicians and patients to engage in shared decision making.[69-71] Infusion nurses can facilitate this process in several ways. Shared decision making requires that the physician and patient understand the science underlying various treatment options.[70] Infusion nurses who provide such information are supporting the patient-physician dialogue. Shared decision making also requires that patients identify and discuss their goals and values as they relate to treatment choices.[70] By encouraging patients to think along those lines, infusion nurses prepare them for that portion of the conversation. Managing patients with persistent Lyme disease may require therapeutic adjustments based on the patient's treatment response. By carefully noting changes in the patient's condition and reporting these observations to both the patient and the physician, infusion nurses help clarify both the benefits and negatives of the current therapy.

Treatment options for persistent Lyme disease will likely change as the scientific understanding of its underlying mechanisms evolves. In the meantime, infusion nurses will continue to see patients with persistent Lyme disease. By staying abreast of the research and sharing this information with colleagues, patients, and physicians, infusion nurses will help diminish the controversy and assist in providing the high-quality care that patients with persistent Lyme disease need and deserve.

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