Posttreatment Lyme disease syndromes: distinct pathogenesis caused by maladaptive host responses

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Lyme disease, which is epidemic in certain communities, primarily in the northeastern United States, is caused by the tick-borne spirochete *Borrelia burgdorferi* (also called *Borreliella burgdorferi*). When untreated, the disease usually occurs in stages with different manifestations at each stage (1). In the northeastern United States, the infection usually begins with a slowly expanding skin lesion, erythema migrans (stage 1), often accompanied by nonspecific symptoms, including headache, myalgias, arthralgias, fever, malaise, and fatigue. Within weeks (stage 2), neurologic or cardiac abnormalities may develop. Months later (stage 3), usually following a latent period, intermittent or persistent monoarticular or oligoarticular arthritis commonly develops, lasting for several years, accompanied by minimal, if any, systemic symptoms. Rarely, patients have late neurologic involvement, characterized by a subtle encephalopathy or sensory polyneuropathy. Thus, in most patients, the natural history of Lyme disease, without treatment, is one of persistent infection for several years, with latent periods and changing system involvement.

Treatment and ongoing disease manifestations

Depending on the disease manifestation, the infection can usually be treated successfully with 2–4 weeks of oral antibiotic therapy. However, arthritis, a late disease manifestation, can be more difficult to treat. We start with oral antibiotic therapy, usually doxycycline, for 30 days (2). If patients have minimal or no response, we treat with IV antibiotics, usually ceftriaxone, for another month, and in most patients, the arthritis improves. One theory to explain this finding is that tendons, a relatively avascular niche in and around affected joints, may be infected, and better tissue penetration with IV antibiotics is necessary for successful treatment (3).

Lyme disease may be complicated by the emergence of disabling postantibiotic syndromes. Importantly, there is more than one posttreatment syndrome, each with a different pathogenesis (Table 1). Physicians are often in a quandary regarding whether these patients still have active infection or postinfectious phenomena. Should patients be treated with more antibiotic therapy, or should they be treated in other ways?

We have focused our studies on postantibiotic (also called postinfectious or antibiotic-refractory) Lyme arthritis (LA). In these patients, the arthritis seems to change after antibiotic treatment. Joint effusions are not as large, but massive synovial proliferation develops, usually in one or both knees, that may even worsen in the postantibiotic period, lasting months to several years. The synovial lesion in these patients is similar to that seen in other forms of chronic inflammatory arthritis, including rheumatoid arthritis, though evidence of vascular damage, including obliterative microvascular lesions, is a feature of postinfectious LA synovia (4).

Causes and consequences of postantibiotic LA

The basic pathogenetic feature of postinfectious LA is the development of an excessive, dysregulated proinflammatory immune response during the infection, characterized by exceptionally high IFN-γ levels, which persists in the postinfectious period (4). Patients with a polymorphism in the TLR-1 gene who are infected with *B. burgdorferi* outer surface protein C (OspC) type A (RST1) strains are at risk for excessively high IFN-γ levels (5). Similarly, presentation of an epitope of *B. burgdorferi* OspA (OspA164–175) by certain HLA-DR alleles, such as DRB1:0401, leads to high IFN-γ levels (6). Furthermore, in patients with postinfectious LA, a high percentage of CD4+CD25+ T cells, which are ordinarily regulatory T cells, become effector cells that secrete large amounts of IFN-γ, leading to an imbalance in Th1 effector–T regulatory cell function (7).

The consequences of this excessive proinflammatory response in Lyme synovia include vascular damage, autoimmune and cytotoxic processes, and fibroblast proliferation and fibrosis (4). An important driver of innate immune responses may be persistence of *B. burgdorferi* peptidoglycan in synovial fluid, which may be especially difficult to clear (8). In addition, patients with postinfectious LA often have T and B cell responses to Lyme disease–associated autoantibodies, endothelial cell growth factor, apolipoprotein B-100, or matrix metalloproteinase-10 (9). These responses may reflect damage to blood vessels and the extracellular matrix, leading to presentation of autoantigens by synovial fibroblasts and endothelial cells, which become unconventional antigen-presenting cells that secrete proinflammatory cytokines (10).

In a transcriptomic analysis of postinfectious LA synovial tissue, a heightened IFN-γ signature correlated inversely with the expression of genes involved in the repair of damaged tissue (4). Thus, high numbers of IFN-γ–producing cells in synovia may prevent repair of tissue damaged by the infection, blocking the return to tissue homeostasis even after spirochetal killing. Analysis of miRNAs supports this paradigm (11). During active infection, miRNA expression in synovial fluid reflects the type of immune response associated with bacterial killing. In postinfectious LA, miRNA expression in synovia reflects chronic inflammation, synovial

proliferation, and breakdown of wound repair processes.

After oral and IV antibiotics, culture and PCR results for *B. burgdorferi* have been uniformly negative in postinfectious LA synovial tissue (12). We treat such patients with disease-modifying antirheumatic drugs, the standard of care for other forms of autoimmune, chronic inflammatory arthritis, and we have not observed reemergence of infection in these patients. Thus, we do not think that this LA complication requires persistent infection for disease expression.

Posttreatment Lyme disease syndrome

The clinical features and pathogenesis of what is often called posttreatment Lyme disease syndrome (PTLDS) are quite different. After any disease manifestation, but perhaps more commonly following neurologic involvement, patients may experience pain, neurocognitive, or fatigue symptoms, emerging during or within several months after antibiotic treatment of the infection, lasting months or years (13). These patients may have severe pain around joints (tender points), headache, brain fog, sleep disorder, and incapacitating fatigue, which have a major impact on the quality of life. Such symptoms may also follow certain other infections or physical or emotional trauma, or the precipitating events may not be apparent. PTLDS or "chronic Lyme disease" has become a diagnosis for this type of syndrome not only in patients with recent Lyme disease but also in those who have little or no evidence of previous Lyme disease.

The pathogenesis of PTLDS is not well understood. Although elevated levels of IL-23 or CCL19 have been reported (14, 15), PTLDS does not seem to be a syndrome characterized primarily by excessive immune responses, as in postinfectious LA. Rather, with infection, the brain is sensitized to pain signals, an alarm signal, and fatigue necessitates rest. One hypothesis is that in patients with PTLDS the enhanced sensory signals during the infection do not reset after infection, and the increased sensitivity to pain, brain fog, and marked fatigue persist, called a "central sensitization syndrome" (16).

These symptoms are often difficult to treat effectively; symptomatic treatments

Table 1. Posttreatment Lyme disease syndromes

Syndrome	Clinical features	Proposed pathogenesis
Postinfectious Lyme arthritis	Massive inflammatory, synovial proliferation usually affecting a knee, emerging from Lyme arthritis	Excessive proinflammatory immune response with high IFN-γ levels persistent in the postinfectious period, blocking appropriate wound repair processes
Posttreatment LD syndrome	Pain, neurocognitive, and fatigue symptoms emerging after any LD manifestation	Increased sensory signals during infection do not reset appropriately after infection, called "central sensitization syndrome"
Autoimmune joint disease	Rheumatoid arthritis, psoriatic arthritis, or peripheral spondyloarthropathy emerging after any LD manifestation	Adjuvant effect of infection activating latent autoimmune disease
Autoimmune neurologic disease	Chronic idiopathic demyelinating polyneuropathy emerging from Lyme radiculoneuropathy	Unknown

LD, Lyme disease.

and stress reduction are generally recommended (13). However, many patients with chronic Lyme disease feel that antibiotic therapy is the only treatment that has helped them, suggesting that they still have active spirochetal infection. This has led some physicians to treat with multiple antibiotic regimens for months or years, and advocacy groups have formed that promote this approach.

The case for and against long-term antibiotic treatment

Many studies have been done to address the persistent infection hypothesis. In bacterial culture systems, some *B. burgdorferi* organisms may persist despite exposure to doxycycline or ceftriaxone (17). In culture, daptomycin plus doxycycline and cefoperazone eradicated the most resistant, aggregated microcolony form of *B. burgdorferi* persisters (18). However, bacterial persisters in culture may be an in vitro phenomenon commonly observed with many bacterial species, which may be explained by the kinetics of antibiotic killing of bacteria not exposed to a host immune system (19).

There is limited evidence for spirochetal persistence after antibiotic treatment in certain animal models of *B. burgdorferi* infection. When C3H/HeN mice, an inbred strain susceptible to severe *B. burgdorferi*–induced arthritis, were infected with stationary-phase, aggregated forms of *B. burgdorferi*, the combination of daptomycin plus doxycycline and cefoperazone for 30 days eradicated the

spirochetes, as assessed by culture of ear punch biopsies, whereas doxycycline or ceftriaxone alone did not (20). In macaque monkeys, 24 animals had positive skin biopsy cultures during the first 4 weeks of infection, prior to antibiotic therapy (21). At postmortem, after treatment with 4 days of ceftriaxone and 28 days of doxycycline, only 1 of 12 monkeys in each of the treated and untreated groups had positive cultures. In a second experiment in which xenodiagnosis was used to assess infection 7 or 11 months after infection, rare spirochetes of unproven viability were visualized in the ticks that fed on 2 of 3 treated monkeys. On postmortem examination of the monkeys, a few spirochetes grew slowly in cultures of organ tissues, but subculture was unsuccessful. Building upon these studies, xenodiagnosis experiments were carried out in human patients with PTLDS (22). *B. burgdorferi* DNA, which may persist after active infection, was detected by PCR in ticks that fed on 1 of 17 patients, but all cultures of the ticks were negative. Additionally, skin biopsies were performed at the site of tick feeding in 11 patients, and all cultures and PCR results of skin samples were negative.

The major problem with the persistent infection hypothesis is that 4 double-blind, placebo-controlled trials have not shown a sustained difference between case and control patients (23–26). In the largest trial, 129 patients were randomized to receive IV ceftriaxone for 1 month followed by oral doxycycline for 2 months or placebo

IV and oral preparations for the same duration (23). Before treatment, culture and PCR tests for *B. burgdorferi* on blood or cerebrospinal fluid were uniformly negative. After 6 months, the percentage of patients whose symptoms had improved, remained the same, or worsened was equivalent in antibiotic-treated and placebo-treated patients. Are there other antibiotic regimens, such as the 3-antibiotic regimen used to kill spirochetal persisters in culture, that may be more effective in human patients than doxycycline or IV ceftriaxone? To answer that question, it would be necessary to do a double-blind, placebo-controlled trial of the 3-antibiotic regimen in patients with PTLDS, accompanied by appropriate culture and PCR testing, as done in the IV ceftriaxone and doxycycline trial.

Both doxycycline and ceftriaxone have the potential for beneficial effects other than bacterial killing, including antiinflammatory or neuroprotective effects. However, if these mechanisms accounted for improvement in symptoms with antibiotics, the antibiotic-treated group would still be expected to do better than the placebo-treated group, which was not the case. Moreover, prolonged use of antibiotics has the potential for significant adverse effects, including untoward reactions during treatment, and antibiotic-induced gut dysbiosis is a risk factor for the later development of certain autoimmune diseases or malignancies (27). With the current lack of evidence of persistent infection or antibiotic efficacy in human patients with PTLDS, the Infectious Diseases Society of America recommends against treatment of such patients with long-term antibiotics (28).

Systemic autoimmune diseases following Lyme disease

Finally, systemic autoimmune or autoinflammatory joint diseases, including rheumatoid arthritis, psoriatic arthritis, or peripheral spondyloarthropathy, may develop weeks to months after Lyme disease, most commonly following antibiotic-treated erythema migrans (29). These complications may be due to the chance occurrence of two diseases, or alternatively, the infection may serve as an adjuvant activating latent autoimmune disease. In addition, we have observed several cases

of chronic idiopathic demyelinating polyneuropathy, an autoimmune neurologic disease, emerging from Lyme radiculoneuropathy. Importantly, these autoimmune diseases have required immunosuppressive or antiinflammatory therapy for successful treatment, not further antibiotic therapy.

Conclusions

Lyme disease can usually be treated successfully with 2–4 weeks of oral antibiotic therapy, or if necessary, with 4 additional weeks of IV antibiotics. However, disabling posttreatment syndromes may still develop, which appear to result primarily from disadvantageous or maladaptive host responses to the infection that persist after spirochetal killing with antibiotics.

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