Response to meta-analysis of Lyme borreliosis symptoms
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Although some Lyme disease patients treated with recommended antibiotic regimens have symptoms post-treatment, the usual course is a slow resolution of these symptoms.1–3 Subjective symptoms, i.e. fatigue as well as musculoskeletal pain, and certain objective extracutaneous signs, i.e. motor paresis, cognitive difficulties, or joint swelling, tend to resolve over the course of weeks to months rather than days. However, whenever studied, the rate of resolution of symptoms or signs is unrelated to the duration of treatment.1,2

Cairns and Godwin4 in their meta-analysis of five selected United States studies5–9 on the outcome of Lyme borreliosis concluded that the prevalence of the symptoms of persistent fatigue, musculoskeletal pain or neurocognitive difficulties (post-Lyme disease syndrome, chronic post-treatment Lyme disease, or chronic Lyme disease) exceeds that of comparison populations without Lyme disease by ≥5%. Based on these findings, a conservative estimate of the incidence of this syndrome in the United States would be at least 3000 cases per year (≥20 000 reported cases × 3; to include unreported cases, ≥0.05).10,11 Given the chronic nature of the process, the prevalence of cases should be many times higher. Furthermore, post-Lyme disease symptoms are occurring on a high background rate of indistinguishable symptoms in the general population. Based on the studies cited in the meta-analysis, the frequency of musculoskeletal symptoms alone among the control groups of adults was 25.8%. Thus, more than 30% of adults after treatment for Lyme disease (25.8% + ≥5%) could be regarded as having post-Lyme disease syndrome. This prompts one to wonder why so many difficulties were encountered in enrolling patients in four different controlled treatment trials of Lyme disease patients with post-treatment symptoms.12–14 Three of the four studies never met their enrollment goals, and the only study13 to meet its enrollment objective of 55 patients included several patients, that, in retrospect, failed to satisfy entry criteria. Taken together, all four studies managed to recruit <200 patients during an enrolment period of several years.

The findings of this meta-analysis4 are uninformative and misleading, since the studies upon which it was based have substantive limitations including retrospective study design, lack of timely antimicrobial therapy (or in some instances no treatment at all), use of antimicrobial regimens no longer recommended,13 lack of 2-stage conditional serologic testing to establish the original diagnosis of Lyme disease,16 a distorted case mix with an over representation of patients with extracutaneous manifestations, failure to consider pre-Lyme disease traumatic psychologic experiences,17 and the likely inclusion of an unknown number of non-Lyme disease patients whose original complaints were exclusively subjective in nature and consisted of chronic arthralgias, fatigue, or cognitive difficulties. The last group of patients may have been evaluated for Lyme disease based on the mistaken notion that patients with such complaints are likely to have ‘chronic Lyme disease.’ What is more and very important is that the laboratory testing in many of the studies used older serological methods. Methods that are now known to be associated with high rates of false positive results18 are no longer considered valid. Indeed, the majority of patients who carry the diagnosis of ‘chronic Lyme disease’ have no evidence of ever having been infected with Borrelia burgdorferi.19 It should be noted that in the study included in the meta-analysis involving the largest number of subjects,5 at least one-third did not meet the national surveillance case definition for Lyme disease.

In many studies of ‘chronic’ Lyme disease a form of ‘protopathic bias’ can be a major problem.20 Such bias can occur when persons are diagnosed with ‘chronic Lyme disease’ because they have the outcomes of interest (e.g. chronic pain, fatigue). In addition, it is likely that there is reporting or recall bias in patients who are labeled as having Lyme disease.21 Thus, a person diagnosed with Lyme disease would be more likely to recall and/or to report subsequent symptoms such as arthralgia, myalgia or fatigue than would another person with the same symptoms who was never diagnosed as having Lyme disease. In this context, the Seltzer study5 showed that responses to questions about the ability to conduct the normal tasks of daily living were not significantly different than those of controls without Lyme disease. In addition, the results of a battery of formal neuropsychological tests administered to patients who had Lyme disease were normal in the study reported by Vazquez et al.8

Several prospective studies of well-defined populations of Lyme disease patients treated without excessive delay indicates a quite benign outcome (Table 1).1,12–15 In contrast to studies of poorly characterized patients cited by Cairns, the frequency of persistent complaints among patients with well-characterized Lyme disease was consistently less than, or at worst comparable to, those of the control groups without Lyme disease presented in the meta-analysis. In the one study that specifically addressed the treatment of patients with early disseminated infection, the treatment outcome was excellent at the 9 month evaluation.25 Definitive assessment of the outcomes of patients with Lyme disease, however, will require the performance of well-designed, controlled prospective studies, which are long overdue.

A separate but related question is whether symptomatic chronic B. burgdorferi infection exists despite recommended treatment with 10–28 day courses of antibiotics.1,14 Certainly, this is biologically implausible given the lack of antibiotic
resistance in this genus, the lack of documentation of this event in either humans or animals (including highly immunocompromised animals), lack of correlation of subjective symptoms with seropositivity or signs of inflammation, lack of precedent for such a phenomenon in other spirochetal infections, and the resolution (or stabilization) of all objective manifestations in treated patients. Furthermore, in none of the published controlled treatment trials of patients who are believed to have post-Lyme disease syndrome has long-term intensive antibiotic therapy been convincingly demonstrated to have any clinical benefit.

It is possible that ‘chronic Lyme disease’ is a functional somatic syndrome, especially since both the epidemiology and the phenomenology of ‘chronic Lyme disease’ are very similar to those of a number of other functional somatic syndromes such as hypersensitivity to candida, Gulf War syndrome, chronic fatigue syndrome, and sick building syndrome. Physiologic explanations, whether they should exist for persistent symptoms, have not been elucidated. Evidence does not support the hypothesis that co-infection with other recognized tick species pathogens is the cause of persistent symptoms. Regardless of the eventual explanation(s) for post-Lyme disease symptoms, direct or indirect linkage to currently active B. burgdorferi infection is not justified and only serves to encourage unnecessary use of antibiotics that is inconvenient for the patient, costly, and potentially dangerous, and may contribute to an increase in antibiotic resistance in the community. Moreover, it may delay or prevent patients from receiving other more helpful interventions or delay the diagnosis and treatment of other illnesses.

References
Babesia, Anaplasma, Ehrlichia, tick-borne agents such as tick-borne disease or those who are coinfected with other initially go untreated owing to lack of recognition of the chronic infection in certain patients, especially those who immune response and perfunctory antibiotic therapy to produce such as properties that are found in other agents of chronic infection, * Corresponding author. California Pacific Medical Center, 450 Sutter Street, Bethesda, MD 20827-1461, USA. International Lyme and Associated Diseases Society, PO Box 341461, Suite 1504, San Francisco, CA 94108, USA. E-mail: rstricker@usmamed.com

FROM STEVEN E PHILLIPS, JOSEPH J BURRASCANO, NICK S HARRIS, LORRAINE JOHNSON, PATRICIA V SMITH AND RAPHAEL B STRICKER*

Chronic infection in ‘post-Lyme borreliosis syndrome’
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Cairns and Godwin provide strong evidence that patients with Lyme borreliosis may have persistent fatigue, musculoskeletal pain, and neurocognitive difficulties despite ‘adequate’ antibiotic therapy.1 The authors state that ‘ongoing infection has not been excluded’ in these patients with ‘post-Lyme borreliosis syndrome’. Based on the evidence, we postulate that ongoing infection is the most likely explanation for chronic Lyme disease symptoms.2–6

Recent molecular, biochemical, and immunological studies of *Borrelia burgdorferi*, the causative agent of Lyme borreliosis, have demonstrated the complexity and elusiveness of this tick-borne spirochete.3,6,7 The Lyme spirochete possesses functional properties that are found in other agents of chronic infection, such as *Mycobacteria*, *Brucella*, and *Treponema* species.7 Thus it is highly likely that *B. burgdorferi* would evade both the human immune response and perforcutaneous antibiotic therapy to produce chronic infection in certain patients, especially those who initially go untreated owing to lack of recognition of the tick-borne disease or those who are coinfected with other tick-borne agents such as *Babesia*, *Anaplasma*, *Ehrlichia*, and *Bartonella* species.3,6 In fact, the medical literature contains numerous examples of persistent human infection with *B. burgdorferi*.3,6

What is the evidence for ‘post-Lyme borreliosis syndrome’, defined as the persistence of symptoms in the absence of chronic infection with *B. burgdorferi*? Cairns and Godwin cite a study that found negative PCR testing in blood samples from 1800 patients with chronic Lyme disease. This study has been criticized for the lack of sensitivity of its non-nested PCR testing because it is highly unlikely that not a single patient in this Lyme disease cohort would have a positive PCR test.3,5,6 Moreover, it is widely recognized that when minimal numbers of organisms are present in the blood, a negative blood PCR test does not exclude the presence of infection because rigorous tissue sampling may yield positive results.8,9 For example, a necropsy study in dogs using PCR analysis of 25 tissue samples per dog demonstrated persistent infection after treatment.9 Thus the argument that negative blood PCR testing excludes persistent infection is erroneous.

Cairns and Godwin also cite the hypothesis that infection with *B. burgdorferi* may trigger some autoreactive inflammatory processes leading to persistent symptomatology. Despite the attractiveness of this hypothesis, there is no convincing evidence to support it, and attempts to identify a candidate autoantigen have consistently failed.3,6,10 The studies that have shown persistent inflammation in animal models of chronic Lyme disease have not excluded ongoing infection, and persistent