Chronic Lyme Disease: A Review

Adriana Marques, MD

Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 10/11N234 10 Center Drive, Bethesda, MD 20892, USA

"The beginning of wisdom is the definition of terms."
—Socrates

Chronic Lyme disease is probably the most confusing term in the Lyme disease field. The term chronic Lyme disease has been used to describe vastly different patient populations that should not be grouped together. These include patients with objective manifestations of late Lyme disease (for example, arthritis, encephalomyelitis, or peripheral neuropathy, addressed in detail in other articles), patients who have post-Lyme disease syndrome, and patients who have nonspecific signs and symptoms of unclear cause who receive this diagnosis based on unproven and/or nonvalidated laboratory tests and clinical criteria. In a recent article [1], patients diagnosed with chronic Lyme disease were classified in four categories:

- Category 1—symptoms of unknown cause, with no evidence of *Borrelia burgdorferi* infection
- Category 2—a well-defined illness unrelated to *B. burgdorferi* infection
- Category 3—symptoms of unknown cause, with antibodies against *B. burgdorferi* but no history of objective clinical findings that are consistent with Lyme disease
- Category 4—post-Lyme disease syndrome

This article addresses mainly patients who have post-Lyme disease syndrome (category 4), as there have been relatively fewer studies addressing patients in categories 1 and 2, and no studies focusing on patients in category 3.

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Chronic Lyme disease

Most patients who are labeled as having chronic Lyme disease will fall into categories 1 and 2. Patients in category 1 are diagnosed with chronic Lyme disease based on unexplained symptoms without objective or valid laboratory evidence of infection *Borrelia burgdorferi*. Patients in category 2 have other recognized diseases and have been misdiagnosed with Lyme disease. The distribution of patients who fall into these categories can be estimated by the difficulty in accruing patients into the placebo-controlled studies of antibiotic treatment in patients with post-Lyme disease syndrome (Category 4), where only 1% to 10% of the screened individuals were eligible [2–4].

There have been numerous studies addressing the issue of overdiagnosis of Lyme disease (Table 1), and although these studies represent the experience of referral centers, they are informative regarding the range of patients seeking further evaluation for suspected Lyme disease. In general, only about one quarter to one third of the patients evaluated were thought to have Lyme disease; in comparison, between 50% to 60% of the patients had no present or past evidence of Lyme disease. A large portion of patients presented with fatigue, myalgias, arthralgias, sleep disturbances, memory complaints, and/or depression, and many fulfilled criteria for chronic fatigue syndrome or fibromyalgia [5–10]. Common and related problems contributing to the overdiagnosis of Lyme disease included the use of serologic testing in clinical situations in which the pretest probability of Lyme disease was low, misinterpretation of test results, and use of nonvalidated methods and criteria for interpretation of laboratory results.

Post-Lyme disease syndrome

Many studies have shown that Lyme disease is treated successfully with antibiotics in most cases, and patients who have objective evidence of treatment failure are rare with currently recommended regimens [11–14]. Patients who have late manifestations can have a slower response to therapy, sometimes taking weeks or months to recover [15–23]. Some patients may have incomplete resolution because of irreversible damage, as can occur in facial nerve palsy with residual facial weakness. A few patients may develop antibiotic-refractory Lyme arthritis, when synovitis persists for months to years after antibiotic therapy, most likely due to autoimmunity triggered by the infection [24].

A minority of patients treated for Lyme disease will have persistent or relapsing nonspecific symptoms (such as fatigue, musculoskeletal pain, and cognitive complaints) after receiving an adequate course of antibiotic therapy. In the absence of another condition that would explain these nonspecific symptoms, such patients are classified as having post-Lyme disease syndrome (Box 1). The best estimates of the prevalence of post-Lyme

disease syndrome come from studies of patients with erythema migrans who received appropriate antibiotic treatment. Approximately 10% to 20% of such patients have persistent or intermittent subjective symptoms of mild-to-moderate intensity 12 months after completion of therapy (Table 2). The most common post-Lyme disease symptoms are fatigue, arthralgias, myalgias, headache, neck stiffness, paresthesias, sleeplessness, irritability, and difficulty with memory, word finding, and concentration [12,13,25–28]. The appearance of post-Lyme disease symptoms seems to correlate with disseminated disease, a greater severity of illness at presentation, and delayed antibiotic therapy [12,29–33], but not with the duration of the initial antibiotic therapy [13,23]. Children appear to be less likely to develop post-Lyme disease symptoms [34–42].

The possible causes of post-Lyme disease symptoms

The mechanisms underlying post-Lyme disease symptoms are not known and are likely to be multifactorial. Possible explanations include persistent infection with *B. burgdorferi*, other tick-borne infections, part of the expected resolution of symptoms after treatment, postinfective fatigue syndrome, autoimmune mechanisms, and intercurrent conditions.

In many patients, these symptoms probably represent the natural evolution of response after therapy, as the percentage of patients reporting symptoms after antibiotic treatment decreases over time. In one study of patients treated for erythema migrans, 34% had symptoms at 3 weeks, 24% at 3 months, and 17% at 12 months [13]. In other patients, a postinfective fatigue syndrome may be triggered by Lyme disease, as has been shown to occur with other infections. Prolonged fatigue after infections is relatively common, and it can be disabling and persistent. A recent study showed that postinfective fatigue syndrome could be predicted by the severity of the acute illness, and its incidence was similar after the different infections [43]. In this cohort, the case rate for provisional postinfective fatigue syndrome was 35% (87/250) at 6 weeks, 27% (67/250) at 3 months, and 9% (22/250) at 12 months [43], rates similar to those reported in patients treated for erythema migrans [13]. The mechanisms that are triggered during the acute illness and that sustain the persistent symptoms in postinfective fatigue syndrome are currently unknown.

It also important to recognize that there is a substantial background prevalence of similar symptoms in the general population. Musculoskeletal pain is a very common complaint. For example, in a random survey of 3664 persons aged 25 years and over, stratified by age and gender, 44.4% of the individuals reported musculoskeletal pain lasting longer than 3 months, with lower back, shoulder, neck and knee being the most frequently affected sites, and 15.6% reporting chronic pain involving two to three sites. The prevalence of chronic widespread pain was 5.2% [44]. In another population-based cross-sectional survey that included 2299 subjects, 15% reported chronic widespread pain,

Table 1
Experience of referral centers with patients suspected of Lyme disease

Reference	Patients	Results
[5]	100 patients referred to the Lyme Disease Center at Robert Wood Johnson Medical School, New Brunswick, New Jersey	37 patients had Lyme disease; 25 patients fulfilled criteria for fibromyalgia (15 had a history compatible with previous Lyme disease; 3 were thought to have fibromyalgia coincidently with Lyme disease). Other diagnoses were made in 22 patients, while in 14 patients, no specific diagnosis was reached. The authors considered that approximately half of the 91 courses of antibiotic therapy given to these patients were unnecessary.
[75]	65 patients referred to the Borrelia Referral Clinic at University Hospital in Vancouver, Canada	Only two patients were judged to have probable Lyme disease. Definite alternative diagnoses were made for 50 patients (77%). Chronic fatigue syndrome and fibromyalgia were diagnosed in 11 patients (17%).
[6]	788 patients referred to the Lyme Disease Clinic at the New England Medical Center, Boston, Massachusetts.	180 (23%) had active Lyme disease, usually arthritis, encephalopathy, or polyneuropathy. 156 patients (20%) had previous Lyme disease and another current illness, with 84 presenting mainly with musculoskeletal pain or fatigue. 452 patients (57%) did not have Lyme disease. Most of these patients had chronic fatigue syndrome (142) or fibromyalgia (84); the others were diagnosed with rheumatic (143), neurologic (41), or other diseases (17).
[7]	227 children referred to the Pediatric Lyme Disease Clinic at the Alfred I. duPont Institute, Wilmington, Delaware.	138 children did not have Lyme disease and were divided in four groups: predominantly subjective symptoms (54 children), alternative diagnosis (52 children) or previous Lyme disease (8 children); 20 children were referred because of tick bites, and 4 children because of a family member with Lyme disease. Most of the children who had subjective symptoms had chronic fatigue. Most had received previous antibiotic therapy, and six children had received prolonged intravenous antibiotic therapy (range 3 to 36 weeks).

[8]	146 pediatric patients referred with possible Lyme disease to the University of Connecticut Health Center, Farmington, Connecticut	56 (38%) were considered overdiagnosed; 12 (8%) were underdiagnosed, and 75 (51%) were diagnosed correctly with Lyme disease.
[9]	209 patients referred to the Yale University Lyme Disease Clinic, New Haven, Connecticut	44 (21%) met criteria for active Lyme disease; 40 (19%) had previous but not active Lyme disease, and 125 (60%) had no evidence of current or previous infection. Patients who had previous Lyme disease and patients who had no evidence of Lyme disease had a longer median duration of symptoms, and about one third had received antibiotic therapy for more than 100 days. At follow-up about 4 months later, 71% of the patients who had previous Lyme disease and 82% of patients who had no evidence of Lyme disease reported persistent symptoms, and about 50% disagreed with the diagnosis provided at the Yale clinic. 31% of patients who had previous Lyme disease and 20% of patients who had no evidence of Lyme disease had sought further evaluation for Lyme disease, and 21% and 11%, respectively, received additional antibiotic therapy.
[10]	216 children referred for Lyme disease to the Pediatric Infectious Diseases Clinic at State University of New York at Stony Brook, Stony Brook, New York	68 (31%) children had active Lyme disease. 39 (18%) children had a prior history of Lyme disease, with 23 having an intercurrent illness or lower school grades and 16 referred because of confusion in the interpretation of immunoblot results. 109 (50%) children had no past or current evidence of Lyme disease, yet 86 (79%) had been started on therapy before referral.
[76]	86 patients referred to the Rheumatology Unit at the Medical University Policlinic in Bonn, Germany	Only eight patients had ongoing or recent Lyme disease. The most common diagnoses were degenerative disorders of the spine (29%), arthropathies related to psoriasis or rheumatoid arthritis (17%), and spondiloarthropathy.

Box 1. Proposed definition of post-Lyme disease syndrome

Inclusion criteria

An adult or child who has a documented episode of early or late Lyme disease fulfilling the case definition of the Centers for Disease Control and Prevention; if based on erythema migrans, the diagnosis must be made and documented by an experienced health care practitioner.

After treatment of the episode of Lyme disease with a generally accepted treatment regimen, there is resolution or stabilization of the objective manifestation(s) of Lyme disease.

Onset of any of the following subjective symptoms within 6 months of the diagnosis of Lyme disease and persistence of continuous or relapsing symptoms for at least a 6-month period after completion of antibiotic therapy:

    Fatigue

    Widespread musculoskeletal pain

    Complaints of cognitive difficulties

Subjective symptoms are of such severity that, when present, they result in substantial reduction in previous levels of occupational, educational, social, or personal activities.

Exclusion criteria

An active, untreated, well-documented coinfection, such as babesiosis

The presence of objective abnormalities on physical examination or on neuropsychological testing that may explain the patient's complaints

A diagnosis of fibromyalgia or chronic fatigue syndrome before the onset of Lyme disease

A prolonged history of undiagnosed or unexplained somatic complaints, such as musculoskeletal pains or fatigue, before the onset of Lyme disease.

A diagnosis of an underlying disease or condition that might explain the patient's symptoms

Laboratory or imaging abnormalities that might suggest an undiagnosed process distinct from post–Lyme disease syndrome

Although testing by either culture or polymerase chain reaction for evidence of *Borrelia burgdorferi* infection is not required, should such testing be done by reliable methods, a positive result would be an exclusion.

and 8% reported chronic fatigue [45]. Insomnia is also common, and can be associated with anxiety, depression, and pain [46]. Musculoskeletal pain, fatigue, and sleep disturbance often are reported together [47].

Recent studies showed little evidence of a substantial role of other tick-borne infections in most patients who had post-Lyme disease syndrome [4,48–50]. There has been little research in the role of autoimmunity in post-Lyme disease syndrome, but one study showed no association between a class 2 allele or genotype [51].

A major concern has been that the symptoms of post-Lyme disease syndrome may represent persistent infection with *B. burgdorferi*. A review of the earliest studies of patients who had Lyme disease demonstrates the uncertainty that surrounded the disease and explains in part some of the confusion regarding chronic Lyme disease. During those initial years, nonspecific symptoms were classified as part of minor late manifestations or complications of Lyme disease, to differentiate from the major manifestations, which included arthritis, meningoencephalitis, and carditis [25, 29–31]. In some cases, facial palsy and brief episodes of arthritis were grouped together with nonspecific symptoms as part of minor manifestations of late Lyme disease [29,30], and, in some studies, all patients were grouped together [29,31]. Although arthritis, meningoencephalitis, carditis and other objective manifestations of Lyme disease are clear evidence of treatment failure and require antibiotic therapy [14], there was uncertainty about whether nonspecific minor symptoms also could represent treatment failures and whether longer courses of antibiotics or different antibiotic regimens may be needed in some of the patients [30,31,52,53].

As the studies progressed, and antibiotic therapy for Lyme disease evolved, it became rare for patients who had erythema migrans treated with currently recommended antibiotic regimens to develop an objective manifestation of Lyme disease [13]. Physicians also gained more experience following patients who were treated with antibiotics, and, with longer periods of observation, it became apparent that these nonspecific symptoms frequently resolved without further antibiotic treatment, and that antibiotic therapy did not hasten their resolution [33,54]. Further studies also showed that symptomatic patients were not more likely to be seropositive than patients without symptoms and that patients did not develop objective manifestations of late Lyme disease [12,18]. Although earlier, smaller studies showed a higher prevalence of recurrent arthralgias, symptoms of memory impairment, and other symptoms in persons with a history of Lyme disease compared with controls [32,33], larger cohort studies showed no differences on physical examination and neurocognitive testing [55], and no difference in the frequency of symptoms between patients who had Lyme disease and age-matched controls [39].

Objective evidence of *Borrelia* infection in patients who have post-Lyme disease syndrome has not been found using polymerase chain reaction (PCR) [4,49] or culture [4,49]. It should be noted, however, that

Table 2
Symptoms after antibiotic therapy in patients with erythema migrans

Year	Country	Study design	Patients and treatment	Results	Post-Lyme disease symptoms	Reference
1992	United States	Randomized investigator-blinded multicenter study	63 patients were randomized to cefuroxime 500 mg orally twice a day for 20 days and 60 patients to doxycycline by mouth 100 mg three times a day for 20 days	Satisfactory outcome was seen in 51 (93%) patients who received cefuroxime and 45 (88%) patients who received doxycycline at 1 month. Ten patients were considered to not have a satisfactory outcome. In 9 patients, the erythema migrans (EM) had resolved but they had arthralgias, myalgias, paresthesias, fatigue, and headache.	At 1 year, 43 (90%) in the cefuroxime group and 35 (92%) in the doxycycline had satisfactory outcomes, while 8 patients were considered failures, as they had arthralgias, myalgias, headache, and fatigue. Patients who were assessed as clinical improvements at 1 month after treatment were more likely to become clinical failures at 1 year follow up.	[54]
1993	Slovenia	Randomized open-label single-center study	55 patients received azithromycin 500 mg orally twice a day for the first day followed by 500 mg once a day for 4 days, and 52 patients received doxycycline 100 mg orally twice a day for 14 days.	There were three definite and four probable treatment failures in the doxycycline group and one probable treatment failure in the azithromycin group.	At 1 year, 15 patients on doxycycline and 10 on azithromycin had minor symptoms (arthralgias, myalgias, fatigue, headache, and concentration disturbances). Most minor symptoms appeared in the first 6 months after therapy.	[26]

1995	United States	Randomized investigator-blinded multicenter study	119 patients receive cefuroxime axetil 500 mg orally twice a day, and 113 patients received doxycycline 100 mg orally three times a day for 20 days	Satisfactory clinical response was seen in 90% of patients on cefuroxime and 95% of patients on doxycycline. Presenting with paresthesias, arthralgias, and irritability at the initial visit was associated with failure at 1 month.	Of the 118 patients evaluated at 1 year, satisfactory outcomes were seen in 95% of the patients in the cefuroxime group and 100% in the doxycycline group.	[77]
1996	United States	Observational cohort multicenter study	Prospective evaluation of 201 children with Lyme disease in Connecticut. 132 (66%) presented with single EM; 56 (28%) presented with early disseminated disease, and 13 (6%) with Lyme arthritis. All were treated with 2 to 4 weeks of antibiotics, (94% for 3 to 4 weeks), and 96% were treated orally. 137 received amoxicillin, and 51 received doxycycline.	All children responded promptly, and 94% were asymptomatic by 4 weeks, with 5% having arthralgia, myalgia, and fatigue, and 1% had residual facial palsy. All patients recovered completely at 6 months, but for one patient who had mild recurrent arthralgia.	At 2-year follow-up, only 1 child had mild recurrent arthralgia.	[35]
1996	United States	Randomized double-blinded multicenter study	111 patients received azithromycin 500 mg orally once a day (with placebo orally twice a day) for 7 days (followed by placebo three times a day for 13 days) compared with 106 patients given amoxicillin 500 mg orally three times a day for 20 days.	At day 20, 84 (76%) had a complete response in the azithromycin group versus 93 (88%) in the amoxicillin group. Partial response was seen in 24 (22%) patients in the azithromycin group versus13 (12%) in the amoxicillin group. There were three failures in the azithromycin group.	At 180 days, 17 patients in the azithromycin group versus 4 patients in the amoxicillin group were considered relapses. A partial response at day 20 was predictive of relapse	[53]

Table 2 (*continued*)

Year	Country	Study design	Patients and treatment	Results	Post-Lyme disease symptoms	Reference
1997	United States	Randomized open-label multicenter study	68 patients received ceftriaxone parenterally 2 g once a day for 14 days, and 72 patients received doxycycline 100 mg orally twice a day for 21 days.	At 3 months, 55 (92%) of patients in the ceftriaxone group and 63 (94%) in the doxycycline group had recovered completely.	At 9 months, 56 (97%) patients in the ceftriaxone group and 58 (94%) in the doxycycline group were considered cured. At the last follow-up visit, there were persistent symptoms in 18 patients treated with ceftriaxone and 10 patients treated with doxycycline. Most symptoms were considered mild.	[27]
2000	Croatia	Randomized open-label multicenter study	48 patients received azithromycin 500 mg orally twice a day for the first day followed by 500 mg daily for 4 days, and 40 patients received doxycycline 100 mg orally twice a day for 14 days.	There was one clear treatment failure in the azithromycin group.	At 1 year, minor symptoms occurred in 2 of 47 patients who received azithromycin and 3 of 35 patients who received doxycycline.	[78]
2002	United States	Observational cohort multicenter study	Follow-up of 118 patients participating in a vaccine study who had EM with positive PCR and/or culture. Most patients were treated with oral doxycycline or amoxicillin for 14–30 days.	Most patients had resolution of all symptoms by 3 weeks. At 30 days after therapy, 13 (11%) still had symptoms, and 5 (4%) had symptoms for more than 60 days (3 with fatigue, headache, arthralgia; 2 had residual facial numbness or weakness).	One patient had myalgias at the end of the study.	[11]

| 2002 | Slovenia | Randomized open-label single-center study | 42 children received azithromycin 20 mg/kg/d (maximum 1000 mg/d) for the first day followed by 10 mg/kg/d (maximum 500 mg/d) for 4 days, and 42 children received phenoxymethylpenicillin 100,000 IU/kg/d (maximum 3 million IU/d) divided in three daily doses for 14 days | Appearance of minor manifestations (17.5% versus 24.4%) and major manifestations of Lyme (one patient in each group) was not different between the groups. | At 1 year, all patients were asymptomatic. | [40] |
| 2003 | United States | Observational cohort single-center study | From 99 patients with 101 episodes of EM who were culture positive, there were 96 evaluable cases. 87 cases (91%) received a first-line oral antimicrobial regimen, such as doxycycline, amoxicillin, or cefuroxime axetil, or received intravenous ceftriaxone for 10 to 21 days. Nine cases received a 7-day course of azithromycin. | After 3 months, 84% to 92% of cases were asymptomatic. | Only 8 (10%) of the 81 cases followed for ≥ 1 year were symptomatic at their last visit, a mean of 5.6 ± 2.6 years of follow-up. Their symptoms tended to be intermittent and mild, with only three patients (4%) consistently symptomatic at each follow-up visit. Presenting with symptoms during follow up was associated with presenting with more symptoms and of greater severity, and presenting with multiple EM at the first visit. | [12] |

Table 2 (*continued*)

Year	Country	Study design	Patients and treatment	Results	Post-Lyme disease symptoms	Reference
2003	United States	Randomized double-blinded single-center study	60 patients received a single 2g dose of intravenous ceftriaxone followed by doxycycline 100 mg orally twice a day for 10 days, followed by placebo orally twice a day for 10 days. 61 patients received a single dose of intravenous placebo, followed by doxycycline 100 mg orally twice a day for 10 days, followed by placebo twice a day for 10 days. 59 patients received a single placebo injection followed by doxycycline 100 mg orally twice a day for 20 days.	The complete response rate was similar in the three groups at all time points. At 20 days, 97 patients had a complete response; 47 had a partial response, and 1 was a failure. The only failure was a patient treated with doxycycline for 10 days who developed meningitis at 18 days and was treated with ceftriaxone.	At 12 months, 103 patients had a complete response, and 24 had a partial response. At 30 months, 86 patients had a complete response, and 12 had a partial response.	[13]

B. burgdorferi culture and PCR have low sensitivity in most body fluids from patients who have Lyme disease [56,57]. The initial report claiming frequent isolation of *B. burgdorferi* from patients who had post-Lyme disease syndrome using MPM media [58] has not been reproduced by other researchers [49,59,60]. One study reported a high percentage of *B. burgdorferi* PCR in urine samples of patients diagnosed with chronic Lyme disease [61], but these results have not been validated. Other tests that have not been helpful to evaluate patients who have post-Lyme disease syndrome include changes in C6 antibody levels [62] and antibodies in immune complexes [63].

There have been interesting reports of *B. burgdorferi* being present after antibiotic therapy in dogs and mice as assessed by PCR, but not by culture [64–66]. More detailed studies suggested that these organism were attenuated, noninfectious spirochetes [66]. The significance of these findings is, at present, unclear. A recent study reported that *B. burgdorferi* was found by culture in a few mice treated with antitumor necrosis factor (TNF) antibody either simultaneously or 4 weeks after ceftriaxone therapy [67]. The number of mice treated in this study, however, was small, and the findings need further verification.

Studies of antibiotic treatment in post-Lyme disease syndrome

There are now four randomized, placebo-controlled, double-blinded studies of antibiotic therapy in patients who had post-Lyme disease syndrome, and all showed that prolonged antibiotic therapy offers no sustained benefit and has potential serious adverse effects (Table 3). The first two studies, one for patients who were IgG seropositive for *B burgdorferi* at enrollment, and the other for seronegative patients, were published together [49]. All patients had well-documented Lyme disease and had received antibiotic therapy previously. These studies enrolled 78 seropositive patients and 51 seronegative patients. Patients were randomized to receive intravenous ceftriaxone, 2 g daily for 30 days, followed by oral doxycycline, 100 mg twice a day for 60 days, or matching intravenous and oral placebos. The primary outcome was improvement in the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) score on day 180 of the study. Patients previously had received an average of three courses of antibiotic therapy and had had symptoms for a median of 4.6 years. Most patients complained of pain, fatigue, and cognitive changes. The studies were stopped early because a planned interim analysis showed that there was little chance of demonstrating a difference between treatment groups. Intention-to-treat analyses showed no significant differences between patients in the antibiotic groups and those in the placebo groups in the seropositive study, the seronegative study, or both studies combined. About one-third of the patients improved; one-third of the patients remained unchanged, and one-third of the patients worsened at each time point. There were two serious adverse events related to treatment.

Table 3
Placebo-controlled, double-blinded randomized treatment studies in post-Lyme disease syndrome

Reference	Patients	Regimen and primary endpoints	Results	Serious adverse events
[49]	78 seropositive and 51 patients seronegative for IgG antibodies to *Borrelia burgdorferi* at the time of enrollment	IV ceftriaxone, 2 g/d for 30 days, followed by oral doxycycline, 100 mg twice a day for 60 days (64 patients), or matching intravenous and oral placebos (65 patients). The primary outcome was improvement on SF-36 score at day 180 of the study.	Intention-to-treat analyses at 30, 90, and 180 days showed no significant differences between the antibiotic group and the placebo group in the seropositive study, the seronegative study, or both studies combined. During the 6-month evaluation period, about a third of the patients improved; a third worsened and a third were unchanged by SF-36.	Two patients had serious adverse events associated with treatment that required hospitalization.
[3]	55 patients with persistent severe fatigue after Lyme disease	IV ceftriaxone 2 g/d (28 patients) or IV placebo (24 patients) for 28 days. Primary clinical outcomes were improvement in fatigue score and cognitive function at 6 months. Follow-up at 6 months was completed by 26 patients in the ceftriaxone group and 22 patients in the placebo group.	Patients who received ceftriaxone showed improvement on fatigue, but there was no benefit in cognitive function. Exploratory analyses showed that patients with positive Western blot, no prior IV therapy, and less pain had a significant treatment effect.	Four patients had serious adverse events associated with treatment that required hospitalization.

| [4] | 37 seropositive patients with objective memory impairment and at least 3 weeks of previous IV antibiotic therapy. | Patients were assigned in a 2:1 randomization schedule to receive 10 weeks of IV ceftriaxone 2 g/d (23 patients) or IV placebo (14 patients). The primary outcome was improvement at 12 weeks. Durability of benefit was evaluated at 24 weeks. 20 patients in the ceftriaxone group and 12 patients in the placebo group completed follow up. | There was a slightly greater cognitive improvement in the antibiotic group at week 12, but there was no difference at week 24. | Eight patients withdrew from therapy, seven because of adverse events associated with treatment. One patient on ceftriaxone underwent cholecystectomy at week 16. |

Abbreviations: IV, intravenous; SF-36, Medical Outcomes Study 36-item Short-Form General Health Survey.

The third study enrolled 55 patients with post-Lyme disease syndrome who had significant fatigue [3]. These patients were randomized to ceftriaxone 2 g (28 patients) or placebo (24 patients) intravenously daily for 28 days. The primary clinical endpoints were improvement in the fatigue and mental speed at 6 months. Eighteen patients (64%) in the ceftriaxone group and 19 patients (70.4%) in the placebo group were ELISA and Western blot seropositive at enrollment, while 12 (43%) in the ceftriaxone group and 14 (52%) in the placebo group had received at least 2 weeks of intravenous ceftriaxone before the study. The intent-to-treat analysis showed modest improvement of fatigue with ceftriaxone therapy, with similar results for patients who received therapy and completed follow up. There was no improvement in mental speed or other neurocognitive measures. Three patients in each group discontinued therapy because of adverse effects, and four had to be hospitalized. In this study, significantly more patients who received ceftriaxone were able to correctly guess their assignment compared with placebo recipients.

The fourth study enrolled patients with post-Lyme disease syndrome who were seropositive by IgG Western blot, had objective memory impairment, and had received at least 3 weeks of intravenous antibiotic therapy [4]. There were only 37 patients enrolled, and they were randomized 2:1 to receive 10 weeks of intravenous ceftriaxone (23 patients) or intravenous placebo (14 patients). The primary outcome was improvement in memory performance at 12 weeks. Patients were evaluated at 24 weeks for durability of benefit. Twenty patients in the ceftriaxone group and 12 patients in the placebo group completed the follow-up. In comparisons using a model with an aggregate of the six domains of neurocognitive performance measured in the study, the ceftriaxone group showed a slightly greater improvement at 12 weeks. At 24 weeks, both groups had improved similarly from baseline. Exploratory analysis suggested a greater improvement in physical functioning and pain among patients, with greater baseline impairment treated with ceftriaxone. There were nine patients who discontinued therapy because of adverse effects, and in seven patients, these effects were related to the treatment.

Three of these randomized trials have been criticized as offering too little, too late [68–70], based on retrospective, open-label case-series that suggested a possible role of prolonged antibiotic therapy in patients diagnosed with chronic Lyme disease [71,72]. In general, case series studies are fraught with potential for biases. For example, both patients and physicians' choices will affect the decision to prescribe a drug to a particular patient. The lack of blinding can affect outcomes, especially for subjective measures. Without a comparison group, it is not possible to know if an outcome is related to an intervention, or to a placebo effect, time, or chance. Case series and case reports are classified at the lowest level of strength in the hierarchy of evidence-based medicine [73]. They are best used for hypothesis generation to be investigated by stronger study designs.

Summary

At this point, the overwhelming evidence shows that prolonged antibiotic therapy, as tested in the clinical trials, does not offer lasting or substantive benefit in treating patients who have post-Lyme disease syndrome. Therefore, it is time to move forward to test other approaches that may help these patients. Unfortunately, no prospective studies of other treatment modalities for patients who have post-Lyme disease syndrome have been performed. Because of the significant placebo effect and the variation in symptom intensity seem in these patients, interventional studies should have a randomized controlled design, with clearly defined target patient populations. For the health care provider taking care of these patients, as always, one should review carefully the evidence for the diagnosis of Lyme disease and not lose sight that these patients can develop other unrelated conditions. It is important that patients be offered the best advice based on current, evidence-based information [74]. Most importantly, there should be a collaborative approach to the treatment process with the patient. Hopefully, further research to understand chronic Lyme disease and the reasons underlying persistent symptoms after Lyme disease will lead to the development of beneficial therapies.

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