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Chronic Lyme Disease: An appraisal

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Synopsis

"Chronic Lyme disease" is a confusing term that has been used to describe very different patient populations. Studies have shown that most patients diagnosed with "chronic Lyme disease" either have no objective evidence of previous or current infection with *B. burgdorferi* or are patients that should be classified as having post-Lyme disease syndrome, which is defined as continuing or relapsing non-specific symptoms (such as fatigue, musculoskeletal pain, and cognitive complaints) in a patient previously treated for Lyme disease. Despite extensive study, there is currently no clear evidence that post-Lyme disease syndrome is due to persistent infection with *B. burgdorferi*. Four randomized placebo-controlled studies have shown that antibiotic therapy offers no sustained benefit to patients with post-Lyme disease syndrome. These studies also showed a substantial placebo effect and a significant risk of treatment-related adverse events. Further research to elucidate the mechanisms underlying persistent symptoms after Lyme disease and controlled trials of new approaches to the treatment and management of these patients are needed.

Keywords

Lyme disease; Borrelia burgdorferi; Post-Lyme disease syndrome

'The beginning of wisdom is the definition of terms'. Socrates

Introduction

"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 chapters), patients with post-Lyme disease syndrome, and patients with nonspecific signs and symptoms of unclear cause who receive this diagnosis based on unproven and/or non validated laboratory tests and clinical criteria. In a recent article [1], patients diagnosed with "chronic Lyme disease" were classified in 4 categories (Table 1). This article addresses mainly patients with 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 B. *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 a number of studies addressing the issue of over diagnosis of Lyme disease (Table 2), and while 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 over diagnosis of Lyme disease included the use of serological testing in clinical situations in which the pre-test probability of Lyme disease was low, misinterpretation of test results, and use of non-validated 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 the majority of cases, and patients with objective evidence of treatment failure are rare with currently recommended regimens [11–14]. Patients with late manifestations can have a slower response to therapy, sometimes taking weeks or months to recover [15–23]. Some patients may have incomplete resolution due to 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, it is most likely due to autoimmunity triggered by the infection [24].

A minority of patients treated for Lyme disease will have persistent or relapsing non-specific 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 non-specific symptoms, such patients are classified as having post–Lyme disease syndrome (Table 3). The best estimates of the prevalence of post-Lyme disease syndrome come from studies of patients with erythema migrans who received appropriate antibiotic treatment. From 10–20% of such patients have persistent or intermittent subjective symptoms of mild to moderate intensity 12 months after completion of therapy (Table 4). 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, post-infective 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 post-infective 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 post-infective 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 post-infective fatigue syndrome was 35% (87/250) at six weeks, 27% (67/250) at three months, and 9% (22/250) at 12 months [43]; rates similar to those reported in patients treated for erythema migrans (see above) [13]. The mechanisms that are triggered during the acute illness and that sustain the persistent symptoms in post-infective 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 2 to 3 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, 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 are often reported together [47].

Recent studies showed little evidence of a substantial role of other tick-borne infections in the majority of patients with 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 II 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 with Lyme disease demonstrate the uncertainty that surrounded the disease and explain 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]. While 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 could also represent treatment failures and that 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 with 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]. While 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 with Lyme disease and age-matched controls [39].

Objective evidence of Borrelia infection in patients with post-Lyme disease syndrome has not been found using PCR [4,49] or culture [4,49]. It should be noted however, that *B. burgdorferi* culture and PCR have low sensitivity in most body fluids from patients with Lyme disease [56,57]. The initial report claiming frequent isolation of *B. burgdorferi* from patients with 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 with 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 [64,65,66]. More detailed studies suggested that these organism were attenuated, non infectious 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 anti-TNF antibody either simultaneously or 4 weeks after ceftriaxone therapy [67]. However, the number of mice treated in this study was small and the findings need further verification.

Studies of antibiotic treatment in post-Lyme disease syndrome

There are now 4 randomized, placebo-controlled, double-blinded studies of antibiotic therapy in patients with post-Lyme disease syndrome and all showed that prolonged antibiotic therapy offers no sustained benefit and has potential serious adverse effects (Table 5). The first 2 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 previously received antibiotic therapy. 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, 200 mg daily 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 had previously 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 2 serious adverse events related to treatment.

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 due to side effects, and 4 had to be hospitalized. In this study, significant more patients who received ceftriaxone were able to correctly guess their assignment comparing 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 9 patients who discontinued therapy due to side effects, and in 7 patients these side 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.

Conclusion

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 with 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 with post-Lyme disease syndrome have been performed to date. Due to the significant placebo effect and the variation in symptoms 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, they should review carefully the evidence for the diagnosis of Lyme disease and not loose 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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Table 1

Categories of "Chronic Lyme Disease"

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

From Feder, H.M., Jr., et al., *A critical appraisal of "chronic Lyme disease"*. N Engl J Med, 2007. **357**(14): p. 1422–30

vided at the Yale clinic. 31% of patients with previous Lyme disease and 20% of patients with no evidence of Lyme disease had sought further evaluation for Lyme disease, and 21% and 11%, respectively, received additional antibiotic therapy.

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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 PCR for evidence of *Borrelia burgdorferi* infection is not required, should such testing be done by reliable methods, a positive result would be an exclusion.

eriod after completion of antibiotic therapy:

al practice guidelines

Infect Dis Clin North Am. Author manuscript; available in PMC 2009 June 1.

	Reference
ue. Patients who were assessed as clinical improvements at1 month post- treatment were more likely to become clinical failures at 1 year follow up.	[54]
t 6 months after therapy.	[26]
	[77]
	[35]
	[53]
ftriaxone and 10 patients treated with doxycycline. Most symptoms were considered mild.	[27]
	[78]
	[11]
	[40]
(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]
	[13]

	Serious Adverse Events
hird of the patients improved, a third worsened and a third were unchanged by SF-36.	2 patients had serious adverse events associated with treatment that required hospitalization.
	4 patients had serious adverse events associated with treatment that required hospitalization.
	8 patients withdrew from therapy, 7 due to adverse events associated with treatment. One patient on ceftriaxone underwent cholecystectomy at week 16.