EXPERT REVIEWS

Chronic Lyme disease: the controversies and the science

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The diagnosis of chronic Lyme disease has been embroiled in controversy for many years. This is exacerbated by the lack of a clinical or microbiologic definition, and the commonality of chronic symptoms in the general population. An accumulating body of evidence suggests that Lyme disease is the appropriate diagnosis for only a minority of patients in whom it is suspected. In prospective studies of Lyme disease, very few patients go on to have a chronic syndrome dominated by subjective complaints. There is no systematic evidence that *Borrelia burgdorferi*, the etiology of Lyme disease, can be identified in patients with chronic symptoms following treated Lyme disease. Multiple prospective trials have revealed that prolonged courses of antibiotics neither prevent nor alleviate such post-Lyme syndromes. Extended courses of intravenous antibiotics have resulted in severe adverse events, which in light of their lack of efficacy, make them contraindicated.

Keywords: *Borrelia burgdorferi* • chronic fatigue • chronic Lyme disease • fibromyalgia • Lyme disease

Each year, tens of thousands of North Americans and Europeans become infected with *Borrelia burgdorferi* sensu lato, the group of related tick-borne spirochetes that cause Lyme disease (Box 1). It is widely assumed that this disease is under-reported, and the actual incidence may approach the hundreds of thousands. Its variety of manifestations continues to pose a challenge to clinicians. As many as 80–90% of patients present with the characteristic erythema migrans rash of early Lyme disease, but if unrecognized and untreated, the organism can disseminate to skin, the heart, the central or peripheral nervous system, and joints. The resultant disease manifestations are usually recognizable based on objective clinical findings, such as aseptic meningitis, nerve palsies, cardiac conduction delays and frank arthritis, and have been definitively attributed to *B. burgdorferi* based on culture nucleic acid detection, or seroreactivity.

It is well-established that some patients experience prolonged somatic or neurocognitive symptoms during convalescence from Lyme disease, and a subset suffer significant functional impairment [1–8]. Whether this phenomenon occurs frequently or rarely, and whether it is caused by persistent infection with *B. burgdorferi*, lie at the heart of the often acrimonious controversy over what has been termed 'chronic Lyme disease'. This controversy primarily exists in the public dialogue, as the concept of chronic Lyme disease is not widely accepted within the scientific or clinical community. At least 19 independent societies representing the USA and numerous European countries have produced remarkably similar clinical practice guidelines for Lyme disease, discouraging the diagnosis of chronic Lyme disease and recommending against treating patients with prolonged or repeated antibiotic courses [9–27,201]. These recommendations are also shared by national public health agencies throughout the Lyme-endemic world. A small minority of physicians accounts for most diagnoses of chronic Lyme disease: one study found that only six of 285 (2.1%) randomly surveyed physicians in Connecticut, USA, gave patients this diagnosis [28]. Still fewer depart from published guidelines by prescribing extended courses of antibiotics [29].

Does chronic Lyme disease exist?

Most patients who are diagnosed with chronic Lyme disease have prolonged somatic and/or neurocognitive symptoms, such as fatigue, arthralgias or memory impairment, but usually lack the objective findings classically associated with Lyme disease. The term 'chronic Lyme disease' implicitly suggests that these symptoms are caused by infection with *B. burgdorferi*, and it is often argued that infection

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Box 1. Nomenclature of *Borrelia burgdorferi* sensu lato genospecies.

Borrelia burgdorferi sensu lato refers to a complex of 18 related genospecies. Of these, *B. burgdorferi* sensu stricto, *B. garinii* and *B. afzelii* are responsible for Lyme disease in Europe. *B. burgdorferi* sensu stricto is the sole agent of Lyme disease in North America. Other genospecies within the complex may have medical importance, but this is currently investigational. As the clinical, microbiologic and taxonomic distinctions within this group are beyond the scope of this article, the designation *B. burgdorferi* is used here for brevity in place of *B. burgdorferi* sensu lato [125].

with this organism may become persistent despite antimicrobial therapy. These assumptions, however, have not translated to any accepted clinical, pathologic or microbiologic definition of the term. One clinical practice guideline devoted to the management of chronic Lyme disease included a provisional definition so broad that Lyme disease could not be differentiated from the myriad other medical conditions (Box 2) [30]. Without a definition, the term lacks meaning and it becomes fruitless to debate about whether or not 'chronic Lyme disease' exists as such.

Unable to precisely say what chronic Lyme disease is, we must next examine the features of patients referred for Lyme disease to discern whether there emerges a subset who have verifiable Lyme disease, and who appear to have chronic, treatment-refractory infection. In seven studies conducted in endemic areas, comprising a total of 1902 patients referred for suspected Lyme disease, only 7–31% had active Lyme disease and 5–20% had previous Lyme disease [31–37]. Among the remainder, 50–88% had no evidence of ever having had Lyme disease (Figure 1). Most of these patients had either an alternative medical diagnosis or a functional somatic syndrome such as chronic fatigue syndrome or fibromyalgia. A substantial number were diagnosed with Lyme disease based on an inability to make an alternative diagnosis – referred to in one paper as 'diagnosis of Lyme disease by exclusion' [36]. Primary psychiatric diagnoses, psychiatric comorbidity and psychological traits such as catastrophization and negative affect are also common [32,34]. Many had symptoms of long duration and had received multiple courses of antibiotics directed at Lyme disease. Similar observations were made in Vancouver, British Columbia, where Lyme disease is very rare; of 65 patients referred for Lyme disease, 61 had either an alternative medical diagnosis or a functional somatic syndrome, and nine had a primary psychiatric diagnosis [38].

These studies underscore the degree of concern about Lyme disease in clinical practice, but even in the most highly endemic areas, less than a third of referred patients prove to have the disease in the end. The remainder appears to divide into at least three broad categories: those with alternative medical diagnoses, those with functional somatic syndromes, and a minority who have persistent symptoms that follow treatment for Lyme disease. This is true, notwithstanding the results of diagnostic testing: while a negative test may help exclude Lyme disease in patients with a low pretest probability, a positive test does not necessarily confirm the diagnosis in this scenario [39]. The positive predictive value of Lyme serodiagnostics is poor in patients with only nonspecific symptoms. Patients may coincidentally have positive Lyme serology for a variety of reasons, including asymptomatic seroconversion, generation of cross-reactive antibodies in other infectious or inflammatory diseases, or a previous treated episode of Lyme disease, and the prevalence of asymptomatic seropositivity may match or exceed the cumulative incidence of confirmed disease [31,35,36,39–46].

Box 2. Operational definition of chronic Lyme disease published by the International Lyme and Associated Diseases Society.

For the purpose of the ILADS guidelines, 'chronic Lyme disease' is inclusive of persistent symptomatologies including fatigue, cognitive dysfunction, headaches, sleep disturbance and other neurologic features, such as demyelinating disease, peripheral neuropathy and sometimes motor neurone disease, neuropsychiatric presentations, cardiac presentations including electrical conduction delays and dilated cardiomyopathy and musculoskeletal problems.

ILADS: International Lyme and Associated Diseases Society.
Taken from [30].

The differential diagnosis of chronic Lyme disease

Many patients referred for Lyme disease are often found to have a rheumatologic or neurologic diagnosis. Osteoarthritis, rheumatoid arthritis (RA), degenerative diseases of the spine and spondyloarthropathies are the most common rheumatologic conditions identified in these patients [32,33,47]. Some patients are found to have neurologic diseases, including multiple sclerosis (MS), demyelinating diseases, amyotrophic lateral sclerosis (ALS) and neuropathies [33]. Some authors and patient advocates have proposed that in actuality Lyme disease is the true or underlying etiology in many patients who have received these alternative medical diagnoses [30,48–50]. This seems to be quite unlikely given that many of these diseases result in rather specific medical syndromes that do not concentrate in areas with heavy *B. burgdorferi* transmission, such as the Northeastern and upper Midwestern USA [51]. Even if one were to stipulate that very atypical presentations of Lyme disease (i.e., resembling ALS) went unrecognized by public health authorities, and that surveillance numbers are skewed by too narrow a case definition, one would still expect to see clustering in areas where Lyme transmission is heaviest. This is not the case. MS, for instance, occurs at substantial rates in areas with little or no endemic transmission of *B. burgdorferi*, such as Washington state, USA, Northern Canada, Iceland and arctic Norway [52]. Similarly, the medical literature fails to yield evidence that ALS, Parkinson's disease, RA or spondyloarthropathies cluster in areas with the highest incidence rates of Lyme disease. While there can certainly be clinical overlap between Lyme disease and other clinical entities, objective findings and studies will generally allow the clinician to differentiate between them [53–55].

Syndromes such as fibromyalgia and chronic fatigue syndrome, as well as less specific chronic syndromes (variably called

'medically unexplained systems', 'functional pain syndromes' or 'chronic multisystem illness') account for most of the remaining patients who are referred for chronic Lyme disease. Unlike Lyme disease, these frustrating conditions generally lack objective clinical or histopathological abnormalities, and are dominated by subjective complaints and functional impairment [56–58]. Neither fibromyalgia nor chronic fatigue syndrome is known to geographically cluster with *B. burgdorferi* transmission. Fibromyalgia has been found to temporally follow Lyme disease in some cases: in a prospective study of 287 patients treated for confirmed Lyme disease, 22 (8%) went on to develop fibromyalgia within 5 months of treatment [59]. Additional antibiotics were not beneficial. It must be noted that fibromyalgia and chronic fatigue can temporally follow a variety of infections, including, but not limited to, infection with *B. burgdorferi* [56,60].

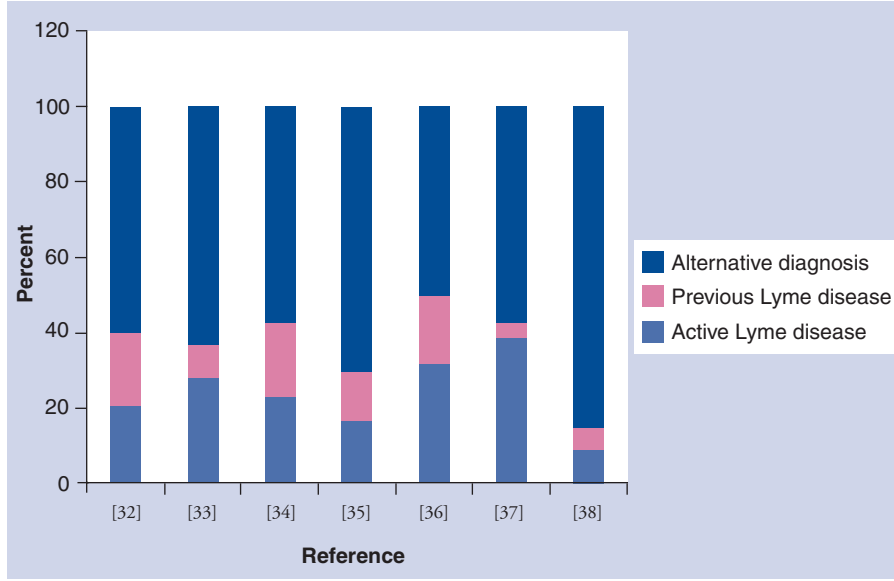

Figure 1. Categorization of persons referred for Lyme disease in endemic areas. Alternative diagnoses are categorized differently in the cited references, but include definite alternative medical diagnoses, chronic functional syndromes (e.g., fibromyalgia), symptomatic persons with no adequate explanation and asymptomatic persons referred because of abnormal test results
Data taken from [31–37].

Post-Lyme disease syndromes

The designation 'post-Lyme disease syndromes' has been proposed to describe patients who experience prolonged subjective symptoms following Lyme disease [26]. It is more properly thought of as a means of categorizing this patient cohort, rather than describing a clinical diagnosis. The case definition of post-Lyme disease syndromes differs from 'chronic Lyme disease' chiefly in its requirements that patients have: unequivocal documentation of appropriately-treated Lyme disease; and persistent subjective symptoms that cannot be explained by other medical illnesses (**Box 3**). The definition contains abundant exclusion criteria. In particular, this concept must be distinguished from treatment failure – for instance, persistence, relapse or development of objective signs of disease as occasionally happens in the treatment of Lyme disease.

The most common complaints among patients with post-Lyme disease syndromes are arthralgias, myalgias, headache, neck and backache, fatigue, irritability and cognitive dysfunction (particularly perceived difficulty with memory and concentration). While some patients have objective cognitive deficits, many who subjectively complain of cognitive dysfunction are found to be normal when formally tested [3,7,61–65]. The attribution of these symptoms to Lyme disease is complicated by their extraordinarily high background rate in the population at large, and in fact their frequency might be no greater than that expected by chance alone. Up to 20% of the general population experiences chronic fatigue [66,67]. In one survey using three different assessment instruments, 3.75–12.1% of the general population suffered severe pain and 36.4–45.1% moderate pain; in fact, only 42.5–59.1% of the general population was pain-free [68]. In a separate study 11.2% of respondents suffered chronic, widespread pain [69]. A quarter to a third of the general population describe chronic cognitive dysfunction [68]. These symptoms often coincide with anxiety or depression, which in turn affected 25% of subjects in this study.

The rarity of post-Lyme disease syndromes is exemplified by the great difficulty three investigative teams had in recruiting subjects for clinical trials investigating this condition [2,4,5]. Of 5846 patients screened over several years, only 222 (3.8%) could ultimately be randomized, a striking finding given that most of the 20,000 annual cases of Lyme disease occur in the region where these studies are conducted. The dominant reason for this is that very few of the screened patients had documentation of prior Lyme disease. This suggests that the attribution of chronic symptoms to Lyme disease is grossly out of proportion to its actual occurrence.

Interestingly, in most longitudinal studies of Lyme disease, the prevalence of chronic post-treatment symptoms is no higher than their prevalence in the population at large. From the many trials that distinguish treatment failures from syndromes with only subjective complaints, the following themes emerge: residual symptoms are common in the first weeks after therapy in persons who have no objective evidence of treatment failure; symptoms persisting many months or years are uncommon; and disabling symptoms lasting months or years are extremely rare. In ten prospective studies of erythema migrans and early disseminated Lyme disease, fewer than 10% of subjects described persistent symptoms such as myalgias and fatigue after 9 or more months (range 0–23%), and the prevalence of severe symptoms was 0–2.8% [65,70–78]. One recently published trial found that after 12 months, patients treated for erythema migrans were no more likely to have subjective symptoms than an uninfected control group [70].

Box 3. Proposed definition of post-Lyme disease syndromes.

Inclusion criteria

- An adult or child with a documented episode of early or late Lyme disease fulfilling the case definition of the CDC. If based on erythema migrans, the diagnosis must be made and documented by an experienced healthcare 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 neuropsychologic testing that may explain the patient's complaints. For example, a patient with antibiotic refractory Lyme arthritis would be excluded. A patient with late neuroborreliosis associated with encephalopathy, who has recurrent or refractory objective cognitive dysfunction, would be excluded.
- 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 (e.g., morbid obesity, with a BMI [calculated as weight in kilograms divided by the square of height in meters] ≥45; sleep apnea and narcolepsy; side effects of medications; autoimmune diseases; uncontrolled cardiopulmonary or endocrine disorders; malignant conditions within 2 years, except for uncomplicated skin cancer; known current liver disease; any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype; anorexia nervosa or bulimia nervosa; and active drug abuse or alcoholism at present or within 2 years).
- Laboratory or imaging abnormalities that might suggest an undiagnosed process distinct from post-Lyme disease syndrome, such as a highly elevated erythrocyte sedimentation rate (150 mm/h); abnormal thyroid function; a hematologic abnormality; abnormal levels of serum albumin, total protein, globulin, calcium, phosphorus, glucose, urea nitrogen, electrolytes or creatinine; significant abnormalities on urine analysis; elevated liver enzyme levels; or a test result suggestive of the presence of a collagen vascular disease.
- 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.

Taken from [26].

Objective clinical residua are well known to follow antibiotic therapy for confirmed Lyme disease. Facial nerve palsy and other objective neurologic defects may persist for months in patients treated for acute neurologic Lyme disease, exceeding 20% in some studies. Less than 1%, however, go on to have chronic fatigue, nonspecific pain or other symptom complexes compatible with the post-Lyme disease syndromes [79–87]. Approximately 10% of patients treated for Lyme arthritis go on to have a unique syndrome termed 'antibiotic-refractory Lyme arthritis', a persistent sterile synovitis that can last for months to years. This condition, based on factors including antibiotic refractoriness and strong association with *HLA-DRB1*0401*, appears to be a postinfectious autoimmune phenomenon [88]. Based on lack of evidence of viable *B. burgdorferi* and unresponsiveness to antibiotics, neither of these phenomena is thought to be an active infection.

Gradual convalescence is observed after many systemic infections. For example, following bacterial pneumonia nonspecific symptoms that impair quality of life can greatly exceed the duration of respiratory symptoms, sometimes by months [89]. It seems unlikely that post-Lyme symptoms are any more common than similar symptoms after other infections.

Biological plausibility

No adequately controlled, hypothesis-driven study using a repeatable method has demonstrated that viable *B. burgdorferi* is found in patients with persistent post-Lyme symptoms any more frequently than in those with favorable outcomes. In three clinical trials, comprising more than 150 subjects with strictly-defined post-Lyme disease symptoms, no patient was found to have positive culture or PCR of cerebrospinal fluid [2,4]. However, these studies were unique in that they investigated evidence of persistent *B. burgdorferi* infection in a prospectively defined group of chronically ill subjects. Other sources of data include case reports and case-series, which however compelling are inherently incapable of testing a hypothesis. Advocates of chronic Lyme disease contend that our ability to detect the organism is hampered by current technology and an incomplete scientific understanding of *B. burgdorferi*, and that conventional diagnostic testing misses patients with chronic Lyme disease [90,91]. However, this begs the question of on what microbiologic basis we assume that chronic *B. burgdorferi* infection exists at all.

Studies meant to support the etiologic role of *B. burgdorferi* in chronic symptom complexes have, at times, relied on investigational testing methods. This has included the use of novel culture

media, detection of *B. burgdorferi* DNA in urine specimens and enumeration of CD57-positive lymphocytes [92–95]. Subsequent investigations, however, have discredited the reliability of these initial reports and cast doubt more generally on their utility as diagnostic tests [96–99]. Other arguments, meant to illustrate the plausibility that *B. burgdorferi* can persist following antibiotic therapy, have noted the detection of the organism by xenodiagnosis, culture or PCR [100–104]. However, these reports are at best circumstantial, in that they have only been performed in patients with early Lyme disease, Lyme arthritis and in laboratory animals – never in patients with a putative diagnosis of chronic Lyme disease. Furthermore, the complete eradication of microorganisms is, only in rare cases, a measure of treatment success; rather, clinical end points are what usually guide anti-infective therapy. Morphologic variants of *B. burgdorferi*, variably known as 'cyst forms', 'spheroplasts' or 'cell wall-deficient forms' have not been isolated from patients with post-Lyme disease [105–109]. Despite their frequent mention as the underlying cause of chronic Lyme disease, their actual role remains purely hypothetical. As these forms have been most often observed in antibiotic-treated specimens or in *ex vivo* conditions, it is possible that they represent sick or stressed microorganisms. Their virulence has not been established.

Risk factors for post-Lyme disease syndromes

As there is a lack of evidence that post-Lyme disease patients remain infected with *B. burgdorferi*, it is perhaps not surprising that the duration of initial antibiotic therapy does not influence the persistence of subjective symptoms. A prospective trial of therapy for 180 patients with early Lyme disease found that after 30 months, neuropsychologic deficits were equally common among patients treated for 10 versus 20 days [77]. In a retrospective study of 607 patients treated for early Lyme disease, 99 ± 0.2% of patients were well after 2 years of follow-up, regardless of whether they had received less than 10, 11–14 or greater than 14 days of therapy [110]. In a randomized, open-label trial of therapy for late Lyme disease, patients treated for 14 days were no more likely to have severe symptoms than those treated for 28 days – despite the fact that objective treatment failures were significantly more likely in the 14-day arm [111]. Lengthy courses of antibiotics, meant to prevent the development of persistent symptoms, are no more effective than conventional courses. Following 3 weeks of parenteral ceftriaxione, an additional 100 days of oral amoxicillin was no better than placebo at improving cognitive and somatic outcomes [112].

Since the earliest treatment trials of Lyme disease, the factor that has most consistently predicted persistence of symptoms is their severity before initiation of therapy [113–115]. Severe headache, arthritis, arthralgias and fatigue at presentation predicted persistent symptoms in a retrospectively examined cohort of 215 patients [116]. In a prospective treatment trial for early Lyme disease, persistent symptoms at several late follow-up visits (6 months through 5 years) were more common in patients who had more symptoms, higher symptom scores and multiple (versus solitary) erythema migrans lesions [75]. Patients with a longer duration of symptoms may also be at higher risk of persistent symptoms: a review of 38 subjects who had been previously treated for Lyme disease found that persistent somatic and neuropsychological sequelae were strongly associated with prolonged illness prior to treatment [7].

Extended antibiotics for the treatment of post-Lyme disease syndromes

To date, three research groups have prospectively examined the utility of prolonged antibiotics in treating post-Lyme disease syndromes [2–5]. All trials had strict entrance criteria, requiring that enrollees have firm documentation of prior Lyme disease and receipt of appropriate antibiotic therapy, followed within 6 months by persistent symptoms. The first study, published in 2001 by Klempner *et al.*, reported two parallel trials in which their cohort of 129 study patients was divided into seropositive (n = 78) and seronegative (n = 51) arms [4]. Patients randomized to treatment groups received 30 days of intravenous (iv.) ceftriaxone followed by 60 days of oral doxycycline. Patients randomized to the placebo arm received a placebo iv. infusion for 30 days, followed by an oral placebo for 60 days. The primary outcome of interest was health-related quality of life as assessed by standardized instruments (the Medical Outcomes Study 36-item Short-Form General Health Survey [SF-36] and the Fibromyalgia Impact Questionnaire). These instruments were administered at baseline, then 30, 90 and 180 days. There was no significant difference in any outcome measure between placebo and treatment groups in either the seropositive or seronegative arm. In a separate publication, the same team of investigators reported the performance of this study cohort on a detailed battery of neuropsychological tests, which included measurements of cognitive function, somatic symptoms and mood [3]. Although all patients complained of cognitive dysfunction at baseline (and the primary complaint in more than 70%), objective measures of cognitive function, such as memory and attention, were normal compared with age-referenced normative data. Depression, anxiety and somatic complaints improved in all groups between baseline and day 180, but there was no difference between the treatment and placebo groups.

In a separate trial, Krupp and colleagues evaluated 28 days of parenteral ceftriaxone (n = 28) versus iv. placebo (n = 24) in a cohort of patients with persistent fatigue following treated Lyme disease [5]. The primary outcome measure was score on the Fatigue Severity Scale (FSS-11). Additional outcomes were visual analogue scales (VAS) of fatigue and pain, the SF-36 and the Center for Epidemiologic Studies Depression Scale, and a comprehensive battery of cognitive function. Outcomes were measured at baseline and at 6 months. Baseline fatigue was severe. At follow-up, there was a statistically significant but partial improvement on the FSS-11 in the ceftriaxone arm compared with placebo, with 18/26 (69%) versus 5/22 (23%) showing improvement from baseline. The fatigue VAS, although not statistically significant, corroborated a benefit for the treatment arm (p = 0.08). No measure of mood or cognitive function differed at 6 month follow-up. It was noted that a much higher proportion of patients on ceftriaxone correctly guessed their treatment assignment. Whether this was a failure of masking or rather a placebo effect (i.e., the majority in both groups believed they

were on active therapy), and whether this would have affected the outcome of a subjective measure like fatigue, is difficult to discern. The commonality and nonspecificity of fatigue, and the observation that antibiotics may improve chronic fatigue in noninfectious or other postinfectious illnesses, raise doubts as to whether it was the elimination of *B. burgdorferi* that resulted in this outcome [117–119].

The efficacy of more prolonged parenteral therapy was investigated by Fallon *et al.* [2]. In this cohort, 23 patients were randomized to receive iv. ceftriaxone and 14 patients to receive iv. placebo for 10 weeks, followed by 14 weeks of observation off of therapy. Six domains of cognitive function were tested and compiled to produce a composite 'cognitive index' score. The primary outcome of interest was cognitive index compared with baseline and between groups at week 24. An interim evaluation at week 12 demonstrated significant improvement over baseline in the ceftriaxone group ($p < 0.01$), whereas this was not the case for the placebo group. A between-group comparison approached statistical significance ($p = 0.053$) at week 12 also. At week 24, however, these differences had disappeared: both groups had significantly and equally improved over their within-group baseline, and there was no difference between groups ($p = 0.76$). Three ceftriaxone and two placebo patients (13.5% of the randomized subjects) withdrew from the trial due to adverse events related to either the iv. catheter or the drug, leaving only 20 drug and 12 placebo patients available for statistical analysis. An additional four ceftriaxone patients remained in the study despite adverse events that truncated their therapy. The patients who dropped out were not analyzed by intention to treat, which, given the small sample size in this trial, might have affected the published statistics.

Adverse events, in fact, abounded in these studies, particularly catheter-associated venous thromboembolism, catheter-associated septicemia, allergic reactions and ceftriaxone-induced gallbladder toxicity. In the Klempner *et al.* trial, one patient on ceftriaxone suffered a pulmonary embolism and one experienced a syndrome of fever, anemia and gastrointestinal bleeding that was thought to be an allergic phenomenon [3,4]. In the Krupp *et al.* trial, three patients on iv. placebo developed line sepsis, and one patient on ceftriaxone had an anaphylactic reaction [5]. In the Fallon *et al.* trial, six patients on ceftriaxone had adverse events: two venous thromboembolic events, three allergic reactions and one case of ceftriaxone-induced cholecystitis (treated with cholecystectomy), in addition to a placebo patient who developed line sepsis [2].

Other studies reiterate the frequency of adverse events in persons with prolonged exposure to intravenous catheters and antibiotics. In an observational study by Stricker *et al.,* there were 19 potentially life-threatening adverse events among 200 patients on long term iv. antibiotics for the treatment of chronic Lyme disease [120]. These included four cases of venous thrombosis, six cases of suspected line sepsis, seven patients with allergic reactions and two patients who developed ceftriaxone-induced gallbladder disease (both cases managed with cholecystectomy). The mean duration of antibiotic therapy in this cohort was 118 days, and the adverse events reported occurred after a mean of 81 days from initiation of therapy. This rate of severe adverse events – nearly 10% of subjects – is exceeded only by the Fallon *et al.* trial (24%) [2]. The duration of exposure to central venous access devices and iv. drug therapy in these two studies differentiate them from the Klempner *et al.* and Krupp *et al.* studies, and this almost certainly explains the high rate of adverse events. While no deaths occurred in these studies, there have indeed been documented fatalities and near-fatalities due to prolonged iv. antibiotic therapy for putative Lyme disease [121–123].

While controlled data demonstrate that prolonged antibiotics are unlikely to be helpful, the critical judgment is whether they are worth the risk. The prospective clinical trials, which were designed to address questions of efficacy, speak much more clearly to the risk of toxicity. Without a doubt there is a significant risk to patients who are on months of iv. antibiotics. Given the risks, it is impossible to argue that prolonged iv. antibiotics are ethically justified for patients with post-Lyme disease syndromes. These same risks naturally apply to other situations in medicine in which prolonged antibiotic therapy is required. The risk/benefit calculus is quite different, though, for infections such as osteomyelitis or endocarditis when the therapy is demonstrably limb-saving or life saving.

A clinical approach to patients seeking treatment for chronic Lyme disease

Patients who seek subspecialty care for chronic Lyme disease are medically heterogeneous and have diverse backgrounds, perspectives and medical literacy. Even the motivation for subspecialty referral can vary. In many cases the referral is driven by concern on the part of the patient or a relative. Some patients come with strongly held expectations based on independent research or on the experiences of their friends and family. Some patients have received other diagnoses that they initially find difficult to accept, and maintain the hope that therapy for Lyme disease will help. In other cases it is a concerned referring physician who makes the referral.

Fundamentally, however, what unites the majority of these patients is their suffering, regardless of whether or not Lyme disease is ultimately to blame. Many have physical impairments, have missed extensive amounts of work or school, their social and family lives have suffered, and they are unable to achieve their personal goals. To make matters worse, some have grown frustrated or cynical with the medical profession because of ineffective treatments, unsatisfying explanations and fruitless testing. A commonly expressed perception is that physicians become impatient or dismissive once it becomes apparent that a patient's symptoms are medically inexplicable. In other words, a dominant feeling is that the suffering of these patients is not effectively heard or validated.

Several strategies can make these challenging encounters both rewarding and beneficial. First, in the absence of a definition, it is impossible to know exactly what is meant by 'chronic Lyme disease' when a patient presents for its evaluation. For this reason, it is usually unproductive to make the visit a referendum on the subject. Rather, as with any consultation, it is best to concentrate on the patient's specific clinical story with the goal of making the best diagnosis *de novo*. This often means that nothing important can be taken for granted, including diagnoses the patient has

previously received. The clinical evaluation must begin 'from scratch', starting with the chief complaint and history of present illness, and verification of important test results by reviewing a patient's medical record. Communication, both verbal and nonverbal, matters greatly. Eye contact, attention, patience, humility and empathy are critical. Although these visits are often lengthy parts of otherwise busy schedules, it is imperative to avoid the appearance of being too busy, or of having come to a rash judgment about a patient based on preconceptions about the chronic Lyme disease controversy. It hardly requires reiteration that these strategies are useful not just for Lyme disease and other controversies, but nearly all aspects of patient care.

Expert commentary & five-year view

Two ongoing NIH-registered clinical trials may enhance our current understanding of the post-Lyme disease syndromes. In September 2010, a Dutch trial began randomizing patients with post-Lyme disease syndromes to receive 12 weeks of doxycycline, clarithromycin plus hydroxychloroquine, or placebo following an initial course of ceftriaxone [202]. The primary outcome measure will be the SF-36 medical outcomes scale at week 14, as well as repeated assessments that include fatigue and neuropsychologic testing up until week 40. This will be the first prospective, placebo-controlled trial of post-Lyme disease syndromes conducted in Europe. A multisite American study is now investigating the use of xenodiagnosis to detect *B.burgdorferi* in patients with post-Lyme disease syndromes [203]. The investigators are allowing laboratory-raised ticks to feed on subjects with a variety of manifestations of Lyme disease in order to identify human-to-tick transmission. The study will include subjects with confirmed pretreatment infection as positive controls and healthy uninfected volunteers as negative controls.

Two important research gaps are: what pathophysiologic mechanisms underlie chronic pain and chronic fatigue?; and what nonantibiotic modalities are helpful for patients with post-Lyme disease syndromes? The former is an area of tremendous general interest given the ubiquity of such symptoms in the general population. The latter is a puzzlingly understudied field, but it has promise to improve the lives of many who suffer chronic symptoms attributed to Lyme disease – whether or not a history of Lyme disease is ultimately to blame. Furthermore, these may be far safer than prolonged antibiotics and indwelling vascular access devices. A variety of such interventions have proved useful in patients with functional pain syndromes, chronic fatigue syndrome and other debilitating chronic medical illnesses. These include antidepressants, pregabalin and gabapentin, analgesics, biofeedback and complementary and alternative medicine. To date, the only published study is a small open-label trial that found that gabapentin reduced pain in 9/10 and improved quality of life in 5/10 patients with chronic post-Lyme neuropathic pain [124]. Until the medical community has better explanations and therapies for the millions who suffer unexplained chronic symptoms, some patients looking for answers will still come to blame Lyme disease for their illness. This is likely to remain the case 5 years from now.

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Key issues

- Chronic Lyme disease lacks an accepted clinical definition, and in practice the term has been applied to a wide variety of patients. The majority of patients referred for chronic Lyme disease have no objective evidence of the infection, and most often have an alternative medical diagnosis or a 'functional' syndrome such as fibromyalgia or chronic fatigue syndrome.
- Fatigue, pain and cognitive impairment are the primary complaints among patients who are diagnosed with chronic Lyme disease. However, these symptoms are very common in the general population, and the evidence does not show that they occur any more commonly in patients with a history of Lyme disease.
- A small minority of patients treated for Lyme disease will go on to have prolonged pain, fatigue or cognitive impairment in the absence of objective signs of treatment failure. Still fewer have severe or disabling symptoms.
- There is no controlled evidence that viable *Borrelia burgdorferi* persists in patients with prolonged, subjective symptoms following confirmed Lyme disease.
- The duration of initial antibiotic therapy for Lyme disease does not influence the likelihood of prolonged somatic or cognitive symptoms. On the other hand, the duration and severity of symptoms prior to treatment do predict the likelihood of prolonged symptoms during convalescence.
- To date, four prospective, double-blinded, placebo-controlled trials have investigated the utility of prolonged antibiotics in patients with subjective 'post-Lyme disease syndromes'. With only one exception (fatigue) in one trial, no primary outcome measure favored treatment over placebo.
- Potentially severe adverse events due to antibiotic therapy and intravascular access devices are common in patients being treated for post-Lyme disease syndromes. These events directly correlate with duration of treatment. Thus, because of a lack of benefit and strong evidence of harm, lengthy courses of antibiotics are not justified in patients with post-Lyme disease syndromes.

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