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Chronic Lyme Disease

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THE CHRONIC LYME DISEASE CONTROVERSY

Chronic Lyme disease (CLD) is a poorly defined term that describes the attribution of various atypical syndromes to protracted *Borrelia burgdorferi* infection. These syndromes are atypical for Lyme disease in their lack of the objective clinical abnormalities that are well-recognized in Lyme disease and, in many cases, the absence of serologic evidence of Lyme disease as well as the absence of plausible exposure to the infection. The syndromes usually diagnosed as CLD include chronic pain, fatigue, neurocognitive, and behavioral symptoms, as well as various alternative medical diagnoses—most commonly neurologic and rheumatologic diseases. Perhaps the most recognized and contentious facet of this debate is whether it is effective, appropriate, or even acceptable to treat patients with protracted antibiotic courses based on a clinical diagnosis of CLD.

The dialogue over CLD provokes strong feelings, and has been more acrimonious than any other aspect of Lyme disease. Many patients who have been diagnosed with CLD have experienced great personal suffering; this is true regardless of whether *B burgdorferi* infection is responsible for their experience. On top of this, many patients with a CLD diagnosis share the perception that the medical community has failed to effectively explain or treat their illnesses. In support of this patient base is a community of physicians and alternative treatment providers as well as a politically active advocacy community. This community promotes legislation that has attempted to shield CLD specialists from medical board discipline and medicolegal liability for unorthodox practices, to mandate insurance coverage of extended parenteral antibiotics, and most visibly to challenge legally a Lyme disease practice guideline. The advocacy community commonly argues that Lyme disease is grossly underdiagnosed and is responsible for an enormous breadth of illness; they also argue that the general scientific and public health establishments ignore or even cover up

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evidence to this effect. A large body of information about CLD has emerged on the Internet and other media, mostly in the forms of patient testimonials and promotional materials by CLD providers. For a medical consumer and for the physician unfamiliar with this subject, this volume of information can be confusing and difficult to navigate.

The CLD controversy does not, however, straddle a simple divide between 2 opposed scientific factions. Within the scientific community, the concept of CLD has for the most part been rejected. Clinical practice guidelines from numerous North American and European medical societies discourage the diagnosis of CLD and recommend against treating patients with prolonged or repeated antibiotic courses.[1–21] Neither national nor state public health bodies depart from these recommendations. Within the medical community, only a small minority of physicians have accepted this diagnosis: 1 study found that only 6 of 285 (2.1%) randomly surveyed primary care physicians in Connecticut, among the most highly endemic regions for Lyme disease, diagnosed patients with CLD and still fewer were willing to prescribe long courses of antibiotics.[22,23]

THE CONFUSING TERMINOLOGY OF CHRONIC LYME DISEASE

The mere name “chronic Lyme disease” is in itself a source of confusion. Lyme disease, in conventional use, specifically describes infection with the tick-borne spirochete *B burgdorferi* sensu lato. The diagnosis “chronic Lyme disease,” by incorporating that terminology, connotes a similar degree of microbiologic specificity; the addition of the word “chronic” further implies that there is some distinction between “chronic” Lyme disease and other manifestations of the infection. This distinction in itself is problematic because several manifestations of Lyme disease may indeed present subacutely or chronically, including Lyme arthritis, acrodermatitis chronicum atrophicans, borrelial lymphocytoma, and late Lyme encephalopathy.

“Chronic Lyme disease,” however, has no clinical definition and is not characterized by any objective clinical findings. The only published attempt to define CLD provisionally produced a description too broad to distinguish CLD from myriad other medical conditions, and the case definition did not mention evidence of *B burgdorferi* infection (Box 1).[24] The absence of a definition makes it impossible to investigate whether a patient population with putative CLD has evidence of infection with *B burgdorferi*; this would seem to be a basic requirement to include a syndrome within the term “Lyme disease.” It stands to reason that it is impossible to even posit a well-designed antibiotic trial when the study population is undefined.

Box 1

Working definition of chronic Lyme disease proposed by ILDAS

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 neuron disease, neuropsychiatric presentations, cardiac

presentations (including electrical conduction delays and dilated cardiomyopathy), and musculoskeletal problems.

Abbreviation: ILADS, International Lyme and Associated Diseases Society.

From Cameron D, Gaito A, Harris N, et al. Evidence-based guidelines for the management of Lyme disease. Expert Rev Anti Infect Ther 2004;2(Suppl 1):S4.

In the absence of a definition, it is instructive to examine the circumstances under which patients receive a diagnosis of CLD. These circumstances can be inferred from the breakdown of patients referred for suspected Lyme disease. In 7 studies conducted in endemic areas, comprising a total of 1902 patients referred for suspected Lyme disease, 7% to 31% had active Lyme disease and 5% to 20% had previous Lyme disease, based on concordance of their clinical presentations with recognized manifestations of Lyme disease.[25–31] The remaining 50% to 88%, however, had no evidence of ever having had Lyme disease. Most of these patients had either alternative medical diagnoses or had medically unexplained symptoms, such as chronic fatigue syndrome or fibromyalgia. Lyme disease was in many cases diagnosed simply for lack of an alternative diagnosis—referred to in 1 paper as a "diagnosis of Lyme disease by exclusion."[30] Two studies documented that many of the referred patients had psychiatric diagnoses and/or mal-adaptive psychological traits, such as catastrophization and negative affect.[26,28] Many patients had symptoms of long duration and had received multiple courses of antibiotics.

A common reason for referral was a positive Lyme disease serologic test. On clinical review, however, the patients lacked clinical findings concordant with a Lyme disease diagnosis. This is certainly a side effect of a great volume of Lyme disease testing conducted in the United States—more than 3 million tests are thought to be ordered annually.[32] Most such tests are ordered with a very low pretest probability in settings such as chronic nonspecific fatigue, based on patient request, after a tick bite (when even an infected patient would be most likely seronegative), or as part as a general neurologic or rheumatologic evaluation. In the absence of specific clinical findings, however, Lyme disease testing has a very low positive predictive value.[33] Patients may have positive Lyme serology for a variety of reasons, including asymptomatic seroconversion, cross-reactive antibodies generated by other infectious or inflammatory diseases, or a previous treated episode of Lyme disease; asymptomatic seropositivity is well-described in endemic areas.[25,29,30,33–40] Thus, the misattribution of chronic symptoms to Lyme disease is an inevitable consequence of high-volume, low-probability testing.

THE MISDIAGNOSIS OF CHRONIC LYME DISEASE

Many patients referred for Lyme disease are ultimately found to have a rheumatologic or neurologic diagnosis. Rheumatologic diagnoses commonly misdiagnosed as Lyme disease include osteoarthritis, rheumatoid arthritis, degenerative diseases of the spine, and spondyloarthropathies.[26,27,41] Some patients are found to have neurologic diseases, including multiple sclerosis, demyelinating diseases, amyotrophic lateral sclerosis, neuropathies, and dementia.[27] Some CLD advocates have argued that these various conditions are simply manifestations of Lyme disease,[24,42–44] but these hypotheses are

untenable. Lyme disease is transmitted quite focally,[45] and there is no epidemiologic evidence that these alternative diagnoses cluster in regions with high Lyme disease transmission. There has been no association between diagnoses such as multiple sclerosis, amyotrophic lateral sclerosis, or rheumatoid arthritis and antecedent Lyme disease, these diagnoses do not arise concurrently with other recognized manifestations of disseminated Lyme disease (such as Lyme arthritis), and there is no quality evidence associating any of these diagnoses with seroconversion to *B burgdorferi*. Although there can certainly be clinical overlap between Lyme disease and other conditions, objective findings and studies will generally allow them to be differentiated.

Medically unexplained symptoms, whether resulting in entities such as fibromyalgia and chronic fatigue syndrome or syndromes with a less distinct pattern, account for most of the remaining patients who are diagnosed with CLD. Unlike Lyme disease, these frustrating conditions generally lack objective clinical or other objective abnormalities, and they are dominated by subjective complaints and functional impairment.[46–48] No evidence suggests that these clinical entities geographically cluster in regions with *B burgdorferi* transmission. Fibromyalgia has been found to follow Lyme disease temporally 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.[49] Additional antibiotics were not beneficial. This finding, however, is contradicted by a prospective cohort study in which only 1 of 100 patients treated for culture-confirmed Lyme disease developed fibromyalgia during the subsequent 11 to 20 years.[50] Severe fatigue was found in 9 of these patients, but it was attributable in all cases to other causes.[51] Many patients experience prolonged symptoms during convalescence from systemic infections, including symptoms of fibromyalgia and chronic fatigue.[49,52] Such symptoms, however, do not seem to be associated particularly with antecedent Lyme disease; in fact, the prevalence of fatigue and fibromyalgia among patients with past Lyme disease is similar to their prevalence in the general population.

BIOLOGICAL EXPLANATIONS FOR CHRONIC LYME DISEASE

Several arguments have been made to support the biological plausibility of CLD and to justify its treatment with lengthy courses of antibiotics. One is that *B burgdorferi* localizes intracellularly in the infected host, and that the antibiotics typically chosen to treat it do not penetrate cells effectively. Aside from the fact that *B burgdorferi* predominantly occupies the extracellular matrix,[53] the antibiotics currently recommended to treat Lyme disease are well-established to treat a variety of intracellular infections. For example, doxycycline and azithromycin are first-line drugs for the treatment of *Mycoplasma*, *Chlamydia*, and *Legionella*, and doxycycline is the drug of choice for *Rickettsia* and related species. Ceftriaxone is effective against *Salmonella* and *Neisseria*, both of which are predominantly intracellular; amoxicillin is effective against *Listeria*.

Another commonly voiced argument is that *B burgdorferi* assumes a round morphology, variously described as “cyst forms,” “spheroplasts,” “L-forms,” and “round bodies.” These variants are said to be resistant to antibiotic treatment and require alternative antibiotics and dosing strategies. On close review of the literature there is little evidence that these variants

arise in vivo in humans, let alone that they are associated with CLD-like symptom complexes or that they require treatment.[54]

MICROBIOLOGIC INVESTIGATIONS INTO CHRONIC LYME DISEASE

There is very little microbiologic evidence that supports persistent *B burgdorferi* infection in patients who lack objective manifestations of Lyme disease, such as erythema migrans, arthritis, meningitis, and neuropathies. Advocates for CLD contend that our ability to detect *B burgdorferi* is hampered by current technology and an incomplete scientific understanding of *B burgdorferi*, and that conventional diagnostic testing misses patients with CLD.[55,56] Naturally, this raises the question of why we should assume that chronic *B burgdorferi* infection exists at all if we are so ill-equipped to detect it. Even when chronically symptomatic patients have a well-documented history of treated Lyme disease, investigators have been unable to document persistent infection.[57–59] A recent study in which ticks were allowed to feed on persistently symptomatic posttreatment patients yielded molecular evidence of *B burgdorferi* in 1 of 16 patients and no patient had cultivatable organisms.[60]

Studies reporting the retrieval of *B burgdorferi* from antibiotic-treated animals are indirect and have limited generalizability to human disease. First, it is impossible to create an animal model of CLD when this diagnosis is usually based on symptoms described by a patient. Second, rodents serve as reservoir species for *B burgdorferi* in nature and may tolerate persistent asymptomatic infection. Third, some experimental studies use large inocula of *B burgdorferi* that have been grown to stationary phase; the organism assumes a more drug-resistant phenotype under these growth conditions and this may not reflect natural infection.

Because validated testing methods fail to support the connection between *B burgdorferi* and clinically diagnosed CLD, physicians who specialize in CLD often turn to alternative tests. This has included the use of novel culture techniques, detection of *B burgdorferi* DNA in urine specimens, and enumeration of CD57-positive lymphocytes.[61–65] Independent investigations, however, have repudiated the validity of these tests.[66–70]

COINFECTIONS

Some CLD advocates emphasize that CLD is a polymicrobial infection in which patients suffer from multiple tick-borne coinfections.[71,72] In practice, patients with a diagnosis of CLD are often diagnosed with and treated for numerous superimposed infections, including *Babesia* spp and *Anaplasma phagocytophilum* (well-described tick-borne pathogens), *Bartonella henselae* (which is not known to be transmitted by ticks), pathogens of unclear clinical relevance such as the xenotropic murine leukemia virus-related virus, and even completely fictitious pathogens such as "*Protomyxozoa rheumatica*." There is no evidence to support chronic anaplasmosis; chronic symptomatic babesiosis when present invariably is associated with fever and molecular or microscopic evidence of parasitemia. *Bartonella* species are readily identified in ticks, but there is virtually no quality evidence of tick-borne transmission to humans or of simultaneous Lyme disease and bartonellosis.[73] It is important to recognize that, in the context of CLD, a diagnosis of coinfection may be just as spurious.

PERSISTENT SYMPTOMS AFTER TREATMENT FOR LYME DISEASE

It is well-recognized that some patients experience prolonged symptoms during convalescence from Lyme disease, and a subset suffer significant functional impairment.[57–59,74–78] The most common complaints among such patients are arthralgias, myalgias, headache, neck and backache, fatigue, irritability, and cognitive dysfunction (particularly perceived difficulty with memory and concentration).[57–59]

A working definition was developed to categorize patients with 'post-Lyme disease symptoms' (PLDS), those patients with persistent clinical symptoms after treatment for Lyme disease, but who lack objective evidence of treatment failure, reinfection, or relapse (Box 2).[20] PLDS is not strictly speaking a coherent clinical diagnosis; its primary value has been to define a patient cohort for further study. Nonetheless, it is worth considering how it conceptually differs from CLD. To meet criteria for PLDS, patients must have unequivocal documentation of appropriately treated Lyme disease, lack objective manifestations of Lyme disease, and have persistent symptoms that cannot be explained by other medical illnesses. Thus, of patients with chronic symptoms that have been *attributed* to Lyme disease, those meeting criteria for PLDS are those for whom infection with *B burgdorferi* is most plausible. This makes the studies of PLDS paradigmatic for the understanding of CLD.

Box 2

Proposed definition of post-Lyme disease syndromes from the Infectious Disease Society of America

Inclusion criteria

- An adult or child with 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 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 (eg, morbid obesity, with a body mass index [calculated as weight in kilograms divided by the square of height in meters] of 45 kg/m^2 or greater; 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 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.

From Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;43(9):1121; with permission.

The frequency of PLDS is difficult to estimate, but as a function of patients with a known history of Lyme disease, it seems to be rare. This is exemplified by the great difficulty 3 investigative teams had in recruiting subjects for clinical trials investigating this condition.[57–59] Of 5846 patients screened over several years, only 222 (3.8%) could be randomized ultimately, which is striking considering that between 30,000 and 300,000 Americans are thought to contract Lyme disease annually. PLDS also seems to be

uncommon among subjects in clinical trials. In 10 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% to 2.8%.[79–88] One trial found that, after 12 months, patients treated for erythema migrans were no more likely to have subjective symptoms than an uninfected control group.[80]

If PLDS is rare among patients with a history of Lyme disease, in the general population it becomes impossible to discern from the high background rate of similar symptoms among adults. Up to 20% of surveyed adults report chronic fatigue.[89,90] In 1 report, 3.75% to 12.1% of the general population suffered severe pain and 36.4% to 45.1% moderate pain, whereas only 42.5% to 59.1% of the general population was pain free.[91] In a separate study, 11.2% of respondents suffered chronic, widespread pain.[92] One-quarter to one-third of the general population describe chronic cognitive dysfunction.[91] These symptoms often coincide with anxiety or depression, which in their own right are common in the general population. Interestingly, many who complain of cognitive dysfunction are found to be normal when formally tested.[59,75,79,93–96] In all likelihood, subjective post-Lyme symptoms are not unique to Lyme disease but rather are common to the recovery from many systemic illnesses. Bacterial pneumonia, for example, can be followed by months of nonspecific symptoms that impair quality of life.[97]

RISK FACTORS FOR PERSISTENT SYMPTOMS AFTER TREATMENT FOR LYME DISEASE

Patients with the most severe symptoms on clinical presentation are the most likely to have persistent symptoms during convalescence.[98–100] Severe headache, arthritis, arthralgias, and fatigue at presentation predicted persistent symptoms in a retrospectively examined cohort of 215 patients.[101] 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 (vs solitary) erythema migrans lesions.[85] Patients with a longer duration of symptoms may also be at greater 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 before treatment.[77]

On the other hand, the duration of antibiotic therapy does not influence the persistence of subjective symptoms after treatment. In a prospective trial of therapy for 180 patients with early Lyme disease, neuropsychologic deficits were equally common among patients treated for 10 versus 20 days at follow-up 30 months later.[87] 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 fewer than 10, 11 to 14, or more than 14 days of therapy.[88] 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, even though objective treatment failures were significantly more likely in the 14-day arm.[102] After 3 weeks of parenteral ceftriaxione, an additional 100 days of oral amoxicillin was no better than placebo at improving cognitive and somatic outcomes.[103]

We have an incomplete picture as to why some patients are left with chronic symptoms after Lyme disease whereas the majority does well. Genetic variability among *B burgdorferi* isolates and its significance for clinical disease is an important emerging area of research. This is difficult to link with clinical outcomes, however, because different strains of the organism cannot be discriminated by standard clinical testing. Anti-*Borrelia* antibody titers are higher among patients with PLDS compared with those with an uncomplicated post-Lyme disease course; antibody profiles are different between these 2 groups as well.[104] Patients with neurologic Lyme disease have elevated cerebrospinal fluid biomarkers, including CXCL13 and neopterin.[105] These return to normal after antibiotic therapy, and are not increased in patients with PLDS. Further research is needed to better characterize the biology of PLDS.

EXTENDED ANTIBIOTICS FOR THE TREATMENT OF POST-LYME DISEASE SYNDROMES

Three research groups have examined prospectively the effectiveness of prolonged antibiotic courses for post-Lyme disease syndromes.[57–59,75] All trials had strict entrance criteria similar to the aforementioned definition of PLDS. The Klempner and colleagues[58] study reported 2 parallel trials in which their cohort of 129 subjects was divided into seropositive (n = 78) and seronegative (n = 51) arms. Subjects randomized to treatment groups received 30 days of intravenous (IV) ceftriaxone followed by 60 days of oral doxycycline. Those randomized to the placebo arm received IV placebo for 30 days, followed by an oral placebo for 60 days. The primary outcome 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, and then 30, 90, and 180 days. There was no difference in any outcome measure between placebo and treatment groups in either the seropositive or seronegative arm, or in a detailed battery of neuropsychological tests that was published subsequently.[75] Although all patients had complained of cognitive dysfunction at baseline (and this was the primary complaint in >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 both the antibiotic and placebo arms groups between baseline and day 180.

In a separate trial, Krupp and colleagues[59] investigated the effect of antibiotics for persistent severe fatigue after treatment for Lyme disease. Twenty-eight patients were randomized to receive 28 days of IV ceftriaxone and 24 received IV placebo. The primary outcome measure was score on the Fatigue Severity Scale (FSS-11). Additional outcomes were visual analog scales (VAS) of fatigue and pain, the SF-36, the Center for Epidemiologic Studies Depression Scale, and a comprehensive battery of cognitive function. Outcomes were measured at baseline and at 6 months. At follow-up, there was a significant but partial improvement on the FSS-11 in the ceftriaxone arm compared with placebo, with 18 of 26 (69%) versus 5 of 22 (23%) patients showing improvement from baseline ($P = .001$). The fatigue VAS, although not significant, corroborated a benefit for the treatment arm ($P = .08$). No measure of mood or cognitive function differed at the 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, 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.[106–108]

Fallon and colleagues[57] investigated a more prolonged IV treatment course. 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 ($P<.01$), whereas this was not the case for the placebo group. A between-group comparison at week 12 approached statistical significance ($P = .053$) as well. At week 24, however, these differences had disappeared: both groups had improved over their within-group baseline, but there was no difference between groups ($P = .76$). Five of the randomized patients withdrew from the study owing to adverse events, leaving only 20 drug and 12 placebo patients available for statistical analysis. An additional 4 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 were common in these studies, particularly catheter-associated venous thromboembolism, catheter-associated bacteremia, allergic reactions, and ceftriaxone-induced gallbladder toxicity. In the Klempner and colleagues[58] trial, 1 patient on ceftriaxone suffered a pulmonary embolism and 1 experienced a syndrome of fever, anemia, and gastrointestinal bleeding that was felt to be an allergic phenomenon. In the Krupp and colleagues[59] trial, 3 patients on IV placebo developed line sepsis and 1 patient on ceftriaxone had an anaphylactic reaction. In the Fallon and colleagues[57] trial, 6 patients on ceftriaxone had adverse events: 2 venous thromboembolic events, 3 allergic reactions, and 1 case of ceftriaxone-induced cholecystitis (requiring cholecystectomy), in addition to a placebo patient who developed line sepsis. Other studies reiterate the frequency of adverse events in persons with prolonged exposure to IV catheters and antibiotics. In an observational study by Stricker and colleagues,[109] there were 19 potentially life-threatening adverse events among 200 patients on long-term IV antibiotics for the treatment of CLD. These included 4 cases of venous thromboembolic disease, 6 cases of suspected line sepsis, 7 patients with allergic reactions, and 2 who developed ceftriaxone-induced gallbladder disease (both necessitating 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. Although no deaths occurred in these studies, there have indeed been documented fatalities and near fatalities owing to prolonged IV antibiotic therapy for the treatment of Lyme disease.[110–112]

CLINICAL APPROACH TO PATIENTS WITH A CHRONIC LYME DISEASE DIAGNOSIS

Even if CLD lacks biological legitimacy, its importance as a phenomenon can be monumental to the individual patient. This is because many if not most patients who believe they have this condition are suffering, in many cases for years. Many have undergone frustrating, expensive, and ultimately fruitless medical evaluations, and many have become quite disaffected with a medical system that has failed to provide answers, let alone relief.

Beyond this generalization, patients referred for CLD have heterogeneous medical, social, and educational backgrounds. Furthermore, there is great variation in their “commitment” to a CLD diagnosis. Some patients are entirely convinced they have CLD, they request specific types of therapy, and they are not interested in adjudicating the CLD diagnosis. By contrast, others are not particularly interested in CLD per se, and are content to move on to a broader evaluation. In the author’s experience most patients fall somewhere in between—a certain amount of time must be spent reviewing past experiences and past laboratory tests, then explaining why Lyme disease may not account for their illnesses.

Several strategies are generally helpful in approaching CLD in the clinic. First, the physician needs to suppress preconceptions or biases about such patients. Some encounters are long, some are short, some are tense, and some are congenial—but this is hardly unique to Lyme disease. Second, the process of clinical information gathering in medicine, that is, complaint, history, physical examination, and diagnostic testing, is no different in the context of CLD. Even if much discussion is centered on CLD, the goal of the encounter should still be to evaluate the patient and make the soundest assessment and plan.

Finally, it is of utmost importance to not seem to be impatient, dismissive, or rushed. Many patients who seek care for CLD already have accumulated frustration if not outright disaffection with the medical community. Subtle cues like body language, tone of voice, and affect can be critical to gaining or losing a patient’s trust. Furthermore, each patient’s clinical story and personal history is unique and valid, even if one concludes that they do not have Lyme disease.

SUMMARY

A limitation of modern medicine is our ability to explain and treat chronic pain, fatigue, and other disabling symptoms. It should come as no surprise that patients suffering from these symptoms have placed their hope in treatable conditions. Over time, a number of infectious diseases have been hypothesized as responsible, including *Candida*, *Brucella*, Epstein–Barr virus, xenotropic murine leukemia virus-related virus, and *B burgdorferi*. The scientific community has largely rejected chronic, treatment-refractory *B burgdorferi* infection, usually termed CLD, based on the absence of a defined patient population, the failure to detect cultivatable, clinically relevant organisms after standard treatment. Because the label CLD is applied to a highly heterogeneous spectrum of patients, the term CLD is better thought of as describing a phenomenon of attribution rather than a single disease. Even the subset of chronically symptomatic patients with a well-documented history of Lyme disease,

usually termed PLDS, have little evidence of active infection, and their symptoms do not respond to antibiotics any better than to placebo. Controversies such as that over CLD are likely to persist for as long as patients suffer from poorly explained, disabling symptoms. We must hope that future research will provide better explanations and safe, effective treatments.

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KEY POINTS

- There is no accepted clinical definition for chronic Lyme disease.
- Most patients with a diagnosis of chronic Lyme disease have no evidence of Lyme disease.
- Persistent subjective symptoms during recovery from Lyme disease are not active infection.
- Prolonged antibiotic courses are ineffective and unsafe patients for patients with prolonged symptoms after Lyme disease.