HHS Public Access

Author manuscript

Infect Dis Clin North Am. Author manuscript; available in PMC 2023 September 01.

Published in final edited form as:

Infect Dis Clin North Am. 2022 September ; 36(3): 621–638. doi:10.1016/j.idc.2022.04.004.

Persistent symptoms after treatment for Lyme disease:

"Confusion worse confounded." John Milton, Paradise Lost. Book ii

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Keywords

Lyme Disease; Post-Treatment Lyme Disease Syndrome; Chronic Lyme Disease; Long-Term Symptoms; Misdiagnosis

Chronic Lyme Disease and Post-treatment Lyme Disease

Lyme disease, caused by infection with *Borreliella (Borrelia) burgdorferi* and transmitted by the bite of the ticks of the *Ixodes ricinus* complex, is the most common vector-borne disease in the United States and Europe.[1] Antibiotic treatment is effective for most patients, but some patients report persisting or relapsing nonspecific symptoms after treatment.[2] These symptoms are referred to as post-treatment Lyme disease symptoms (PTLDs) or syndrome (PTLDS), depending on their severity and functional impact.[3]

Patients with PTLDs are a small subset of what is called "chronic Lyme disease" (CLD) (Figure 1), a term avoided by academic literature and mainstream medical providers, as there are no clear criteria or agreement as to what constitutes "chronic Lyme disease" and the term can refer to very different groups of patients. For example, CLD is defined by one society as a "multisystem illness with a wide range of symptoms and/or signs that are either continuously or intermittently present for a minimum of six months." CLD has evolved into a "multiple chronic infectious disease syndrome" and patients are diagnosed with multiple infections (*Babesia, Ehrlichia, Anaplasma, Rickettsia*, *Bartonella*, Powassan virus, *Mycoplasma, Chlamydia,* multiple herpesviruses*)* and poorly defined conditions ("immune dysfunction, inflammation, toxin damage by heavy metals and mold, food and environmental allergies, nutritional and metabolic abnormalities, hormonal imbalances, mitochondrial dysfunction, free radical/oxidative stress, and autonomic system dysfunction". These diagnoses are based on clinical judgment, together with unvalidated tests and

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Disclosures: AM has a patent US 8,926,989 issued; and is an unpaid Scientific Advisor to the Global Lyme Alliance and to the American Lyme Disease Foundation.

interpretation criteria. A study found that 57.5% of healthy controls could be interpreted as positive using the in-house criteria of a Lyme specialty laboratory.[4] Culture assays claiming high positivity have raised serious concerns [5, 6] and could not be replicated.[7] A urine antigen assay had false-positive results and the same sample varied from negative to highly positive when testing 5 fractions from each of 10 negative control samples.[8] Natural killer cells measurements are unhelpful.[9] Practitioners treating CLD often market themselves as integrative, functional, naturopathic, and Lyme-literate. Patients are charged high fees and spend significant amount of money on multiple unproven tests and unvalidated treatments that range from innocuous to highly dangerous.[10–16] Once a patient has received the diagnosis of “chronic Lyme disease”, the inclination is to assign any signs and symptoms to it, leading to missed or delayed diagnosis of other medical conditions.[17, 18] Patients diagnosed with “chronic Lyme disease” can be reluctant to accept the diagnosis of other diseases, even when this can have dire consequences.[14, 18] These patients frequently disagree with the different diagnosis provided, seeking further evaluation and receiving additional antibiotic therapy for Lyme disease.[19]

The majority of patients diagnosed with CLD have conditions whose symptoms are misdiagnosed or are patients with medically unexplained physical symptoms (MUPS) who receive the diagnosis based on unproven and/or non-validated laboratory tests and clinical criteria (Figure 2). Studies have shown that 47 to 80% of the patients seeking further evaluation for Lyme disease had no evidence of *B. burgdorferi* infection.[19–26] An alternative diagnosis was made in 15 to 55% (median 34%) of the cases, while MUPS accounted for 19% to 54% (median 32%). Patients with PTLDs accounted for 3 to 15% (median 9%) of the cases.

Patients with MUPS, or persistent physical symptoms, are common across general medicine.[27–29] MUPS encompasses a range of conditions, including fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS); with substantial overlap of symptoms between patients.[30] These symptoms are caused and maintained by complex interactions between biological, psychological, and social mechanisms.[31] A possible mechanism is central sensitization, where maladaptive changes lead to alterations in how pain and other sensory stimuli are processed with the development of chronic symptoms.[31] Interestingly, patients with “alternatively diagnosed chronic Lyme syndrome” (another name for CLD) were similar to ME/CFS patients when compared to controls, with no differences in gene expression, B-cell/T-cell receptor profiles and potential viral infections. The CLD diagnosis was due to false-positive results from alternative laboratory tests.[32, 33]

Post-treatment Lyme Disease Symptoms and Syndrome

The remainder of this chapter will focus on research addressing PTLDs. To fulfill criteria for PTLDs,[34] patients must have a documented episode of Lyme disease, have received a recommended course of antibiotic therapy, with resolution or stabilization of the objective manifestation(s) of Lyme disease, have non-specific symptoms (persistent or relapsing) that started within 6 months of the Lyme disease diagnosis and lasted for at least 6 months after completion of antibiotic therapy, and have no other condition that explain the symptoms. Symptoms need to cause a substantial reduction in previous levels of activity to be classified

as PTLD syndrome. A standardized approach is very important as it would allow for systematically quantification of the severity level of symptoms in PTLDs patients and allow for comparison between studies of outcomes and other data.[3, 35, 36]

Most patients who present with defined manifestations of Lyme disease will have a good outcome after antibiotic treatment with recommended regimens,[2] returning to their previous level of health. Patients with later manifestations may have a delayed response to therapy, and recovery can take weeks or months.[37] Incomplete resolution due to non-reversible damage can occur, as seen in patients with facial palsy and residual facial weakness[38]. Some patients with Lyme arthritis have persistent synovitis after antibiotic therapy, known as post-infectious Lyme arthritis.[39] Treatment failure with current antibiotic regimens (where patients have objective signs of disease after treatment) can occur, but it is very uncommon.

Persisting or relapsing subjective nonspecific complaints, mostly of mild to moderate intensity, occurred in between 0 to 26% of patients with erythema migrans evaluated 6 to 12 months after completion of treatment (Figure 3).[36, 40–62] Risk factors for PTLDs include antibiotic treatment delay, symptom severity at the time of treatment, presentation with multiple erythema migrans or with non-erythema migrans manifestations of Lyme disease, and presence of tingling or an abnormal skin sensation at the initial visit.[42, 49, 63–65] Other risk factors include a history of stressful events,[61, 65] the presence of comorbidities unrelated to Lyme disease,[66] older age and female sex.[42, 61] Children are less likely to develop PTLDs.[45, 51, 52, 56, 62]

Possible causes of post-treatment Lyme disease symptoms

The mechanisms underlying PTLDs are not known and are likely to be multifactorial. The pathogenesis of the nonspecific symptoms is likely to differ among individuals (Table 1).[67] Possible explanations include both related and unrelated causes.

Natural course of response to treatment

For many individuals, these nonspecific symptoms are part of the natural course of the response to the treatment of the infection, and they will continue to improve after completing antibiotic treatment. Studies of patients with erythema migrans show that the proportion of patients reporting symptoms after antibiotic treatment decreases over time (Figure 4).[36, 40, 46–48, 68] A prospective study of patients with Lyme disease showed that, regardless of disease stage or severity at diagnosis, their quality-of-life scores increased to just above the United States national average after 3 years of follow-up time. Comorbidities unrelated to Lyme disease were the only factors significantly associated with long-term symptoms or lower quality of life scores.[66] Similar results were seen in a study of patients with culture-confirmed erythema migrans evaluated 11–20 years after diagnosis.[69]

Post infective fatigue syndrome

Prolonged fatigue after infections is relatively common, can be disabling and persistent, and it is associated with the severity of the acute illness.[70–74] The mechanisms triggered during the acute illness that sustain the persistent symptoms are currently unknown. However, prolonged fatigue in patients with early Lyme disease after treatment is not common, with

only 3% of patients with erythema migrans having persistent fatigue possibly due to Lyme disease when evaluated 11 to 20 years after treatment.[75]

Misattribution and other conditions, including background prevalence of nonspecific symptoms and coinfections

Symptoms and signs due to other conditions can be wrongly attributed to Lyme disease, and these patients would be expected to have a less favorable response to specific anti-borrelial therapy. This was shown in a study of patients with disseminated Lyme disease, where 90% of the patients with definite diagnosis had excellent or good outcomes, comparing with only 47% of possible cases.[76] Similarly, patients with definite Lyme neuroborreliosis had better long-term outcomes than those with possible Lyme neuroborreliosis. [37, 77, 78]

Nonspecific symptoms like fatigue, chronic pain and sleep disorders are common in the general population, often reported together and associated with anxiety and depression.[79] Studies where Lyme disease patients and matched controls were followed prospectively showed similar prevalence of symptoms at follow up [36, 41, 46, 47, 68, 80, 81], while two studies showed a higher prevalence of persistent symptoms in a small subset of Lyme disease patients.[60, 61] All these studies demonstrate substantial (some more than 20%) background prevalence of nonspecific symptoms in the general population.

Co-infection with other tick-borne pathogens is rare in PTLDs patients.[82–84] Patients with concurrent Lyme disease and untreated *Babesia* infection had increased symptoms in one study [85] but another study showed no difference in symptoms between patients with and without *Babesia* co-infection.[86]

Microbiome changes

A study compared patients with PTLDS with healthy controls and intensive care unit patients.[87] As expected, intensive care unit controls were distinct from both PTLDS and healthy controls. There was a relative abundance of *Blautia sp* and Enterobacteriaceae over 10% in PTLDS patients when compared with healthy controls but PTLDS patients had received extensive antibiotic therapy (median of 56 days) and the effect of antibiotics in the gut microbiome can be prolonged.[88] A prospective study of patients with Lyme disease before and at intervals after antibiotic therapy will be necessary to assess the validity and relevance of these findings.

Metabolic Changes

The metabolic response was studied in 23 non-PTLDs and 24 PTLDs patients (11 symptoms and 13 syndrome).[89] Metabolite classes including glycerophospholipid, bile acid, and acylcarnitine metabolism were altered between the groups. Interestingly, PTLDs patients' metabolic patterns looked similar at post-treatment and 1-year follow-up, while there were greater differences for the non-PTLDs patients, particularly at the post-treatment timepoint, suggesting the end of treatment as the most informative metabolic biosignature.

Immune dysregulation or maladaptive host responses

Immune dysregulation or maladaptive host responses has been best studied in patients with post-infectious Lyme arthritis [39], which is associated with both host genetic factors and *B. burgdorferi* factors that together contribute to dysregulated and excessive inflammatory immune responses, increased T-helper 1 and T-helper 17 immune responses, and autoreactive T and B cells. PTLDs differs substantially from post-infectious Lyme arthritis. However, it is possible that immune dysregulation and/or infection-induced autoimmune mechanisms could contribute to symptoms. A few studies considered this question, but no reproducible marker has been identified. An important issue is that, in prospective studies, the number of patients with early Lyme disease who will develop PTLDs is small. Because many variables are being examined with a small number of patients, there is a risk of a type I error. Other reasons include differences in methods and technologies used, and differences in the patient groups studied.

PTLDS patients had higher levels of antibodies against neural proteins than recovered patients or healthy controls[90, 91] and higher antibody reactivity frequencies against certain *B. burgdorferi* antigens [91–93]. PTLDS cases had higher levels of anti-lysoganglioside GM1 antibody than controls, but not other antineuronal antibodies [94]. Antibodies against endothelial cell growth factor were found more frequently in patients with persistent symptoms in one study [95], but not in another study. [96]

Differences in the host response and their association with persistent symptoms have been investigated in the Study of Lyme disease Immunology and Clinical Events (SLICE) cohort [97]. One study measured 58 cytokines and chemokines, and six acute-phase markers, on 76 patients with erythema migrans (36 recovered, 29 patients with symptoms-only and 11 PTLDS), and 26 healthy controls. C-C motif chemokine ligand 19 (CCL19), ferritin, fibrinogen, C-X-C motif chemokine ligand (CXCL) 10, CXCL9, C-reactive protein, and serum amyloid A were differentially regulated between Lyme disease and healthy controls at the pretreatment visit. Generalized logistical regressions were used to predict Lyme disease clinical outcome group using these 7 markers. An increase in CCL19 of 0.5 standard deviation for the Lyme disease group at post-treatment visits was associated with PTLDS, and the hypothesis was that elevated CCL19 levels could reflect an ongoing reaction at distal sites to the secondary lymphoid tissue. For comparison, a European study measured 23 cytokines in serum of 45 patients with erythema migrans with at least 1 post-treatment Lyme symptom, compared with 41 recovered patients. In this study, interleukin (IL)-23 levels were higher before therapy, and stayed higher up to 12-month follow up in patients with persistent symptoms,[95] a finding not seen in the previous study.[97] CCL19 was not found to be significantly different between the groups. A study evaluating serum samples from 19 patients with a history of Lyme disease and objective memory impairment [83] showed increased serum interferon alpha activity in patients when compared with recovered (n=11) and healthy controls (n=20). There were no changes with prolonged antibiotic therapy.[91]

Blum at al. [98] showed that blood plasmablasts were increased in 32 untreated Lyme patients (7 PTLDS and 25 recovered patients, also part of the SLICE study) and returned to baseline levels by 6 months following antibiotic treatment. As expected, patients with disseminated erythema migrans (10 recovered and 1 PTLDS) had higher plasmablasts numbers compared

with those with single erythema migrans (15 recovered and 6 PTLDS). PTLDS patients had significantly lower blood plasmablasts than patients who returned to health at the pretreatment timepoint, and less seroreactivity to surface proteins and peptides from *B. burgdorferi*. This finding contrast with the studies showing patients with PTLDS have higher levels of autoantibodies and certain *B. burgdorferi* antigens.[90–96]

The longitudinal transcriptomic response in blood was studied in 29 individuals with Lyme disease (15 who returned to health, 9 with symptoms only, and 4 PTLDS) and 13 matched controls, part of the SLICE study [99]. There were no genes significantly differentially expressed at any single time point between the 15 patients who returned to health and the 13 patients with persistent symptoms. Four differentially expressed genes were identified when all timepoints were combined, and GPR15 was found differentially expressed when comparing patients with resolved Lyme disease with PTLDS at the time of diagnosis visit. A recent publication (also using data from the SLICE study) claims that, based on the projection of the RNA-seq data, cases are separated from controls and stay separate over time, but could not distinguish the patients that would go on to develop post-treatment persistent symptoms.[100] Further corroboration of the results will need to wait until the actual dataset for this study is made available to the scientific community.

Persistence of *B. burgdorferi* remnants

It is possible that leftover *B. burgdorferi* products may stay trapped and preserved in tissue after infection, playing a role in post-treatment symptoms.[101] Deposits of antigens were shown to persist near the cartilage and within joint entheses after antibiotic treatment in mice, and this material was capable of stimulating an inflammatory and immune response in uninfected mice.[102] Recently *B. burgdorferi* peptidoglycan was detected in synovial fluid samples from patients with Lyme arthritis, including patients with post-infectious Lyme arthritis after antibiotic therapy, and its systemic administration elicited acute arthritis in mice.[103] Although these observations do not exclude the possibility that these antigens could be produced by residual live bacteria, treatment of patients with post-infectious Lyme arthritis with potent immunosuppressive agents have not led to reemergence of infection.

Persistent infection with *B. burgdorferi*

The possibility that a persistent infection could be driving PTLDs has been a major concern. Arguments against this hypothesis include studies showing that symptomatic patients were not more likely to be seropositive than recovered patients and that patients did not develop objective manifestations of late Lyme disease. [49, 104] Also, no direct evidence of *B. burgdorferi* infection was found in these patients (however, *B. burgdorferi* culture and PCR have low sensitivity in most body fluids from patients with Lyme disease).[105]

In animal studies, *B. burgdorferi* DNA and RNA can be detected in tissues for months after antibiotic treatment but is not found by culture in antibiotic-treated animals, while untreated control mice are culture positive, and have significantly higher DNA and RNA copy numbers.[106–108] One hypothesis is that some of the spirochetes could become “persisters”. Persistence is a survival mechanism that allows organisms to endure diverse adverse environmental conditions by entering a physiologically dormant state.[109] This mechanism is

nongenetic and nonheritable (as opposed to acquisition of antibiotic resistance, which does not appear to occur with *B. burgdorferi*). Resuscitation (exiting the persistent state) is a hallmark of the persistence phenotype, and persister cells will restart proliferating when the adverse condition is removed.[110] For *B. burgdorferi*, persister bacteria have been identified *in vitro*, where, as expected, *B. burgdorferi* persisters are able to grow back after removal of the adverse condition.[111] The inability to culture bacteria from animals, particularly mice, months after antibiotic therapy is difficult to explain if persisters remained in the tissues of treated animals. One possibility would be that the bacteria is in a viable, but non-culturable (VBNC) state. It is unclear if VBNC actually occurs, or that persisters that do not resuscitate are dead cells.[112] There is no convincing data that *B. burgdorferi* forms true biofilms.[113]

B. burgdorferi DNA was detected by xenodiagnosis after antibiotic treatment in mice and non-human primate studies, while cultures of tick contents were almost always negative. A clinical study showed that xenodiagnosis using pathogen-free *I. scapularis* larval ticks was safe; and the procedure, while quite cumbersome, was well tolerated.[114] Xenodiagnosis was positive for *B. burgdorferi* DNA in one of the 10 patients with PTLDS tested. The discussion has been the significance of the detection of borrelial DNA by xenodiagnosis in relation to the presence (or not) of viable spirochetes, when it was not possible to demonstrate the recovery of live spirochetes by culture.[115] On the other side, the question is how *B. burgdorferi* DNA reached the xenodiagnostic ticks if the spirochetes were not alive. The possibility that very sensitive PCR tests could be detecting rare DNA fragments leftover in the skin is unlikely, as all 39 skin biopsy specimens collected 6 months post therapy from the area of erythema migrans lesions were negative using the same assay as the clinical study.[116] Another interesting question is how to interpret a negative result in a non-reservoir competent host for *B. burgdorferi* and what these findings can teach us about borrelial infection in humans. A larger study to assess whether a positive xenodiagnosis correlates with persistence of symptoms in ongoing.

The results from the antibiotic treatment trials

An important question is if PTLDs patients benefit from additional treatment. To answer this question, five randomized, placebo-controlled, double-blind clinical trials have been conducted.[82, 83, 117, 118] These studies have shown that prolonged antibiotic treatment offered no sustained benefit, while having potential serious risks.

The first two studies, one for patients who were IgG seropositive for *B. burgdorferi* at enrollment, and the other for seronegative patients, were published together.[82] Participants were randomized to either ceftriaxone 2 g intravenous daily for 30 days, followed by oral doxycycline, 200 mg daily for 60 days (n=64), or matching intravenous and oral placebos (n=65). The studies were stopped early when a planned interim analysis showed it was highly unlikely that a significant difference in treatment efficacy between the groups would be observed. There were no significant differences in quality-of-life scores between the treatment groups at 30, 90, and 180 days in the studies, with about a third of the patients improving, a third worsening and a third unchanged. There were 2 severe adverse events related to treatment.

The next study was the STOP-LD (Study and Treatment of Post Lyme Disease) and enrolled 55 PTLDS patients with persistent significant fatigue.[117] Patients were randomized to 28 days of intravenous ceftriaxone 2 g or placebo. There was improvement of fatigue with ceftriaxone therapy at 6 months but no improvement in mental speed or other neurocognitive measures. Exploratory analysis showed that patients who had positive immunoblot, had not received previous intravenous antibiotic therapy, and had less pain were more likely to improve. Three patients in each group discontinued therapy due to side effects, and 4 had to be hospitalized.

The fourth study enrolled PTLDS patients treated with at least 3 weeks of intravenous antibiotic therapy, seropositive by IgG western blot, and objective memory impairment.[83] Patients were randomized 2:1 to receive 10 weeks of intravenous ceftriaxone (23 patients) or placebo (14 patients), with 20 patients in the ceftriaxone group and 12 patients in the placebo group completing follow up. Using a model with an aggregate of the six domains of neurocognitive performance measured in the study (chosen by a data-driven selection process, which complicated the interpretation of the results),[119] the authors reported a borderline significant small improvement at 12 weeks in the ceftriaxone group. However, both placebo and ceftriaxone groups had similar improvements from baseline when analyzed at 24 weeks. Nine patients discontinued therapy due to side effects. These included three allergic reactions, two thrombus, one staphylococcal infection, and two due to pain. One patient on ceftriaxone underwent cholecystectomy at week 16.

The fifth study is the Persistent Lyme Empiric Antibiotic Study Europe (PLEASE).[118] This study, performed in the Netherlands, enrolled 280 participants with persistent symptoms attributed to Lyme disease. About 90% of the patients had received antibiotic treatment, and the median duration of symptoms was more than 2 years. After an initial 2-week treatment with open-label intravenous ceftriaxone, participants were randomized to receive 12 weeks of oral doxycycline with a placebo twice a day, clarithromycin with hydroxychloroquine twice a day, or two placebos twice a day. All groups improved when compared with their initial scores but there were no differences between groups at any time point during follow-up.[120] Because all participants received ceftriaxone therapy, it is unknown if the initial improvement was due to the therapy or a placebo effect. The improvement on fatigue was similar to the improvement seen in the intravenous placebo arm of two other studies.[121] Regarding safety, 9 patients had a serious adverse event, and 19 patients had an adverse event that led to discontinuation of the study drug.

An interesting analysis, derived from the PLEASE study, examined predictors of symptom improvement.[122] Pre-treatment functioning, higher pre-treatment expectancy to improve, and thinking that one had received antibiotics at the end of therapy were positively associated with physical and mental improvement at both end-of-treatment and at follow-up. This highlights the important role of patients' positive or negative expectancies on symptom course and treatment outcome. This is a well-known issue within the area of placebo (and nocebo) research, and it is important to consider the patient's expectations of therapeutic benefit as a confounding aspect in clinical trials. Similarly, these considerations apply when evaluating personal reports of the success of alternative therapies and practices. In these contexts, the many variables shown to increase placebo effect are being combined.

These include costly doctor's visits and tests, perceived expertise, complex (and expensive) treatment regimens, priming, social influence and emotional investment, to cite a few.[123] How to integrate these multiple variables into therapeutic research is an interesting and challenging topic.

Summary

The controversy regarding the underlying mechanisms of PTLDs, and the increasingly bitter debate over CLD, continues unabated over the past years. If anything, it has become more contentious. For health care providers, it is important that patients be offered the best advice based on current, evidence-based information. Patients treated for Lyme disease can be reassured that most will fully recover after recommended antibiotic therapy,[2] and that nonspecific symptom will improve over time. Evaluation of patients with PTLDs and CLD can be quite challenging. Practitioners should carefully review the evidence for the diagnosis of Lyme disease, and not lose sight that symptoms may be due to unrelated conditions. Most importantly is a collaborative approach to the treatment process with the patient, with warmth, empathy, and positive communication. More research on the pathogenesis of PTLDs, particularly biomarkers that would allow for differentiation accordingly to the underlying process, is urgently needed. Such markers could give insights into pathways and lead to valuable treatments. Current evidence shows that prolonged antibiotic therapy, as tested in the randomized placebo-controlled clinical trials, does not offer substantive benefits for PTLDs patients. These studies also showed significant placebo effect and variability of the intensity of subjective symptoms over time. Therefore, interventional studies in this population must have a double-blind, randomized controlled design. There is a critical need for high-quality research to better understand "chronic Lyme disease", and how to best help this large and heterogenous group of patients.

Acknowledgments:

Funding for this study was provided by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

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Synopsis:

Most patients with Lyme disease will fully recover with recommended antibiotic therapy. However, some patients report persisting nonspecific symptoms after treatment, referred to as post-treatment Lyme disease symptoms (PTLDs) or syndrome (PTLDS), depending on the degree which the individual's symptoms impacts their quality of life. PTLDs occurs in a portion of patients diagnosed with chronic Lyme disease (CLD), a controversial term describing different patient populations, diagnosed based on unvalidated tests and criteria. Practitioners should review the evidence for the Lyme disease diagnosis and not overlook unrelated conditions. Current evidence shows that prolonged antibiotic therapy provides little benefit and carries significant risk. Further research to elucidate the mechanisms underlying persistent symptoms after Lyme disease and to understand CLD is needed.

Key points

- Lyme disease is treated successfully with recommended antibiotics in the majority of cases; however, some patients have persisting nonspecific symptoms after treatment, referred to as post-treatment Lyme disease symptoms (PTLDs) or syndrome (PTLDS).
- Chronic Lyme disease (CLD) is a controversial term, with no defined diagnostic criteria, used to describe different patient populations. Patients with PTLDs represent a small portion of CLD patients.
- Most CLD patients suffer from other conditions or are patients with medically unexplained physical symptoms and are diagnosed with CLD based on unvalidated tests and criteria.
- There is a critical need for more research to elucidate the mechanisms underlying PTLD, together with research into patients who fall under the CLD heading.

Clinical Care Points

- Patients treated for Lyme disease can be reassured that most will fully recover after recommended antibiotic therapy and that nonspecific symptom will improve over time.
- Evaluating patients with symptoms after Lyme disease or with the diagnosis of chronic Lyme disease can be challenging. Different factors are likely to play a role in an individual case.
- Symptoms and signs due to other conditions can be wrongly attributed to Lyme disease. Practitioners should carefully review the evidence for the diagnosis of Lyme disease, and not lose sight that symptoms may be due to unrelated conditions.
- Current evidence shows that prolonged antibiotic therapy for PTLDs provides little benefit and carries significant risk.

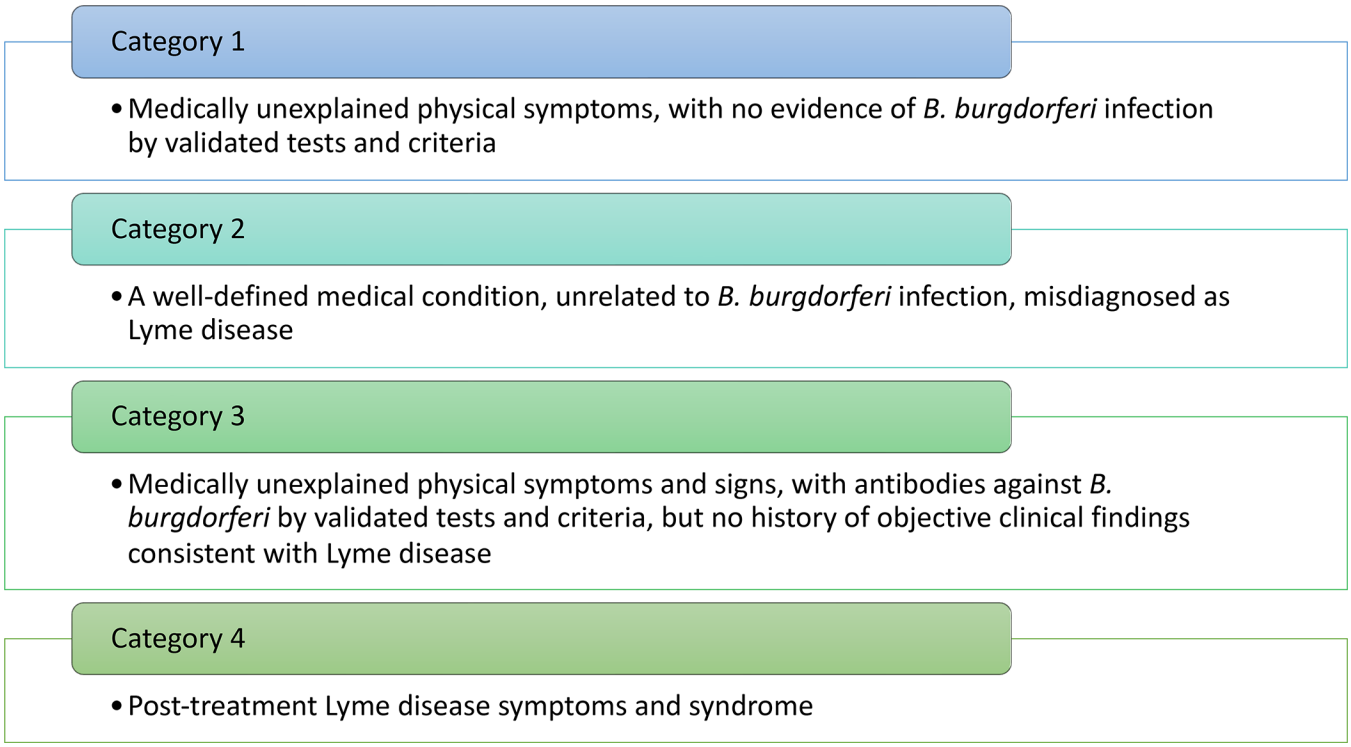

Figure 1.

Categories of "Chronic Lyme Disease". (*Data from* Feder HM, Jr., Johnson BJ, O'Connell S, et al. A critical appraisal of "chronic Lyme disease". N Engl J Med. Oct 4 2007;357(14):1422–30. doi:10.1056/NEJMra072023)

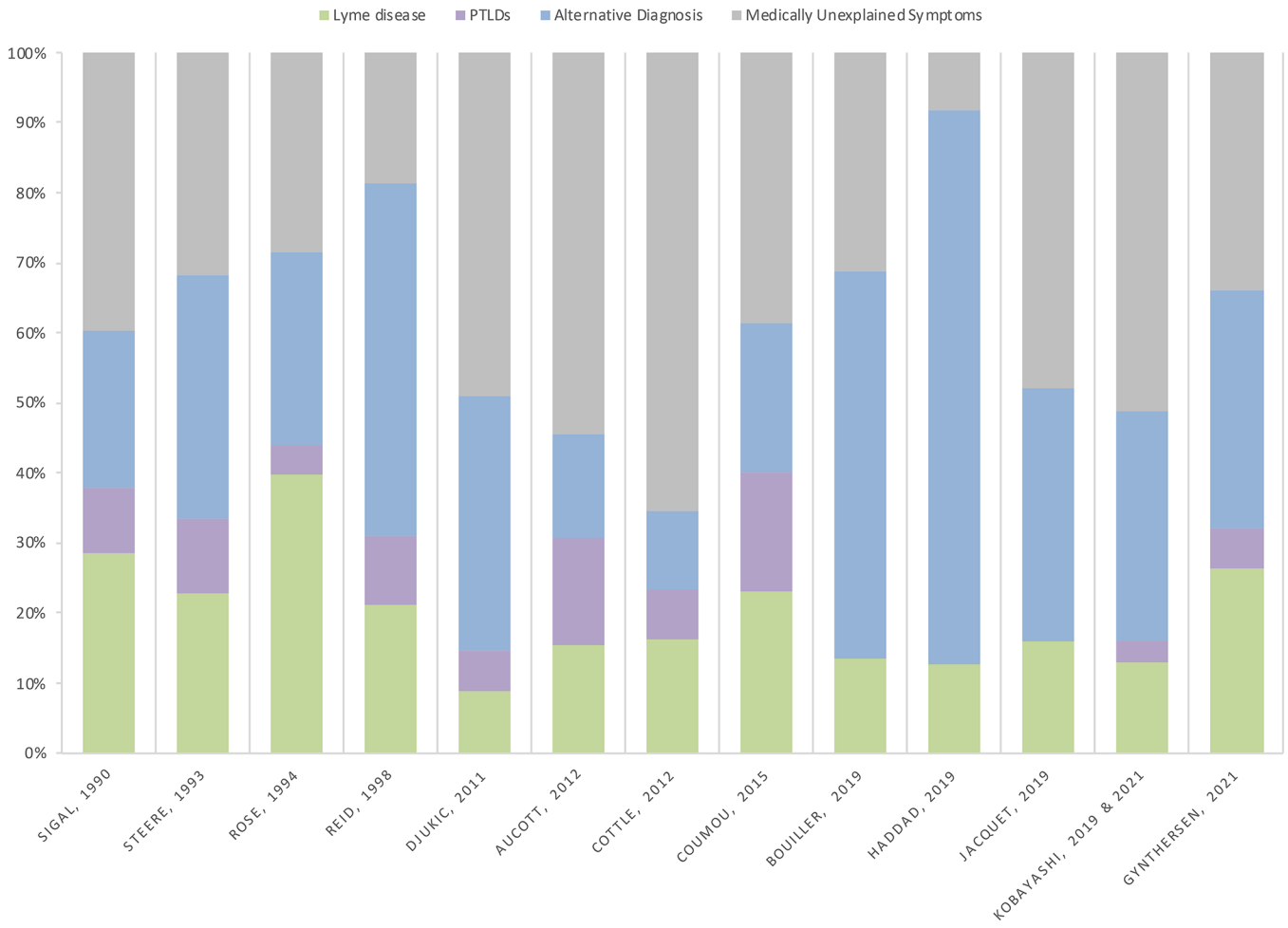

Figure 2.

Classification of patients referred for evaluation of possible Lyme disease. Post treatment Lyme disease symptoms (PTLDs).

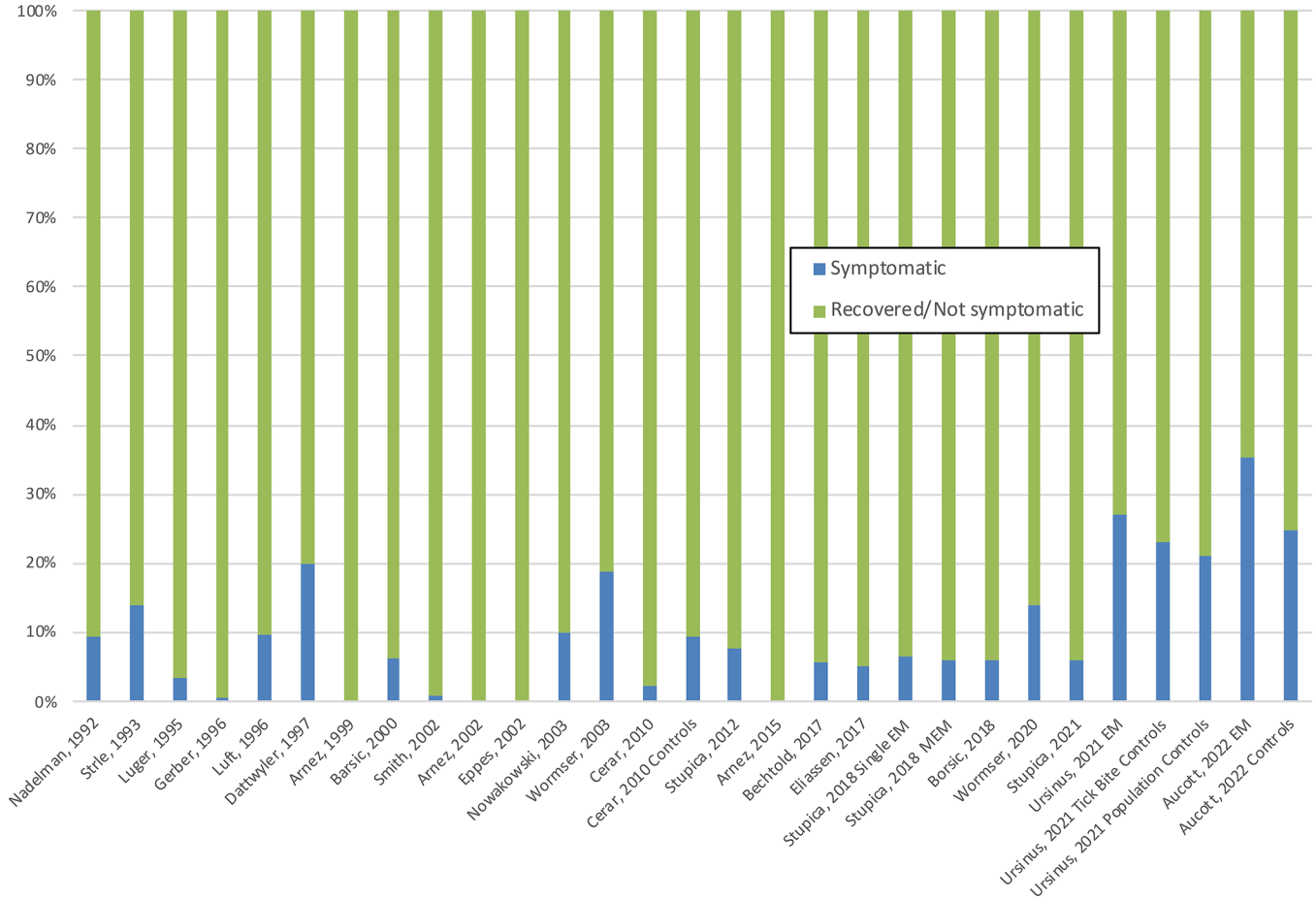

Figure 3.

Symptoms after antibiotic therapy in patients with erythema migrans. Erythema migrans (EM). Multiple erythema migrans (MEM)

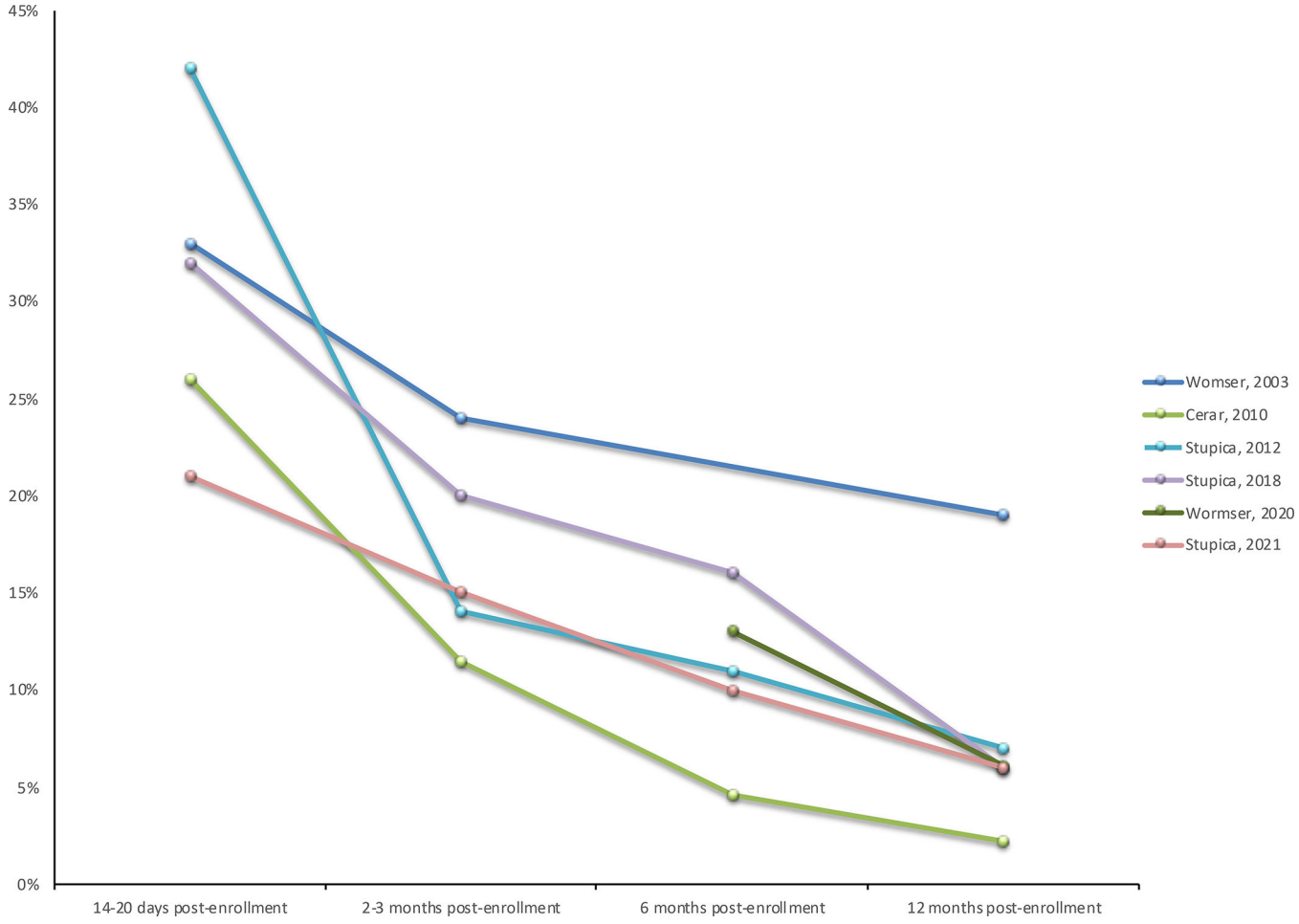

Figure 4.
The number of patients reporting symptoms after antibiotic treatment decreases over time.

Table 1.

Possible causes of post-treatment Lyme disease symptoms

Part of the expected resolution of symptoms after treatment
New and preexisting conditions unrelated to Lyme disease
Post-infective fatigue syndrome
Other tick-borne infections
Microbiome changes
Metabolome changes
Dysregulated immune response/autoimmunity
Persistence of *B. burgdorferi* remnants
Persistent infection with *B. burgdorferi*