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Update of the Swiss guidelines on post-treatment Lyme disease syndrome

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Summary

Lyme borreliosis is caused by *Borrelia burgdorferi* sensu lato infection, which responds well to antibiotic therapy in the overwhelming majority of cases. However, despite adequate antibiotic treatment some patients report persisting symptoms which are commonly summarised as post-treatment Lyme disease syndrome (PTLDS). In 2005, the Swiss Society of Infectious Diseases published a case definition for PTLDS. We aimed to review the scientific literature with a special emphasis on the last 10 years, questioning whether the definitions from 2005 are still valid in the light of current knowledge. Furthermore, we describe the clinical history of infection with *Borrelia burgdorferi* sensu lato, the estimated prevalence of PTLDS, the possible pathogenesis of PTLDS, and treatment options with an emphasis on clinical studies.

In summary, we were unable to find a scientific reason for modification of the PTLDS definitions published in 2005. Thus, the diagnostic criteria remain unchanged, namely documented clinical and laboratory evidence of previous infection with *B. burgdorferi*, a completed course of appropriate antibiotic therapy, symptoms including fatigue, arthralgia, myalgia, cognitive dysfunction or radicular pain persisting for >6 months, a plausible timely association between documented *B. burgdorferi* infection and onset of symptoms (i.e., persistent or recurrent symptoms that began within 6 months of completion of a recommended antibiotic therapy for early or late Lyme borreliosis), and exclusion of other somatic or psychiatric causes of symptoms. The main therapeutic options remain cognitive behavioural therapy and low-impact aerobic exercise programmes. Growing and unequivocal evidence confirms that prolonged or repeated antibiotic therapy for PTLDS is not beneficial, but potentially harmful and therefore contraindicated.

The Guidelines of the Swiss Society of Infectious Diseases offer an evidence based, diagnostic and therapeutic framework for physicians caring for patients suffering from presumptive PTLDS in Switzerland.

Key words: *Lyme borreliosis; post-treatment Lyme disease syndrome; antibiotics*

Introduction

Lyme borreliosis is caused by infection with *Borrelia burgdorferi* sensu lato, which responds well to antibiotic therapy in the overwhelming majority of cases. Nevertheless, various reports suggest that 2 to 40% of appropriately treated patients may subsequently suffer from persisting minor to severe symptoms, including fatigue, musculoskeletal or neurocognitive symptoms, lasting for months or even years [1–9]. The aetiology of such post-Lyme symptoms, however, was fiercely debated. In 2005, the Swiss Society for Infectious Diseases published guidelines for the diagnosis and treatment of Lyme borreliosis [10–15], including a case definition for post-treatment Lyme disease syndrome (PTLDS) (table 1). The Infectious Diseases Society of America proposed a case definition for PTLDS in 2006 (table 1) [16].

Ongoing controversies on whether post-Lyme disease symptoms reflect a distinct clinical syndrome, how to define the syndrome, how to distinguish the syndrome from other unspecific chronic fatigue-like illnesses or chronic pain disorders, and the growing influence of patient advocacy groups [17], urged us to review the literature on PTLDS with a focus on recent data and on current recommendations of European and North American guidelines (table 2) [16, 18–22].

Case definition of post-treatment Lyme disease syndrome

PTLDS refers to a pattern of nonspecific symptoms that persist for more than 6 months after proven and appropriately treated Lyme borreliosis, and which are caused neither by active or persistent *B. burgdorferi* infection nor by other diseases. Symptoms include fatigue, neurocognitive deficits, arthralgias or myalgias, without clinically detectable or measurable signs [10–16, 18, 23–25]. For the diagnosis of PTLDS, a well-documented history of distinct clinical signs and symptoms fitting the case definitions of Lyme borreliosis [10–16, 18, 25], laboratory evidence of a previous infection with *B. burgdorferi,* and a plausible chronology of clinical manifestations of Lyme borreliosis and subsequent symptoms (i.e., persistent or recurrent symptoms that began within 6 months of completion of therapy with a recommended antibiotic for early or late Lyme borreliosis, and persist for 6 months or longer) are required. Furthermore, other somatic, psychiatric or behavioural aetiologies for the reported symptoms must meticulously be excluded (table 1). Of note, positive Lyme serology without previous manifestations of Lyme borreliosis does not qualify for the diagnosis of PTLDS (table 3).

Strle et al. [26] speculated that post-Lyme symptoms might be attributed to more than one syndrome, possibly encompassing conditions of less severe symptoms such as malaise, fatigue or minor arthralgias lasting for months after adequate treatment of Lyme *Borrelia* infection, and more disabling conditions of severe musculoskeletal pain and in-

Table 1: Swiss and US case definitions of post-treatment Lyme disease syndrome (PTLDS).

Criteria of the Swiss guidelines for PTLDS [10–15]	**Criteria of the US guidelines for PTLDS [16]**
Inclusion criteria	
– Documented clinical and laboratory evidence for previous Lyme borreliosis – Completed therapy, documented and adequate for the stage – Persisting or recurrent symptoms such as fatigue, arthralgia, myalgia, cognitive dysfunction or radicular pain, for more than 6 months after antibiotic therapy – A plausible and timely association between documented *B. burgdorferi* infection and the onset of PTLDS symptoms, i.e., persistent or recurrent symptoms began within 6 months of completion of antibiotic therapy, and persist for 6 months or greater – Objective signs obtained from clinical examination are not required	– 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 – Treatment with a generally accepted treatment regimen, with 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	
– Evidence for an active infection – Concurrent other disease, including active and ongoing rheumatologic, neurological or psychiatric disease	– An active, untreated, well-documented co-infection, such as babesiosis. – The presence of objective abnormalities on physical examination or on neuropsychologic testing that may explain the patient's complaints. – A diagnosis of fibromyalgia or chronic fatigue syndrome before the onset of Lyme disease. – A prolonged history of undiagnosed or unexplained somatic complaints, such as musculoskeletal pains or fatigue, before the onset of Lyme disease. – A diagnosis of an underlying disease or condition that might explain the patient's symptoms. – Laboratory or imaging abnormalities that might suggest an undiagnosed process distinct from PTLDS – 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.

Table 2: Post-treatment Lyme disease syndrome in different professional guidelines and position papers.

Country/region, year	**Society or authors, reference**	**Short version of case definition**
Switzerland, 2005	Swiss Society for Infectious Diseases [10–15]	see table 1
USA, 2006	Infectious Diseases Society of America (IDSA) [16]	see table 1
Europe, 2010	European Federation of Neurological Societies (EFNS) [19]	No specific definition of PTLDS is provided. Antibiotic therapy and the treatment trials are being discussed. Antibiotic treatment is strongly discouraged. The evidence for this recommendation is rated as level A, the highest rating possible.
Europe, 2011	European Union Concerted Action on Lyme Borreliosis (EUCALB) [25]	No specific definition of PTLDS is provided. A chapter called "Subjective Long-term Sequelae of Lyme Borreliosis" describes some features of Post Lyme, emphasizing that the symptoms are not due to active infection.
United Kingdom, 2011	British Infection Association [21]	No specific definition of PTLDS is provided. A chapter entitled "Persistent symptoms following treated Lyme borreliosis; chronic Lyme disease" discusses PTLDS, referring to a large extent to the IDSA guidelines.

capacitating fatigue persisting for years after treated Lyme borreliosis [22, 27–31].

Clinical scenarios

In table 4 we describe different possible clinical outcomes of *B. burgdorferi* infection. When evaluating patients with presumed PTLDS, the following scenarios need to be considered in the differential diagnosis:

- Patients with manifest Lyme borreliosis, treated or not treated. This group includes patients with undiagnosed infection due to *B. burgdorferi*, with missed diagnosis, or with correct diagnosis but as yet inadequate antibiotic treatment, i.e., inappropriate choice, wrong dosage, insufficient duration, or inappropriate route of application, or patient's nonadherence to treatment.
- Patients who in the past had proven Lyme borreliosis, were adequately treated and have no active infection. All of them are microbiologically cured, but some may suffer from PTLDS.
- Patients who never had Lyme borreliosis but who believe that *Borrelia* sp. infection is the cause of their complaints. This group includes misdiagnosed patients (e.g., multiple sclerosis) or individuals with self-diagnosis who have no clinical or laboratory evidence of prior infection; patients who experienced adverse effects of nonindicated treatments for wrongly presumed Lyme borreliosis; patients with missed other somatic, psychiatric or behavioural morbidity; patients who prefer the diagnosis of Lyme borreliosis to other diagnoses; or patients with disease conviction.

Clinical course of early and late manifestations of Lyme borreliosis, and post-treatment residual symptoms

Following antibiotic treatment, resolution of the symptoms and signs of Lyme borreliosis and residual symptoms vary depending on the initial clinical manifestations.

In prospective treatment trials of Lyme borreliosis, in which patients were continuously observed after treatment of proven infection, it appears plausible to link persisting symptoms, which were not present before infection, with *B. burgdorferi* infection. In contrast, prevalence studies of fatigue-like symptoms and musculoskeletal pain in Lyme borreliosis are more difficult to interpret, because approximately 1 year after treatment of Lyme borreliosis the prevalence of reported symptoms is often comparable to that of an uninfected population [32–34].

Erythema migrans

Erythema migrans is the most common manifestation of *B. burgdorferi* infection. If treated with antibiotics, skin lesions and, if present, systemic symptoms, usually resolve within 14 days [23]. However, some nonspecific symptoms may persist for weeks or even months after adequate treatment in the absence of any evidence of persisting infection

Table 3: Minimal diagnostic work up before consideration of post-treatment Lyme disease syndrome.

– Complete physical examination including neurological and rheumatological assessment
– Past medical history, including clinical and laboratory (*Borrelia* serology) documentation of prior presumed Lyme borreliosis
– Complete blood count
– Blood chemistry including electrolytes, kidney and liver function
– Thyroid-stimulating hormone
– Anti-nuclear antibodies
– Chest X ray
– Psychiatric consultation
– Computed tomography or magnetic resonance imaging of the head in the case of chronic headache and no plausible explanation
– In the case of focal signs or symptoms: imaging and histopathological evaluation
– In the case of neurological symptoms: CFS examination with Lyme serology (serum and CSF) and CSF/serum index
CSF = cerebrospinal fluid

Table 4: Definitions and outcome of *Borrelia burgdorferi* infection.

Case classification of Lyme borreliosis	Confirmed: (a) a case with erythema migrans; or (b) a case with at least one late manifestation, as defined in [16, 95] that is laboratory confirmed [96]: positive culture for *B. burgdorferi*, or two-tier testing interpreted using established criteria, where positive IgM is sufficient only when ≤30 days from symptom onset, positive IgG is sufficient at any point during illness; single-tier IgG immunoblot seropositivity using established criteria; CSF antibody positive for *B. burgdorferi* corrected with the Reiber-Quotient for intrathecal antibody production.
Asymptomatic seroconversion	Seroconversion after tick bite without clinical signs of Lyme borreliosis.
Progression of disease without treatment	In North America, progression to monoarthritis in untreated patients (*B. burgdorferi* sensu stricto) is frequent (around 60% of cases), whereas in Europe acrodermatitis chronica atrophicans (*B. afzelii*) and neurological involvement (*B. garinii*) are more frequent as a result of differences in organ tropism of different *Borrelia* strains.
Uncomplicated course	Infection with *B. burgdorferi* is diagnosed and treated promptly, and cured.
Delayed cure	Infection with *B. burgdorferi* is diagnosed and treated with delay, resulting in microbiological cure but possibly resulting in protracted clinical symptoms.
Sequelae	State-of-the-art treatment of arthritis, acrodermatitis chronica atrophicans or neuroborreliosis results in microbiological cure but not in complete resolution of symptoms in any case (see section: "Clinical course of Lyme borreliosis, and post-treatment residual symptoms").
Post-treatment Lyme disease syndrome	Persistence of fatigue-like symptoms and musculoskeletal pain for more than 6 months despite correct diagnosis and adequate treatment of proven Lyme borreliosis, and exclusion of other causes of symptoms
Chronic Lyme borreliosis	No scientific evidence that *B. burgdorferi* may persist despite adequate therapy. Persistent symptoms after treatment are not caused by active infection. Thus, chronic Lyme borreliosis after treatment does not exist.

[23, 32]. These symptoms may include fatigue, malaise, arthralgia, headache, myalgia, paraesthesia, dizziness, nausea, insomnia, sleepiness, forgetfulness, concentration difficulties, irritability, and pain [33]. After erythema migrans, 5.6 to 11% of patients experience persisting symptoms 6 months after treatment, depending on the patient populations assessed [8, 33].

Neuroborreliosis

Neuroborreliosis is the second most important acute or subacute clinical manifestation in Europe [35], mainly caused by *B. garinii*. With antibiotic treatment, patients improve rapidly and substantially [36]. After discontinuation of antibiotics, the clinical manifestations continue to improve, albeit often protractedly or incompletely: more than half of patients still experience symptoms after 4 months [36], and many (range: 23–100%) may continue to suffer from persisting neurological sequelae [2, 34, 37]. In a recent review, however, the authors conclude that literature on pharmacological treatments of acute Lyme neuroborreliosis is scarce and of limited quality and does not allow any recommendations regarding more severe forms such as encephalitis [38].

A prospective, randomised trial in Norway comparing intravenous ceftriaxone with oral doxycycline in patients with mostly early neuroborreliosis documented noninferiority of the oral regimen [36]. Of note, only 26 (48%) patients in the doxycycline group and 16 (33%) in the ceftriaxone group had complete clinical recovery after 4 months. This observation indicates that despite bacteriologically successful treatment, more than half of patients may have persistent signs and symptoms.

Lyme arthritis

Lyme arthritis is a common manifestation of borreliosis in North America, where up to 50% of affected patients suffer from intermittent episodes of arthritis, 18% experience arthralgia (independently from arthritis), and 11% develop chronic arthritis. In the USA, 60 to 80% of patients with untreated erythema migrans will develop joint symptoms [39]. In contrast, arthritis occurs less frequently in Europe [23], but clinical manifestations appear to be similar to those described in the USA [40–42]. In surveys in Germany, between 2 and 5% of patients with Lyme borreliosis developed Lyme arthritis [43, 44]: for example, surveillance data from 2009–2012 of human Lyme borreliosis from six federal states found arthritis in 2.0% of the notified 18 894 cases [44]. Lyme arthritis typically responds to an adequate course of antibiotics [39, 45].

Generalised arthralgias may occur shortly after erythema migrans (mean: 2 weeks) and never progress to joint abnormalities. Frank arthritis develops a mean of 6 months (range: 4 days to 2 years) after unrecognised or untreated acute infection, and classically presents as monoarthritis or oligoarthritis mainly involving the knee (in 96% of cases). Patients may experience flare-ups of arthritis after treatment [39], and some may benefit from a second treatment course with antibiotics [16]. However, if arthritis persists after a second course of appropriate antibiotics, persisting arthritis is the consequence of an unabated inflammatory process and not due to persisting bacterial infection. Approximately 10% of patients may develop the so-called "antibiotic refractory" late Lyme arthritis [23]. This disease entity has a defined pathological correlate – persisting proliferative synovitis with a negative borrelial polymerase chain-reaction (PCR) test. This unabated process is probably due to immune dysregulation or infection-induced autoimmunity [46, 47]. Management includes anti-inflammatory treatment with nonsteroidal anti-inflammatory agents, intra-articular corticosteroids, methotrexate, or synovectomy [23, 46]. Importantly, repeated antibiotic courses do not improve clinical outcome [16, 46].

Other manifestations of Lyme borreliosis

Lyme carditis is a rare manifestation of acute to subacute Lyme borreliosis, often presenting with high-grade atrioventricular block, which is potentially fatal [48], and therefore patients should be admitted to hospital for close monitoring. Temporary pacing may be required. In general, conduction disturbances resolve within 6 weeks after antibiotic treatment [16, 23].

Borrelial lymphocytoma is a rare cutaneous manifestation reported mainly in Europe and is observed more often in children than in adults. It responds to antibiotic therapy within weeks [23].

Acrodermatitis chronica atrophicans, mainly caused by *B. afzelii*, is a rare skin manifestation occurring months to years after infection. It responds well to antibiotic treatment, but may take months to years to improve if treatment initiation was delayed [49], or may not completely resolve if treatment was not started before the occurrence of the atrophic phase of the disease.

Long-term clinical course of Lyme borreliosis

Selected studies on the long-term clinical course of Lyme borreliosis with an emphasis on erythema migrans and neuroborreliosis are summarised in table 5, which is divided in six sections: (1) randomised controlled treatment trials; (2) prospective antibiotic treatment trials comparing outcome with matched, healthy individuals as a comparison group; (3) prospective cohort studies, comparing outcome with matched, healthy individuals as a control group; (4) cohort studies without a comparison group; (5) retrospective studies with matched, healthy individuals as a comparison group; (6) retrospective studies without a comparison group.

The best available data were derived from randomised controlled antibiotic treatment trials which show that 5 to 10% of patients report persisting symptoms after 6 to 12 months. In contrast, prospective treatment trials also including a healthy comparison group (without intervention, consisting of age-matched friends or relatives of patients who were asked to answer the same questionnaire as patients in the treatment groups) did not detect any significant differences in long-term outcome between patients and healthy controls:

– A trial assessing different treatment durations for erythema migrans in 225 patients, and including an additional group of 81 healthy volunteers who had no intervention, did not find any significant differences in outcome

between patients and healthy controls after 6 months [33]. The (persisting) symptoms included, among others, fatigue (post-Lyme 56.4% vs control 54.3%), malaise (39.6% vs 45.7%), and arthralgias (41.6% vs 42%).

– A large treatment trial with a total of 285 European patients with erythema migrans, and 259 controls did not find any difference in long-term outcome between patients who had Lyme borreliosis and individuals who did not [32]. Six months after treatment, fatigue (post-Lyme 3.1% vs control 4.7%), arthralgia (3.1% vs 4.7%), headache (0.5% vs 2.5%), and myalgia (2.1% vs 1.7%) did not differ significantly between groups.

Thus, nonspecific symptoms appear frequent in the general population, and nonspecific symptoms after Lyme borreliosis do not appear to be more prevalent in patients than in control groups. However, the frequency of general symptoms in these so-called "healthy control groups" who had no comprehensive medical evaluation, was indeed surprisingly high, suggesting problematical selection of comparison groups; for example, Stupica et al. reported a frequency of around 40% [33]. Furthermore, there were 10-fold differences in the frequencies of symptoms in control groups depending on the respective study, suggesting that the population assessed, or the methods used to evaluate the symptoms, may influence the prevalence of nonspecific symptoms.

Examples of prospective cohort studies include a study on neuroborreliosis in 177 children which showed that residual facial palsy (post-Lyme 6% vs control 0%) was more frequent in children after neuroborreliosis, whereas headache (12% vs 24%) and fatigue (6% vs 20%) were not [35]. In another long-term cohort of 128 patients in the USA with culture-confirmed Lyme borreliosis, followed up over a median of 15 years (range: 11–20 years), 14 (10.9%) were regarded as having PTLDS, of whom 6 (4.7%) still had PTLDS documented at their last study visit, indicating that PTLDS may persist for more than a decade. Nevertheless, none of these patients was considered to be functionally impaired by their symptoms [50].

Two small retrospective studies including control persons showed significantly more symptoms persisting in patients after Lyme disease or initial neuroborreliosis when compared with controls [2, 37].

– A retrospective, population-based cohort study showed a significantly increased frequency of arthralgias, neurocognitive impairment and myelopathy, in the follow-up [2].

– Another small retrospective investigation of 20 patients with past neuroborreliosis revealed significantly more neuropsychological deficits in the long-term course when compared with healthy controls [37].

In summary, the available data suggest that two types of persisting symptoms after initial neuroborreliosis need to be distinguished. First, "focal" and well-defined signs and symptoms caused by irreversible inflammatory tissue damage, such as facial palsy or myelopathy, usually due to delayed onset of therapy. Second, "generalised or diffuse" nonspecific symptoms not attributable to tissue damage, including fatigue, generalised pain and myalgia were found to be of similar frequency when compared with control groups.

A recently published systematic review of residual symptoms after adequate treatment of Lyme neuroborreliosis [51] showed that the mean prevalence of residual symptoms was approximately 28%. Subgroup analyses showed that studies limited to "probable" or "definite" Lyme neuroborreliosis cases had a lower prevalence of residual symptoms than studies including "possible" cases, indicating the importance of specific case definitions to exclude false positive findings.

Can Lyme borreliosis become chronic?

Whether PTLDS is a specific disease remains controversial because of the lack of objective evidence of an ongoing immunological or infectious process in patients with correctly treated Lyme disease. Furthermore, identical symptoms appear to be equally prevalent in individuals without a history of Lyme borreliosis [16, 23]. Also, original data on PTLDS are scarce and heterogeneous, and no standardised, validated and widely accepted case definition is available. Moreover, the debate on PTLDS is confused by the discussion on whether *Borrelia* infection can persist and become chronic after adequate treatment [52].

Indeed, there is no scientific evidence of chronic Lyme borreliosis be it due to either microbiological failure of appropriate antibiotic treatment, antibiotic resistance [16, 53], or pathogen persistence after correct treatment [22, 54]. *B. burgdorferi* culture results from erythema migrans skin lesion biopsies following adequate antibiotic treatment have been negative in almost all patients, including those with persisting symptoms after treatment [32, 33]. Furthermore, there are also no records of a reactivation of hypothetically latently persisting *B. burgdorferi* among immunocompromised hosts, as can be observed in latent infections due to intracellularly persisting pathogens.

However, if unrecognised and untreated, *Borrelia* infection can cause persisting and increasing symptoms over months. Among 240 American patients with "chronic Lyme borreliosis", 19% had active Lyme borreliosis [9], although 60% had no evidence of Lyme disease at all.

Treatment data on PTLDS

The best available evidence on the natural history of PTLDS and the effect of antibiotic treatment can be obtained from randomised, controlled, prospective clinical trials comparing antibiotic treatment with placebo in patients with persisting symptoms following proven acute Lyme borreliosis (table 6) [29–31, 55–57].

Klempner et al. included 115 patients in two double-blind placebo-controlled clinical trials [29]. Patients were eligible if they had a documented clinical history, laboratory findings of Lyme borreliosis, and documented adequate antibiotic treatment. Symptoms attributed to PTLDS had to have begun within 6 months after infection and to have persisted for at least 6 months. Patients with negative serology for borreliosis were included only if an erythema migrans was clearly documented by an experienced physician. Patients were randomly assigned in a 1:1 ratio to receive either antibiotics or placebo. The antibiotic treatment consisted of 1 month of intravenous ceftriaxone followed by

Table 5: Selected studies on the persistence of symptoms after antibiotic treatment of Lyme borreliosis.

Author	Country	Study design	Initial clinical manifestations	Follow-up	Patients with persisting symptoms n (%)	Comparison group n	Comparison group with symptoms n (%)	Remarks
Randomised controlled antibiotic treatment trials of Lyme borreliosis								
Nadelman, 1992 [97]	USA	RCT of two antibiotics, cefuroxime and doxycycline	Early Lyme disease	1 year	8/86 (9.3)	n.a.	n.a.	No difference between antibiotics
Strle, 1992 [98]	Slovenia	RCT of three antibiotics, penicillin, azithromycin, and doxycycline	Erythema migrans	2 years	4/64 (6.3)	n.a.	n.a.	No difference between antibiotics
Strle, 1993 [99]	Slovenia	RCT of two antibiotics, azithromycin and doxycycline	Erythema migrans	1 year	3/107 (2.8)	n.a.	n.a.	No difference between antibiotics
Luger, 1995 [100]	USA	RCT of two antibiotics, cefuroxime and doxycycline	Erythema migrans	1 year	15/232 (6.4)	n.a.	n.a.	No difference between antibiotics
Luft, 1996 [101]	USA	RCT of two antibiotics, azithromycin and amoxicillin	Erythema migrans	6 months	21/217 (9.7)	n.a.	n.a.	Amoxicillin was an effective therapeutic agent.
Dattwyler, 1997 [4]	USA	RCT of two antibiotics, intravenous ceftriaxone and doxycycline	Disseminated Lyme disease	9 months	6/120 (5.0)	n.a.	n.a.	No difference between antibiotics
Prospective clinical antibiotic treatment trials of Lyme borreliosis, comparing outcome with matched, healthy individuals as a comparison group								
Cerar, 2010 [32]	Slovenia	Prospective RCT of two antibiotics. Comparison with matched healthy comparison group	Erythema migrans	6 months 1 year	11/195 (5.6) 7/230 (3.0)	236 individuals without Lyme borreliosis	21 (9.4)	No difference in outcome between patients and comparison group
Stupica, 2012 [33]	Slovenia	RCT of two antibiotics. Comparison with matched healthy comparison group	Erythema migrans	6 months 1 year	21/197 (10.6) 13/177 (7.3)	81 individuals without Lyme borreliosis	Number of symptomatic controls not explicitly stated, only symptoms are reported	Comparison group and patient population with same frequency of symptoms after 6 months
Prospective cohort studies of Lyme borreliosis, comparing outcome with matched, healthy individuals as a control group								
Skogman, 2008 [34]	Sweden	Prospective cohort study	Children with neuroborreliosis	6 months	37/177(20.9)	174	Number of symptomatic controls not explicitly stated, only symptoms are reported	Patients: more facial palsy; comparison group: more headache and fatigue
Prospective cohort studies of Lyme borreliosis without a comparison group								
Hammers-Berggren, 1993 [102]	Denmark	Prospective cohort study	Neuroborreliosis	18 months	7/27(26.0)	n.a.	n.a.	
Gerber, 1996 [103]	USA	Prospective cohort study	Lyme disease in children	25.4 months	0/201 (0)	n.a.	n.a.	
Smith, 2002 [7]	USA	Prospective cohort study	Erythema migrans	2 months	5/118 (4.2)	n.a.	n.a.	Microbiologically confirmed Lyme disease
Berglund, 2002 [104]	Sweden	Prospective population-based survey	Neuroborreliosis	6 months 5 years	44/114 (38.6) 28/114 (24.6)	n.a.	n.a.	
Nowakowski, 2003 [105]	USA	Prospective cohort study	Erythema migrans	≥1 year (mean 5.6 ± 2.6)	8/81 (10)	n.a.	n.a.	Overall excellent clinical outcome
Ljostad, 2008 [36]	Norway	Prospective, clinical trial	Neuroborreliosis	4 months	60/102 (58.8)	n.a.	n.a.	
Weitzner, 2015 [50]	USA	Prospective study	Symptomatic early Lyme borreliosis, *B. burgdorferi* positive skin or blood cultures	15 (11–20) years	14/128 (10.9)	n.a.	n.a.	6 (4.7%) with PTLDS at their last visit

Table 5: Selected studies on the persistence of symptoms after antibiotic treatment of Lyme borreliosis.

Author	Country	Study design	Initial clinical manifestations	Follow-up	Patients with persisting symptoms n (%)	Comparison group n	Comparison group with symptoms n (%)	Remarks
Retrospective studies with matched, healthy individuals as a comparison group								
Shadick, 1994 [2]	USA	Population-based retrospective cohort study	Lyme disease	6.5 years, range 1–11 years	13/38 (34)	43	Comparison group had significantly fewer symptoms in psychometric evaluation.	
Benke, 1995 [37]	Austria	Retrospective cohort study	Lyme encephalopathy	4.3 years (average)	20/20 (100)	20	In a statistical model, differences between groups were not significant.	All patients performed worse compared to healthy comparison group
Seltzer, 2000 [6]	USA	Two-part study including a community-based longitudinal cohort and matched cohort study	All manifestations	51 months, range 15–135 months	13.7–33.5%/ 212 patients, depending on the symptoms assessed	14.2–24.1% of 212 patients, depending on the symptoms assessed	Differences between controls and patients were not significant in logistic regression.	The difference between patients and healthy comparison group were overall not significant, assessing a total of 18 different non-specific symptoms and 2 standardised neuropsychological tests
Vazquez, 2003 [6]	USA	Retrospective, cross-sectional study with matched comparison group	Children with Lyme disease	8 years, range 7–61 months	9/34 (26.4)	Substantial number of nonspecific symptoms in the comparison group		The difference between patients and healthy comparison group was overall not significant, including a total of 20 different nonspecific symptoms
Retrospective studies without a comparison group								
Hammers-Berggren, 1994 [106]	Denmark	Retrospective study	Erythema migrans and neuroborreliosis	2.5 years, median (3 month to 10 years)	23/91 (25)	n.a.	n.a.	5 patients (5%) incapacitated
Hammers-Berggren, 1994 [107]	Denmark	Undefined	Lyme arthritis and acrodermatitis chronica atrophicans	6 months to 5 years	9/41(22)	n.a.	n.a.	
Dersch, 2015 [51]	Various	Meta-analysis	Neuroborreliosis	7 days to 20 years	28% (95% confidence interval: 23–34%)	n.a.	n.a.	Prevalence of residual symptoms significantly higher in studies using the “possible” case definition (compared with “probable”/ “definite”)

n.a. = not applicable; PTLDS = post-treatment Lyme disease syndrome; RCT = randomised controlled trial

2 months of oral doxycycline; clinical response rates were documented after 3 months. The overall status improved in roughly one third of patients, remained unchanged in another one third, and deteriorated in one third of patients, and did not differ between the intervention and the placebo group.

Krupp et al. [30] included 55 patients with fatigue as key feature of the disease. Remarkably, the overwhelming majority of screened patients (512 individuals) were excluded because they lacked documentation of prior infection with *Borrelia* sp. Patients were randomised to intravenous ceftriaxone or placebo for 1 month. After 6 months, 69% of patients in the ceftriaxone arm reported improvement of fatigue as opposed to 23% in the placebo arm ($p < 0.01$). Remarkably, however, neither improvement in mental speed nor other measures from the neuropsychological test battery showed any significant difference between the groups. This is contradictory, since fatigue is in general highly correlated with other neuropsychological measures, such as mental speed. Given the very low number of actually treated patients and the multitude of different measurements, multiple testing may be a problem and is very likely the explanation for an isolated significant measurement. Moreover, masking was most probably compromised in this study. Thus, despite a single significant measurement, the authors concluded that repeated courses of antibiotics for PTLDS are not indicated.

Fallon et al. [31] included 37 patients in a prospective trial. The authors had a significant recruitment problem. Out of 3368 "clinic contacts", 1828 had no documented past infection with *B. burgdorferi*. The other 1503 had either received insufficient antibiotic treatment, were not sufficiently impaired or met other exclusion criteria. Eventually, 23 patients were randomised to receive intravenous antibiotic treatment for 10 weeks; 14 patients were given intravenous placebo. Additionally, 18 healthy individuals were recruited as "control group". Cognitive improvement between baseline and week 12 in the drug-treated patients was better than in the healthy controls ($p < 0.01$) and not significantly better than in the placebo-treated patients ($p = 0.053$), despite being referred to as significant in the paper. Given the low number of patients, the multitude of parameters tested, the highly selected patient population and, last but not least, the absence of statistical significance between the groups, these findings do not support extended antibiotic treatment for PTLDS.

A first double-blind, randomised clinical trial in Europe has recently been completed in the Netherlands. It compared 12 weeks of treatment with either doxycycline, clarithromycin plus hydroxychloroquine or placebo for patients with persistent symptoms after documented *B. burgdorferi* infection and an initial 2-week intravenous ceftriaxone treatment of all study participants [56]. Results of this study suggest that the physical component summary score improved significantly over time in all active treatment groups but that long-term antibiotic therapy was not associated with improved quality of life ($p = 0.35$). Importantly, four serious adverse events were thought to be related to drug use [57].

In summary, the data from these five randomised controlled trials suggest the following conclusions. First, between 20 and 30% of patients with PTLDS appear to improve over time with or without repeated antibiotic treatment. Second, out of 4955 screened patients in the trials of Klempner [29] and Fallon [31], 1963 (39.5%) were excluded because of the absence of documented Lyme borreliosis. Thus, a very large proportion of patients who attributed their symptoms to PTLDS had no evidence of Lyme borreliosis in the past. As pointed out in a thoughtful review by Klempner et al. [55], the trials had a total recruitment time of 123 months. Despite this lengthy total recruitment period, the investigators were able to include only 221 patients [55]. Finally, the results from the USA have now also been confirmed in European patients infected with European borrelial species [56, 57]. Thus, patient advocacy groups appear to consistently overstate the burden of disease attributed to PTLDS [58–60].

Possible pathogenesis of PTLDS

Pathogenic mechanisms that would lead to post-Lyme disease symptoms have not been identified so far. Possible mechanisms other than active infection (which is very unlikely), especially immune system abnormalities or infection-induced autoimmunity, have been suggested. Recently, Strle et al. [26] reported that in European patients with erythema migrans, mostly due to *B. afzelii*, high type 1 T-cell-associated CXCL9 and CXCL10 chemokine responses correlated with more effective immune-mediated spirochaetal killing, whereas high type 17 helper-T-cell-associated cytokines and interleukin 23-associated immune responses correlated with post-Lyme symptoms. Persisting symptoms in this cohort included arthralgias, headache and fatigue, which were not incapacitating and usually resolved within months after antibiotic therapy. However, concerns about the statistical interpretation of such immunological findings due to low statistical power have been raised [61]. Controversial results were reported on the association between humoral immune response to endothelial cell growth factor and PTLDS [47, 62]. Other potential aetiologies of PTLDS include antineural antibodies, bacterial debris and tissue destruction [63]. Chronic pain syndromes, fatigue or neurocognitive deficits were also considered to be a consequence of a central sensitisation syndrome that may be induced by infectious or noninfectious stimuli [64].

Table 6: Summary of randomised controlled trials on antibiotic treatment of post-treatment Lyme disease syndrome.

Study, reference, country	Inclusion criteria	Baseline characteristics	Observation time	Number of patients		Outcome	
				Intervention	Placebo	Intervention	Placebo
Klempner et al. (2 studies) [29], USA	Post-Lyme disease with physical and mental symptoms	Erythema migrans as initial presentation 77%; arthralgia 92%; fatigue 88%; neurocognitive symptoms 65%	3 months	57	58	23 (40%) improvement, 16 (28%) unchanged, 18 (32%) worse	21 (36%) improvement, 17 (29%) unchanged, 20 (34%) worse
Krupp et al. [30], USA	Post-Lyme disease with a focus on fatigue	Erythema migrans as initial presentation, 32.6%; lifetime history of psychiatric disorder, 63.5%	6 months	28	27	18/28 (64%) improvement*	5/27 (18.4%) improvement
Fallon et al. [31], USA	Post-Lyme disease syndrome	Erythema migrans as initial presentation, 54%; arthralgia, 100%; sensory abnormality, 100%	1 year	23	14	Significant improvement after 24 weeks	Significant improvement after 24 weeks
Berende et al. [56, 57], the Netherlands	Persistent symptoms attributed to Lyme borreliosis	Pain, sensory or cognitive disturbances	1 year	172 (two different treatment arms)	86	Significant improvement, not different between treatment arms	Significant improvement, not different from antibiotic treatment

* Despite a significantly better outcome in the treatment arm, this difference is not regarded as clinically relevant. Please refer to the text for further discussion of this matter.

Psychological or psychiatric premorbidity and PTLDS

Psychiatric comorbidity is frequent in many somatic illnesses. Psychogenic comorbidity is common because having an acute or chronic medical condition that restricts one's physical or social functions is depressing or anxiety-provoking, also among resilient individuals without any premorbid factors. In case of PTLDS, the debate rages as to whether PTLDS is a consequence of the patients' perceptions of the widely dispersed belief of the potentially most severe sequelae of Lyme borreliosis, whether premorbid psychological factors play an aetiological role in PTLDS, or whether PTLDS may represent a specific or nonspecific neurobehavioural response to illness [9, 65]. These discussions leave many of the patients frustrated and feeling stigmatised [66].

Among patients referred to Lyme borreliosis specialty clinics, many suffered from depression and somatic diseases other than Lyme borreliosis. In 209 patients from the Yale University Lyme Disease Clinic, 42% reported symptoms of depression, which in 16% was thought to represent primary depression [67]. This number is in line with a more recent investigation by Hassett et al. showing that over 45% of PTLDS patients had a major depressive episode [9]. Differentiating between psychiatric disorders and PLTDS remains challenging [9, 68, 69].

A limited number of studies exploring whether psychiatric comorbidity and PTLDS are causally related yielded contradictory results. Gaudino et al. reported that 26% of PTLDS patients had a psychiatric diagnosis before the onset of PTLDS [70]. In contrast, Hassett et al. were unable to detect an association between baseline psychiatric comorbidity and symptom persistence after treatment for proven Lyme borreliosis [9]. Based on their own prospective observations of patients with recent proven infections, Hassett et al. concluded that 13 to 32% had ongoing post-Lyme symptoms: these symptoms, however, were not primarily related to a psychiatric disorder but rather appeared to be the consequence of a complex interplay between biological, psychological and social factors [9, 71, 72]. Subjective symptoms had no objective correlate in most cases. In particular, in the majority of the cases, physical and neurocognitive examinations were unrevealing and without evidence of ongoing inflammation. Although not causal, psychological factors, including high negative affect and low positive affect – all psychological risk factors contributing to the general experience of psychological stress – appear to contribute to behavioural manifestations of PTLDS, and impact on the patient's subjective experience of illness [71].

Role of tick-borne co-infections and PTLDS

After a tick bite, co-infections may occur with pathogens such as tick borne-encephalitis virus, *Anaplasma phagocytophilum*, *Babesia microti* or other pathogens, and need – if present – specific antimicrobial treatment. A causative relationship of co-infections to PTLDS has not been established [73].

Differences and similarities between chronic fatigue, fibromyalgia and PTLDS

Many patients complaining about increased fatigue or generalised pain associate their condition with a preceding infection [74, 75]. Symptoms of PTLDS may have an aetiological and phenomenological overlap with chronic fatigue syndrome, fibromyalgia and other chronic pain syndromes. As shown in table 7, the diagnostic criteria of chronic fatigue and fibromyalgia do substantially overlap with PTLDS, and the clinical differentiation between fibromyalgia, chronic fatigue and PTLDS may, by definition, be blurred. However, the diagnosis of PTLDS requires a previously documented infection with *B. burgdorferi* and a plausible association between Lyme borreliosis and the beginning of persisting symptoms that were not present before the onset of *B. burgdorferi* infection.

Among the diseases under discussion, the onset of fibromyalgia was found to be subsequent to Lyme borreliosis [27], and *Borrelia* spp. infection has been implicated as the trigger for chronic fatigue as well [28]. Indeed, the temporal relationship between Lyme borreliosis and fibromyalgia may cause a diagnostic dilemma. This can easily be demonstrated in a study which aimed to systematically assess the development of fibromyalgia after Lyme borreliosis [28]. Out of 287 patients with confirmed Lyme borreliosis, 22 (8%) developed fibromyalgia, of whom 15 (5%) participated in the study; 14 patients had erythema migrans, 7 had CNS involvement, 1 patient had carditis and 6 had signs of late borreliosis. The symptoms of fibromyalgia included, among others, widespread joint and muscle pain, fatigue and sleep disturbances. None of the patients had these symptoms before documented Lyme borreliosis. Antibiotic treatment did not influence the clinical course. If the diagnostic criteria for PTLDS were applied (which were introduced only years after publication of this paper), all these patients would have fulfilled these diagnostic criteria and would have been diagnosed accordingly.

State of evidence for the existence of PTLDS

Data from prospective observational studies of previously healthy persons with Lyme borreliosis, as summarised in tables 5 and 6, and clinical experience suggest that there are patients who are essentially free of symptoms until they are infected with *B. burgdorferi*. After treatment, these patients initially show an adequate clinical response with resolution of clinical signs and symptoms, such as erythema migrans or other measurable signs. However, a small percentage of patients start to report fatigue, lack of concentration, musculoskeletal pain or other nonspecific symptoms. Despite comprehensive diagnostic evaluation, no other reasons for these symptoms can be identified, and there is no underlying premorbid or current psychopathology. The clinical course with resolving "acute" symptoms being replaced by nonspecific symptoms, the timely association of acute infection and persisting symptoms, serology and the lack of any other cause match the case definition of PTLDS.

Psychological factors have been suggested to play a role in the aetiology of PTLDS [71]. Indeed, Solomon et al. described a clear association between previous psychological trauma and chronic physical symptoms, such as PTLDS [65]. This observation leads to the hypothesis that a predisposing psychological condition may facilitate the development of PTLDS. Regarding the persistence of symptoms, Hassett et al. showed that functional status and lower positive affect were predictive of persistence of symptoms [71]. Unexpectedly, the functional status after Lyme borreliosis was not related to the functional status at baseline, suggesting that the severity of symptoms does not predict their persistence. The observation that positive affect influences clinical outcome has been described for other diseases such as the common cold [76].

Whether PTLDS is pathophysiologically different from other post-infectious syndromes remains unclear [77]. The aetiology notwithstanding, the clearly defined PTLDS, with an unambiguous clinical course and serology, is separate from post-Lyme sequelae with measurable or observable signs, such as persisting facial palsy, or other irreversible central or peripheral post-Lyme neural damage.

"Post hoc ergo propter hoc"

In our experience, the majority of patients with presumed post-Lyme symptoms do not fulfil the diagnostic criteria of PTLDS. This notion is supported by observations that more than half of patients recruited in randomised controlled trials of PTLDS had to be excluded because they failed to fulfil the diagnostic criteria [31]. Apparently, many patients wrongly attributed their present symptoms to a possible infection in the distant past, or linked their symptoms to a positive serology ("cum hoc ergo propter hoc"). There is research focusing on psychological and societal circumstances, "the contaminated milieu phenomenon", as suggested earlier [78–80], meaning that unscientific societal concepts or contexts of health and disease, errors in judgment by both clinicians and patients, the influence of misleading media reports, misinformation on the Internet, or self-serving support groups, bring patients to neglect any objective findings, such as lack of laboratory evidence for borrelial infection [81–84]. Also, it has been noted that individuals in a society that spends more on healthcare are more likely to consider themselves as sick [85].

Furthermore, individual vulnerability may influence the course of disease, as there is a strong link between a history of psychological trauma and development of chronic physical symptoms [65]. Indeed, psychiatric comorbidity was diagnosed in up to 48% of patients who consider themselves as having "chronic Lyme disease" [9]. Last but not least, misconceptions of some healthcare professionals contribute to iatropathogenesis of "chronic" Lyme borreliosis, by supporting unscientific views – often with substantial financial interests – about Lyme disease [86].

Treatment of PTLDS

Many treatment modalities have been propagated; most of them with no or little scientific evidence – and no proven effect. Among these, neither long-term, "aggressive" high-dose antibiotic combinations, cycling of different antibiotic regimens, nor hyperbaric oxygen, immunomodulators or psychotropic medication have been beneficial [28, 71, 87, 88], although medication for reducing pain or coexistent mood disorders may be tried.

In particular, there are no data suggesting that prolonged antibiotic retreatment after appropriate initial therapy of Lyme borreliosis has any benefit [55]. Claims for a "re-appraisal" of the concept are scientifically not valid [55, 89, 90]. In contrast, there are reports of deaths [91, 92] and substantial morbidity [93] associated with antibiotic therapy for unsubstantiated Lyme borreliosis. Finally, there is no evidence for specific treatment for PTLDS.

Table 7: Definitions of chronic fatigue syndrome and fibromyalgia.

Case definition of CFS from US Centers for Disease Control and Prevention [108]	**Fibromyalgia diagnostic criteria [108]**
Characterised by persistent or relapsing unexplained chronic fatigue	*A patient fulfils the diagnostic criteria for fibromyalgia if the following 3 conditions are met:*
• Fatigue lasts for at least 6 months • Fatigue is of new or definite onset • Fatigue is not the result of an organic disease or of continuing exertion • Fatigue is not alleviated by rest • Fatigue results in a substantial reduction in previous occupational, educational, social and personal activities plus • Four or more of the following symptoms, concurrently present for 6 months: – impaired memory or concentration – sore throat – tender cervical or axillary lymph nodes – muscle pain – pain in several joints – new headaches – unrefreshing sleep – or malaise after exertion	• Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3–6 and SS scale score ≥9 • Symptoms (fatigue, waking unrefreshed, cognitive symptoms) have been present at a similar level for at least 3 months • The patient does not have a disorder that would otherwise explain the pain
Exclusion criteria	*Exclusion criteria*
• Medical condition explaining fatigue • Major depressive disorder (psychotic features) or bipolar disorder • Schizophrenia, dementia or delusional disorder • Anorexia nervosa, bulimia nervosa • Alcohol or substance abuse • Severe obesity	• Exclusion of all potentially relevant somatic diseases and psychiatric diseases

Given the substantial overlap of symptoms between chronic fatigue syndrome, fibromyalgia, chronic fatigue-like syndromes and PTLDS, and based on randomised controlled trials on patients with chronic fatigue-like symptoms, treatment recommendations for PTLDS mainly include nonpharmacological approaches: counselling, regular low-impact aerobic exercise programmes, and cognitive behavioural therapy [28, 87]. A corresponding concept, ExPRESS (E stands for exercise; P stands for psychiatric comorbidity; R stands for regaining function with emphasis on realistic goals and regular activity; E stands for education; S for sleep; and the final S for stress and the need to manage and reduce it), has been introduced by Hassett and Gevirtz for the treatment of fibromyalgia, but might also be a promising approach for the treatment of PTLDS [94].

Conclusions

The case definitions of PTLDS by the Swiss Society for Infectious Diseases, published in 2005, and by the Infectious Diseases Society of America, published in 2006, guide clinicians and health insureres in the evaluation and treatment of post-Lyme disease symptoms (table 1). We found no further data, particularly no prospective controlled studies on Lyme borreliosis, which may change these decade-old case definitions. For the diagnosis of PTLDS, a set of fact-based diagnostic criteria has to be fulfilled. Importantly, positive Lyme serology without previous defined clinical manifestations of Lyme borreliosis does not qualify for the diagnosis of PTLDS, given the high prevalence of asymptomatic seropositivity in populations living in endemic areas.

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