Chronic Lyme Disease: A Working Case Definition

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Abstract
Although Lyme disease is the most common tickborne illness in the USA and Eurasia, the pathophysiology and clinical course of chronic Lyme disease (CLD) have not been formally defined. The purpose of this paper is to present a working case definition of CLD based on analysis of more than 700 peer-reviewed publications. According to this definition, CLD is a multisystem illness with diverse musculoskeletal, neuropsychiatric and/or cardiovascular manifestations that result from ongoing infection with pathogenic members of the *Borrelia* spirochete complex often associated with other tickborne disease (TBD) pathogens. To qualify for the diagnosis of CLD, patients must have Lyme-compatible symptoms and signs that are either consistently or variably present for six or more months. Two subcategories of CLD include untreated chronic Lyme disease (CLD-U) and chronic Lyme disease following a limited course of antibiotic treatment (CLD-T). The symptom patterns and optimal therapy of CLD require further study.

Keywords: Lyme disease; *Borrelia burgdorferi_; Tickborne disease; Chronic infection

Introduction

Lyme disease caused by the spirochete *Borrelia burgdorferi* (Bb) is the most common tickborne illness in the USA and Eurasia [1-5]. The Centers for Disease Control and Prevention (CDC) estimates that at least 300,000 new cases of Lyme disease are diagnosed each year in the USA, and a recent study projects that at least 232,000 new Lyme disease cases occur annually in Western Europe [2,3]. Lyme disease is often characterized as early localized (Stage I), early disseminated (Stage II) or late (Stage III) [4,5]. Although Bb is the best known *Borrelia* genospecies that causes Lyme disease, other *Borrelia* genospecies and associated TBD pathogens may cause similar symptoms due to dissemination of the infectious agents [5]. Bb and associated pathogens have the capacity to invade a variety of eukaryotic cells and tissues including fibroblasts, synovium, skin, ligaments, cardiac tissue, glial and neuronal cells, endothelial cells, lymph nodes and tonsillar lymphoid tissue [6-18].

We propose a working case definition of chronic Lyme disease (CLD) based on evidence that Bb and associated pathogens may cause persistent infection that correlates clinically with invasion of the diverse cells and tissues described above [5,19-25]. The resultant chronic illness may be found in patients with undiagnosed Lyme disease or in patients with an inadequate response to TBD treatment, as outlined below.

Components of CLD

Length of infection

In order to define the chronic form of Lyme disease, it is first necessary to define the minimum duration of the medical condition. Goodman et al. [26], describe the lack of standardization for the definition of chronic medical diseases. The required duration of chronic illness has ranged from more than three months to more than twelve months [27-32] and some researchers have suggested that the medical condition needs to be permanent to qualify [33,34]. In the setting of infectious disease in general, the term “chronic” often implies a minimum duration of six months, and with chronic *Pseudomonas* and *Mycobacterial* infections the chronically infecting pathogens may be capable of “evading or subverting the immune response” to “establish chronic infection with a time course of years to decades, often resulting in persistent inflammation and disease” [35,36]. In the case of TBDs, this process often becomes established and persists after 3-6 months of untreated or inadequately treated infection [5,24,25]. Therefore we define CLD as persistent TBD infection of at least six months’ duration, although we emphasize that treatment should not be withheld for individuals presenting with all the criteria discussed in this paper except for the duration. In addition, we recognize other challenges including the often uncertain nature of symptom onset and the variability of musculoskeletal, neuropsychiatric and cardiovascular symptoms and signs induced by TBDs (see section on Clinical Manifestations below).

Vector exposure

The primary vectors of Lyme disease are members of the *Ixodes* genus of ticks. In the USA, *Ixodes scapularis* transmits disease in the Eastern and Midwestern states and *Ixodes pacificus* in the West [4,5]. The European vector of Lyme disease is *I. ricinus*, and the Eurasian vector is *I. persulcatus* [3-5]. *Ixodes* ticks have a complex life cycle extending over two to three years. Ticks feed as larvae, nymphs, and female adults. Each feeding is an opportunity to acquire TBD pathogens, and the nymphal and adult feedings allow for disease transmission. Nymphal ticks transmit disease more often than adults, presumably because their small size increases the likelihood that they will go undetected during feeding [37,38]. *Ixodes* ticks live in wooded, brushy areas, and tick exposure may be greatest along trails in the woods and at the fringe area where the woods end [37,38]. Ticks may also be found in backyard gardens and on wooden structures [39]. Reservoir hosts vary by region and may include mice, chipmunks, shrews, squirrels and other small mammals; humans and domesticated animals are incidental hosts [40,41]. Deer play...
an important role in tick reproduction and dispersal, and migratory birds may transport ticks to regions previously thought to be non-endemic for Lyme disease [42-45].

Microbiology

CLD may be caused by any of the known pathogenic *Borrelia* genospecies and associated TBD pathogens including *Babesia*, *Anaplasmata*, *Ehrlichia*, *Rickettsia*, *Powassan* virus and possibly *Bartonella*. In the USA, Lyme disease is primarily associated with *B. burgdorferi sensu stricto* (*Bbs*), while in Europe, *B. afzelii*, *B. garinii* and *Bbss* are found in the majority of cases [3-5]. The worldwide distribution and pathogenicity of novel *Borrelia* genospecies such as *B. miyamotoi*, *B. mayonii*, *B. bissettii*, *B. kurtenbachii*, *B. andersoni*, *B. americana* and others remain to be fully characterized [46-51]. Genospecies of *Borrelia* and strains within a given genospecies differ in their clinical presentations, antigenic profiles and response to host immunity [52,53]. These differences may limit a clinician’s ability to recognize the infection, render some diagnostic tests insensitive and possibly increase the risk of developing CLD [52,53]. The role of associated TBD pathogens in patients with CLD is discussed below.

Laboratory testing for Lyme disease

As the CDC acknowledges, “The Lyme disease surveillance case definition was developed to standardize national public health surveillance and reporting of Lyme disease cases; it is not meant to be used as absolute criteria for clinical diagnosis” [1]. Criteria generated for epidemiologic surveillance purposes are often inadequate for the diagnosis of Lyme disease. In fact, the two-tiered testing paradigm of Enzyme-Linked Immunosorbent Assay (ELISA) or Immunofluorescent Assay (IFA) screen and Western blot confirmation is positive in less than 30% of patients with early Lyme disease and in only 46% of patients with Lyme disease for more than six weeks [54-63]. Factors contributing to the insensitivity of Lyme disease testing include use of a single laboratory strain of *Bb* and omission of significant *Borrelia* antigens on the Western blot, emphasis on commercial test specificity rather than sensitivity, gender bias in Western blot interpretation, and the presence of other TBDs [64-67]. The allegedly high sensitivity of two-tiered testing in CLD requires further study.

Categories of CLD

Untreated chronic Lyme disease (CLD-U)

Patients whose exposure was not clearly identified and thus have prolonged untreated infection.

CLD may be the consequence of diagnostic delays, and early recognition of the infection is frequently hindered by the failure to recognize or report a tick bite. For example, one study found that only 14% of patients recalled a tick bite at the site of an EM rash [80]. Thus, a history of potential exposure to *Ixodes* ticks is an important element in the definition of CLD, documentation of a known tick bite is not required.

Many patients may also be unaware of their exposure risks, and clinicians will need to carefully inquire about potential exposures based on a patient’s residential, occupational, recreational and travel history. As stated above, *Ixodes* ticks prefer wooded or brushy areas, and exposure risk is correspondingly high in these areas [38,39]. Tick exposure may also occur through contact with reservoir animals or with other incidental tick hosts including deer, birds and pets.

Another problem is the variable incidence of the EM rash, which ranges from 27% to 70% in Lyme disease studies [81,82]. The CDC found that patients lacked an EM rash in 30% of cases that were diagnosed using the surveillance case definition [1]. The recognition of early Lyme disease may be delayed when the hallmark EM rash is absent or misidentified.

Chronic Lyme disease following limited antibiotic treatment (CLD-T)

Patients who were diagnosed with Lyme disease and completed a limited course of antibiotic therapy, but whose symptoms persist.

This category differs from “Post-Treatment Lyme Disease Syndrome” (PTLDS), a research case definition proposed by the Infectious Diseases Society of America (IDSA) that excludes ongoing TBD infection as the cause of persistent CLD symptoms. In contrast, CLD-T requires that patients had been diagnosed with Lyme disease and treated with a limited course of antibiotic therapy (generally < 4 weeks), but that the treatment regimen was inadequate to resolve the infection and that the symptoms persisted or recurred within six months after completion of treatment without a new tick exposure. Clinicians and researchers have recognized that a substantial portion
of patients remain ill following a limited course of antibiotic treatment for Lyme disease [83-87].

While a relatively short course of appropriately directed antimicrobials may be adequate for individuals who are treated early in the Lyme disease process, treatment is frequently not curative, raising the possibility of TBD pathogen survival [88-96]. Persistent TBD infection in animals and humans involves potential roles for multiple mechanisms:

1. Immune evasion via physical seclusion of pathogens within immunologically protected tissue sites such as the central nervous system, joints, eyes, connective tissue and genital tract [88-96].

2. Alterations in Outer surface protein (Osp) profiles of pathogens through antigenic variation [95-99] and alteration in pathogen morphology (including cell-wall deficient forms, spherocytes, round bodies and biofilm aggregates) [100-107].

3. Immune modulation via complement interference, neutrophil and dendritic cell dysfunction and cytokine/chemokine alterations [108-115].

4. Generation of antibiotic-tolerant “persister cells” in some pathogen populations [116-118].

Clinical Manifestations of CLD

Lyme disease is a multisystem illness that is often referred to as the “new great imitator” due to the diversity of its clinical manifestations that are reminiscent of syphilis [119-123]. The wide spectrum of clinical features can range from an EM rash to severe arthritis, carditis or neuropsychiatric symptoms [4,5]. Another clinical feature often associated with this condition is the Jarisch-Herxheimer reaction whereby symptoms increase after exposure to antimicrobials [124-131]. This is a phenomenon associated with the treatment of spirochetal diseases such as syphilis, louse-borne relapsing fever, leptospirosis and Lyme disease [124-131]. Recent studies suggest that the Jarisch-Herxheimer reaction is triggered by rapid uptake of damaged spirochetes by neutrophils and mononuclear cells with release of lipoproteins and pyrogens that increase inflammatory cytokines [131]. To date, the complete mechanism of this phenomenon remains undefined.

Since clinical features of Lyme disease may change following exposure to antimicrobials, we have proposed two categories for this working case definition of CLD, as outlined above. For CLD-U, the natural course without antimicrobial intervention has been described by Steere et al. in the USA [19,132]. Prior to recognition of the importance of antimicrobial therapy, untreated patients with EM rash displayed the following characteristic clinical features over six years of follow-up: 62% developed intermittent or persistent arthritis; 18% developed arthralgias; 11% developed neurologic abnormalities; 4% developed cardiac complications; 33% developed fatigue; and 33% developed other symptoms and signs including headache, stiff neck, morning stiffness, myalgias and abdominal pain [132]. Further characteristics of CLD-U patients have been described by Wormser et al. in the 2006 IDSA Lyme guidelines [4]. Based on clinical diagnosis with serological confirmation using CDC surveillance criteria, later stages of Lyme disease may feature prominent multisystem symptoms and signs as described above [1,4,5].

Table 1: Untreated chronic Lyme disease (CLD-U)*

| Symptom/Sign             | No. of patients | Category          |
|--------------------------|-----------------|-------------------|
| Chest Pain               | 1               | Cardiovascular    |
| Fibrillation             | 1               | Cardiovascular    |
| Flutter                  | 1               | Cardiovascular    |
| Murmur                   | 1               | Cardiovascular    |
| Myocardial Infarction    | 1               | Cardiovascular    |
| Myocarditis              | 1               | Cardiovascular    |
| Myopericarditis          | 1               | Cardiovascular    |
| Muscle Atrophy           | 1               | Musculoskeletal   |
| Synovitis                | 3               | Musculoskeletal   |
| Tenosynovitis            | 1               | Musculoskeletal   |
| Arthralgia (joint pain)  | 6               | Musculoskeletal   |
| Arthritis                | 6               | Musculoskeletal   |
| Dactylitis               | 1               | Musculoskeletal   |
| Joint Warmth             | 1               | Musculoskeletal   |
| Muscle Weakness          | 2               | Musculoskeletal   |
| Musculoskeletal Pain     | 1               | Musculoskeletal   |
| Periartorial Edema       | 1               | Musculoskeletal   |
| Encephalomyelitis        | 1               | Neuropsychiatric  |
| Paraparesis              | 1               | Neuropsychiatric  |
| Encephalopathy           | 1               | Neuropsychiatric  |
| Neuropathy               | 2               | Neuropsychiatric  |
| Optic Neuritis           | 2               | Neuropsychiatric  |
| Transient Ischemic Attack| 1               | Neuropsychiatric  |
| Blurred Vision           | 2               | Neuropsychiatric  |
| Eye Pain                 | 1               | Neuropsychiatric  |
| Facial Pain              | 1               | Neuropsychiatric  |
| Fatigue                  | 2               | Neuropsychiatric  |
| Headaches                | 3               | Neuropsychiatric  |
| Hypesthesia              | 1               | Neuropsychiatric  |
| Memory Difficulties      | 1               | Neuropsychiatric  |
| Photophobia              | 1               | Neuropsychiatric  |
| Progressive Visual Loss  | 2               | Neuropsychiatric  |
| Plosis                   | 1               | Neuropsychiatric  |
| Radicular Pain           | 3               | Neuropsychiatric  |
| Restriction of Visual Field | 1            | Neuropsychiatric  |
| Tinnitus                 | 1               | Neuropsychiatric  |
| Vertigo                  | 1               | Neuropsychiatric  |
| Total: 37                | Total: 59       |                   |

*Symptoms and signs of chronic Lyme disease without antibiotic treatment (CLD-U). Symptoms/signs were associated with positive B. burgdorferi culture, PCR or microscopy.

Symptom/Sign Category:
- a) Musculoskeletal (%) - 23/59 (39)
- b) Neuropsychiatric (%) - 29/59 (49)
- c) Cardiovascular (%) - 7/59 (12)

In contrast to CLD-U, CLD-T is a term used to describe individuals who have been treated for TBDs with a limited course of antibiotics.
(generally < four weeks) and within six months develop persistent or recurrent and functionally significant fatigue, musculoskeletal pain, cardiovascular disease and/or neuropsychiatric dysfunction that persists for six months or more [133,134]. CLD-T acknowledges the extensive published evidence for persistent TBD infection despite a limited course of antibiotic therapy. In contrast, the research case definition for PTLDS proposed by IDSA includes the following statement: “There is no convincing biologic evidence for the existence of symptomatic chronic B. burgdorferi infection among patients after receipt of recommended treatment regimens for Lyme disease” [4]. Based on animal models and human studies, however, we propose that treatment with limited antibiotic regimens may not consistently clear the infection, and we have provided evidence to support potential mechanisms by which this persistent infection occurs (see above). Thus Lyme patients who remain symptomatic following a limited course of antibiotic therapy likely have an ongoing, active TBD infection similar to CLD-U patients. We characterize this group as having CLD-T.

Other conditions that can mimic the clinical presentation of CLD must be ruled out. However, the diagnosis of “idiopathic” conditions such as multiple sclerosis, motor neuron disease, fibromyalgia or chronic fatigue syndrome is insufficient to rule out the presence of CLD. We analyzed more than 700 peer-reviewed publications featuring symptoms and signs associated with both forms of CLD from a MEDLINE search (Appendix A). From this list, we chose 16 studies that describe symptoms and signs in patients with CLD-U and 13 studies that describe symptoms and signs in patients with CLD-T (Appendix B). In these 29 studies, persistent Bb infection was documented by culture, PCR and/or microscopy, while other studies without this stringent documentation were excluded.

The symptom profiles in patients with persistent Bb infection are indicative of the protean manifestations of CLD. In our representative sample, patients with CLD-U appeared to have relatively more musculoskeletal and cardiovascular symptoms and signs, while patients with CLD-T appeared to have relatively more neuropsychiatric symptoms and signs (Tables 1 and 2). The broader pathology in untreated patients versus more restricted pathology following limited treatment is reminiscent of the immunopathology patterns in untreated versus initially-treated syphilis [134]. To date, however, the number of studies with stringent documentation of persistent Bb infection is too small to draw definitive conclusions about patterns of symptoms and signs in CLD patients. Further comparison of symptom profiles associated with the two forms of CLD is warranted.

Co-Infections

In both categories of persistent Bb infection, the presence of other TBD pathogens may complicate the diagnosis and treatment of Lyme disease. *Ixodes* ticks are known to carry more than 237 species of bacteria and at least 26 viruses [138-142]. Some of these organisms, frequently referred to as co-infections, may alter the manifestations of Lyme disease and make it more difficult to eradicate the spirochete. Known co-infecting organisms include *Babesia, Ehrlichia/Anaplasma, Rickettsia* and Powassan virus [138-142]. Additionally, the evidence supporting tickborne *Bartonella* infection is growing [143,144]. The interplay of other infectious agents with Bb infection may be an important factor in the persistence of symptoms.

### Table 2: Chronic Lyme disease following limited antibiotic treatment (CLD-T)*

| Symptom/sign                          | No. of patients | Category          |
|---------------------------------------|----------------|-------------------|
| Muscle Atrophy                        | 1              | Musculoskeletal   |
| Fibromyalgia                          | 1              | Musculoskeletal   |
| Meningismus                           | 1              | Musculoskeletal   |
| Synovitis                             | 1              | Musculoskeletal   |
| Tenosynovitis                         | 1              | Musculoskeletal   |
| Arthralgia (joint pain)               | 7              | Musculoskeletal   |
| Arthritis                             | 3              | Musculoskeletal   |
| Migratory Pain                        | 1              | Musculoskeletal   |
| Muscle Stiffness                      | 1              | Musculoskeletal   |
| Muscle Weakness                       | 1              | Musculoskeletal   |
| Musculoskeletal Pain                  | 1              | Musculoskeletal   |
| Myalgia                               | 3              | Musculoskeletal   |
| Torticollis                           | 1              | Musculoskeletal   |
| Trigger Finger                        | 1              | Musculoskeletal   |
| Dementia                              | 1              | Neuropsychiatric  |
| Parkinsonism                          | 1              | Neuropsychiatric  |
| Depressed Corneal Reflexes            | 1              | Neuropsychiatric  |
| Hemiapresia                           | 1              | Neuropsychiatric  |
| Recurrent encephalomyeloradiculopathy | 1              | Neuropsychiatric  |
| Trigeminal Sensory Neuropathy         | 1              | Neuropsychiatric  |
| Blunted Affect                        | 1              | Neuropsychiatric  |
| Cognitive Dysfunction                 | 3              | Neuropsychiatric  |
| Cogwheel Rigidity                     | 1              | Neuropsychiatric  |
| Confusion                             | 1              | Neuropsychiatric  |
| Decreased Central Vision              | 1              | Neuropsychiatric  |
| Decreased Verbal Fluency              | 1              | Neuropsychiatric  |
| Depression                            | 1              | Neuropsychiatric  |
| Difficulty Naming Objects             | 1              | Neuropsychiatric  |
| Disorientation                        | 2              | Neuropsychiatric  |
| Drooling                              | 1              | Neuropsychiatric  |
| Fatigue                               | 4              | Neuropsychiatric  |
| Fullness in head                      | 1              | Neuropsychiatric  |
| Headaches                             | 3              | Neuropsychiatric  |
| Hypalgesia                            | 1              | Neuropsychiatric  |
| Hypesthesia                           | 2              | Neuropsychiatric  |
| Impaired Judgment                     | 1              | Neuropsychiatric  |
| Impaired Swallowing                    | 1              | Neuropsychiatric  |
| Memory Difficulties                   | 3              | Neuropsychiatric  |
| Numbness                              | 2              | Neuropsychiatric  |
| Paresthesias                          | 3              | Neuropsychiatric  |
| Perseveration                         | 1              | Neuropsychiatric  |
| Poor Concentration                    | 2              | Neuropsychiatric  |
| Poor Initiation                       | 1              | Neuropsychiatric  |
| Radicular Pain                        | 1              | Neuropsychiatric  |
| Tinnitus                              | 2              | Neuropsychiatric  |
| Tremors                               | 1              | Neuropsychiatric  |
| Vertigo                               | 1              | Neuropsychiatric  |

| Total: 47                             | Total: 73      | (13 Studies)      |

*Symptoms and signs of chronic Lyme disease following limited antibiotic treatment (CLD-T). Symptoms/signs were associated with positive *B. burgdorferi* culture, PCR or microscopy.

**Symptom/Sign Category:**

a) Musculoskeletal (%) - 24/73 (33)
b) Neuropsychiatric (%) - 49/73 (67)
c) Cardiovascular (%) - 0/73 (0)
treated Lyme disease patients had persistent symptoms of CLD, and with no evidence of TBDs. The study found that as many as 63% of those treated for Lyme disease were compared to 263,975 matched controls from medical claims over five years in the USA, 52,795 individuals recently provided by Adrion et al [150]. Based on retrospective data, the four levels of diagnostic criteria are as follows:

### Table 3: Proposed Diagnostic Criteria for CLD*

| Required criteria | Strongly supportive criteria | Supportive criteria | Additional criteria |
|-------------------|-----------------------------|--------------------|---------------------|
| 1. Presence of clinical symptoms and/or signs consistent with Bb infection and/or associated TBDs, as described in Tables 1 and 2 that adversely impact patient quality of life. | 1. Positive culture, molecular testing, or some other technology that directly identifies the presence of Bb spirochetes and/or associated TBD pathogens. | 1. History of EM rash. (Although this clinical sign is diagnostic of Lyme disease, absence of the rash does not rule out Bb infection). | Response to antibiotic intervention |
| 2. Symptom duration greater than six months, either without antibiotic treatment (CLD-U) (1) or following a limited course of antibiotic treatment for Lyme disease (CLD-T) (2). | 2. Positive serological testing (3). a. Fulfills CDC surveillance criteria for Bb-related Western blot testing. b. Fulfills Ma/Engstrom criteria for seroreactivity with at least 2/6 highly specific Bb-related bands on Western blot (23-25, 31, 34, 39, 41, 83-93). Note that this could be either IgG or IgM seroreactivity. c. Seropositivity for Bb-associated TBD pathogens. | 2. Known or possible tick bite: a. Bite from a disease carrying-tick (often not recognized). b. Risk of tick exposure. 1. Individuals residing in a Lyme endemic area may be exposed through: Work, recreation and daily activities 2. Individuals not residing in a Lyme endemic area may be exposed through: Travel to endemic areas or expansion of the tick range into previously non-endemic area. | 2. Development of a Jarisch-Herxheimer reaction. |
| 3. Exclusion of other medical conditions that can completely account for the clinical presentation. Note that unless another disorder can fully explain the entire spectrum of the clinical presentation, the comorbid condition cannot independently rule out CLD. | - | - | - |

**NOTES:**

1. This diagnosis relies on clinical judgment. The more supportive clinical criteria are met, the greater the likelihood of the diagnosis. This cumulative approach emphasizes the limitations of reliable Lyme disease diagnostic testing at the time of publication, as outlined in the ILADS Lyme guidelines [5].

2. This diagnosis requires a history of limited antibiotic treatment for Lyme disease (generally < four weeks) within the previous six months, as outlined in the IDSA Lyme guidelines [4].

3. Testing should be performed by a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory, but the tests do not need Food and Drug Administration (FDA) approval.

*CLD, chronic Lyme disease; Bb, Borrelia burgdorferi; TBD, tickborne disease; EM, erythema migrans.

may complicate the clinical presentation of Lyme disease and prolong the duration of infection, as noted in animal models [145-147]. The effect of co-infecting TBD pathogens on the evolution of CLD merits further study in humans.

**Functional Impact of CLD**

A community-based study of CLD patients found that the Quality of Life (QoL) of these patients was the same or worse compared to that of individuals with depression, diabetes, heart disease, osteoarthritis and rheumatoid arthritis [148]. Using a CDC metric of health-related QoL, a second survey of more than 5,000 respondents with CLD emphasized the limitations of reliable Lyme disease diagnostic testing at the time of publication, as outlined in the ILADS Lyme guidelines [5]. Further support for the adverse impact of CLD was recently provided by Adrion et al [150]. Based on retrospective data from medical claims over five years in the USA, 52,795 individuals treated for Lyme disease were compared to 263,975 matched controls with no evidence of TBDs. The study found that as many as 63% of treated Lyme disease patients had persistent symptoms of CLD, and that Lyme disease was associated with $2,968 higher total health care costs (95% CI: $2,807- $3,128, p<0.001) and 87% more outpatient doctor visits (95% CI: 86%-89%, p<0.001) over a 12 month period compared to TBD-negative controls [150,151]. A more recent study from the Netherlands found that the annual cost of treatment for CLD was €5700 (about $6300) per patient or a total of €19.3 million ($21 million) per year in that country [152].

We recognize that there may be other contributing and at times independent causes for persistent symptoms in CLD patients. In essence, not all patients who remain symptomatic after being treated for Lyme disease suffer from an active, ongoing infection. Proposed mechanisms of persistent symptoms include immune dysregulation of various types, tissue injury, infection-induced secondary conditions and unrelated diseases [153,154]. Based on the clinical evidence, however, we assert that a potentially large number of individuals with CLD are adversely impacted by persistent TBD infection associated with significant functional limitations and financial burdens [148-151]. We hope that technological advances in the characterization of ongoing TBD infection will improve our ability to deal with this condition.

**Clinical Judgment**

Until technological advances provide reliably sensitive and
specific diagnostics, some patients will continue to have a diagnosis that remains unclear. Under these circumstances, the value of clinical judgment will remain an important component in treating these individuals. According to the American Medical Association Code of Medical Ethics, the primary responsibilities of clinical medicine are to alleviate patient suffering and prevent disease [155]. As previously described by Johnson et al [149] and Cameron et al [156,157], patients with CLD are often quite ill, and physicians are charged with finding balanced and effective management strategies for such patients.

Uncertainty about a CLD diagnosis may confound clinical decision making, but clinical uncertainty should not exclude that diagnosis. This process involves both inclusionary and exclusionary criteria. Patient care is dynamic, and clinical judgment requires vigilance in assessing clinical outcomes. As described by Kienle and Kiene, “Clinical judgment is a central element of the medical profession, essential for the performance of the doctor” [158]. Thus given the current absence of a “gold standard” test for Lyme disease, it is essential that healthcare providers should consider this condition if symptoms and/or clinical signs occur in patients with a history consistent with CLD, as summarized in the guidelines of the International Lyme and Associated Diseases Society (ILADS) [5].

Proposed Diagnostic Criteria for CLD

The proposed diagnostic criteria for CLD are shown in Table 3.

Conclusions

This is the first study that provides a working case definition of chronic Lyme disease (CLD) and its subcategories. We propose that CLD is the result of persistent, active infection by pathogenic members of the Borrelia spirochete complex often associated with other TBD pathogens. Infection with these organisms produces a wide array of symptoms and signs that may be expressed in a given individual during the course of the chronic illness [5,122]. Whether due to delayed diagnosis (CLD-U) or as a result of persistence after a limited course of antibiotic treatment (CLD-T), these symptoms and signs may fluctuate but are required to have cumulatively persisted for at least six months.

At this time, clinically available diagnostic testing does not consistently allow for identification of the pathogen(s) affecting individuals with CLD. As such, a hallmark feature of our working case definition is reliance on clinical judgment. This process includes the use of supportive diagnostics, but it does not require laboratory confirmation in light of present technological limitations of TBD testing. We recognize that as diagnostic testing evolves, the ability to define this entity should improve.

We also recognize that other diagnoses may be responsible for symptoms and signs that are similar to CLD and need to be considered in CLD patients. We hope that this outline will provide the clinician with a framework to weigh management options for these often significantly debilitated patients. We also hope to provide additional impetus for public policy to recognize the growing risk of the Lyme disease epidemic. Lastly, we encourage researchers to use the proposed definition of CLD to improve laboratory methodology for identifying patients with this condition, and to facilitate the development of new treatment options for CLD patients.

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References

1. Bacon RM, Kugeler KJ, Madow PS. Surveillance for Lyme disease — United States, 1992–2006. MMWR 2008; 5: 71–79.
2. Centers for Disease Control & Prevention. How many people get Lyme disease?
3. Sykes RA, Makiepo P. An estimate of Lyme borreliosis incidence in Western Europe. J Public Health (Oxf). 2017; 39: 74-81.
4. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steege AC, Klempner MS, 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: 1089-1134.
5. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2012; 11: 1103–1135.
6. Klempner MS, Noring R, Rogers RA. Invasion of human skin fibroblasts by the Lyme disease spirochete, Borrelia burgdorferi. J Infect Dis. 1993; 167: 1074-1081.
7. Georgilis K, Peacocke M, Klempner MS. Fibroblasts protect the Lyme disease spirochete, Borrelia burgdorferi, from ceftriaxone in vitro. J Infect Dis. 1992; 166: 440-444.
8. Snydman DR, Schenkein DP, Berardi VP, Lastavica CC, Pariser KM. Borrelia burgdorferi in joint fluid in chronic Lyme arthritis. Ann Intern Med. 1996; 104: 795-800.
9. Haupl T, Hahn G, Rittig M, Krause A, Schoerner C, Schönher U, et al. Persistence of Borrelia burgdorferi in ligamentous tissue from a patient with chronic Lyme borreliosis. Arthritis Rheum. 1993; 36: 1612-1626.
10. Gischick HJ, Huppert HZ, Rüssmann H, Krenn V, Karch H. Intracellular persistence of Borrelia burgdorferi in human synovial cells. Rheumatol Int. 1996; 16: 125-132.
11. Valesova M, Tmavsky K, Hulinska D, Alusik S, Janousek J, Jirous J. Detection of Borrelia in the synovial tissue from a patient with Lyme borreliosis by electron microscopy. J Rheumatol. 1989; 16: 1502-1505.
12. Nanagara R, Duray PH, Schumacher HR. Ultrastructural demonstration of spirochetal antigens in synovial fluid and synovial membrane in chronic Lyme disease: possible factors contributing to persistence of organisms. Hum Pathol. 1996; 27: 1025-1034.
13. Aebeler E, Kersten A, Klade H, Poltscheek C, Jurecka W. Heterogeneity of Borrelia burgdorferi in the skin. Am J Dermatopathol. 1996; 18: 571-579.
14. Stanek G, Klein J, Bittner R, Glogar D. Isolation of Borrelia burgdorferi from the myocardium of a patient with longstanding cardiomyopathy. N Engl J Med. 1990; 322: 249-252.
15. de Koning J, Hoogkamp-Korstanje JA, van der Linde MR, Crijns HJ. Demonstration of spirochetes in cardiac biopsies of patients with Lyme disease. J Infect Dis. 1989; 160: 150-153.
16. Livengood JA, Gilmore RD. Invasion of human neuronal and glial cells by an infectious strain of Borrelia burgdorferi. Microbes Infect. 2006; 8: 2832-2840.
17. Ma Y, Sturrock A, Weis JJ. Intracellular localization of Borrelia burgdorferi within human endothelial cells. Infect Immun. 1991; 59: 671-678.

18. Dorward DW, Fischer ER, Brooks DM. Invasion and cytopathic killing of human lymphocytes by spirochaetes causing Lyme disease. Clin Infect Dis. 1997; 25: 52-58.

19. Szer IS, Taylor E, Steere AC. The long-term course of Lyme arthritis in children. N Engl J Med. 1991; 325: 159-163.

20. Borgermans L, Godeuris G, Vandevoorde J, Devroey D. Relevance of chronic Lyme disease to family medicine as a complex multidimensional chronic disease construct: A systematic review. Int J Family Med. 2014; 2014: 138016.

21. Oksi J, Marjamäki M, Nikoskelainen J, Viljanen MK. Borrelia burgdorferi detected by culture in clinical relapse. Ann Med. 1999; 31: 225-232.

22. Fallon BA, Petkova E, Keilp JG, Britton CB. A reappraisal of the U.S. clinical trials of post-treatment Lyme disease syndrome. Open Neurol J. 2012; 6: 79-87.

23. Miklossy J, Donta S, Mueller K, Nolte O, Perry G. Chronic or late Lyme neuroborreliosis: Present and future. Open Neurology J. 2012; 6: 78.

24. Donta ST. Macrolide therapy of chronic Lyme disease. Med Sci Monit. 2003; 9: 136-142.

25. Donta ST. Tetracycline therapy for chronic Lyme disease. Clin Infect Dis. 1997; 25: 552-556.

26. Goodman RA, Posner SF, Huang ES, Parekh AK, Koh HK. Defining and measuring chronic conditions: Implications for research, policy, program and practice. Prev Chronic Dis 2013; 10: 120239.

27. US Department of Health and Human Services. Health, United States, 2010, with special feature on death and dying. Hyattsville (MD): National Center for Health Statistics; 2011. 2017.

28. Hwang W, Weller W, Irey H, Anderson G. Out-of-pocket medical spending for care of chronic conditions. Health Aff (Millwood). 2001; 20:267-278.

29. Warshaw G. Introduction: advances and challenges in care of older people with chronic illness. Generations. 2006; 30: 5–10.

30. Friedman B, Jiang HJ, Elixhauser A. Costly hospital readmissions and with multiple chronic conditions. Washington (DC): US Department of Health and Human Services. Multiple chronic conditions: A strategic framework: optimum health and quality of life for individuals with complex chronic illness. Inquiry 2008–2009; 45: 408–421.

31. Anderson G. Chronic care: making the case for ongoing care. Princeton (NJ): Robert Wood Johnson Foundation, 2010-2017.

32. US Department of Health and Human Services. Multiple chronic conditions – a strategic framework: optimum health and quality of life for individuals with multiple chronic conditions. Washington (DC): 2010, 2017.

33. Bernstein AB, Hing E, Moss AJ, Allen KF, Siller AB, Tiggle RB. Health care for older people with multiple chronic conditions. Washington (DC): US Department of Health and Human Services. Health, United States, 2010, with special feature on death and dying. Hyattsville (MD): Centers for Disease Control and Prevention, National Center for Health Statistics; 2011. 2017.

34. Margos G, Piesman J, Lane RS, Ogden NH, Singh A, Straubinger RK, et al. The Borrelia burgdorferi sensu lato species complex in North America. J Insect Sci. 2007; 7: 58.

35. Mattila JT, Munderloh UG, Kurti TJ. Phagocytosis of the Lyme disease spirochete, Borrelia burgdorferi, by cells from the ticks, Ixodes scapularis and Dermacentor andersoni, infected with an endosymbiont, Rickettsia peacockii. J Insect Sci. 2007; 7: 58.

36. Rudenko N, Golovchenko M, Vancová M, Clark K, Oliver JH Jr, Grubhoffer L. Harvested white-tailed deer as sentinel hosts for early establishing Ixodes scapularis populations and risk from vector-borne zoonoses in southeastern Canada. J Med Entomol. 2013; 50: 384-393.

37. Tijsse-Klasen E, Pandak N, Hengeveld P, Takumi K, Koopmans MP, Sproong EH. Ability to cause erythema migrans differs between Borrelia burgdorferi sensu lato isolates. Parasite Vectors. 2013; 6: 22-27.

38. Schedl M, Hillyard J, Hillyard E, Hillyard S, Hillyard S. An annotated checklist of pathogenic microorganisms associated with migratory birds. J Wild Dis. 2004; 40: 639-659.

39. Scott JD, Anderson JF, Durden LA. Widespread dispersal of Borrelia burgdorferi-infected ticks collected from songbirds across Canada. J Parasitol. 2012; 98: 49-59.

40. Golovchenko N, Vancová M, Vincekova M, Clark K, Oliver JH Jr. Borrelia burgdorferi-N. A divergent spirochete strain isolated from a resident of the southeastern United States was identified by multilocus sequence typing as Borrelia bissetti. Parasite Vectors. 2016; 9: 68.

41. Margos G, Piesman J, Lane RS, Ogden NH, Singh A, Straubinger RK, et al. Borrelia burgdorferi sensu lato species complex in North America. J Insect Sci. 2014; 64: 128-130.

42. Mattila JT, Munderloh UG, Kurti TJ. Phagocytosis of the Lyme disease spirochete, Borrelia burgdorferi, by cells from the ticks, Ixodes scapularis and Dermacentor andersoni, infected with an endosymbiont, Rickettsia peacockii. J Insect Sci. 2007; 7: 58.

43. Tijsse-Klasen E, Pandak N, Hengeveld P, Takumi K, Koopmans MP, Sproong EH. Ability to cause erythema migrans differs between Borrelia burgdorferi sensu lato isolates. Parasite Vectors. 2013; 22: 23.

44. Wang G, van Dam AP, Schwartz I, Dankert J. Molecular typing of Borrelia burgdorferi sensu lato: taxonomic, epidemiological, and clinical implications. Clin Microbiol Rev. 1999; 2: 633-653.

45. Coulter P, Lema C, Flaharty D, et al. Two-year evaluation of Borrelia burgdorferi culture and supplemental tests for definitive diagnosis of Lyme disease. J Clin Microbiol 2005; 43: 5080-5084.

46. Wormser GP, Nowakowski J, Nadelman RB, Visinainer P, Levin A, Aguero-Rosenfeld ME. Impact of clinical variables on Borrelia burgdorferi-specific antibody seropositivity in acute-phase sera from patients in North America with culture-confirmed early Lyme disease. Clin Vaccine Immunol. 2008; 15: 1519-1522.

47. Engstrom SM, Shoop E, Johnson RC. Immunoblot interpretation criteria for serodiagnosis of early Lyme disease. J Clin Microbiol. 1995; 33: 419-427.

48. Lede TB, Collins MF, Craig WY. New laboratory guidelines for serologic diagnosis of Lyme disease: evaluation of the two-test protocol. J Clin Microbiol. 1996; 34: 2343-2350.

49. Eisen L, Eisen RJ, Mun J, Salkeld DJ, Lane RS. Transmission cycles of Borrelia burgdorferi and B. burgdorferi sensu lato complex with respect to habitat type in northeastern California. J Vector Ecol. 2009; 34: 81-91.

50. Rudenko N, Golovchenko M, Grubhoffer L, Oliver JH Jr. Updates on Borrelia burgdorferi sensu lato complex with respect to public health. Ticks Tick Borne Dis. 2011; 2: 123-128.

51. Oliver J, Means RG, Kogut S, Prusinski M, Howard JJ, Rayne LJ, et al. Prevalence of Borrelia burgdorferi in small mammals in New York state. J Med Entomol. 2006: 43: 924-935.

52. Bouchard C, Leighton PA, Beauchamp G, Nguon S, Trudel L, Milord F, et al. Harvested white-tailed deer as sentinel hosts for early establishing Ixodes scapularis populations and risk from vector-borne zoonoses in southeastern Canada. J Med Entomol. 2013; 50: 384-393.

53. Elia PS, Smith RP Jr, Morris SR, Rand PW, Lubelczyk C, Lacombe EH. Density of ixodes scapularis ticks on Monhegan Island after complete deer removal: a question of avian importation. J Vector Ecol. 2011; 36: 11-23.
58. Bacon RM, Biggerstaff BJ, Schriever ME, Gilmore RD Jr, Philipp MT, Steere AC, et al. Serodiagnosis of Lyme disease by kinetic enzyme-linked immunosorbasent assay using recombinant VlsE1 or peptide antigens of Borrelia burgdorferi compared with 2-tiered testing using whole-cell lysates. J Infect Dis. 2003; 187: 1187-1199.

59. Bakken LL, Callister SM, Wand PJ, Schell RF. Interlaboratory comparison of test results for detection of Lyme disease by 516 participants in the Wisconsin State Laboratory of Hygiene/College of American Pathologists Proficiency Testing Program. J Clin Microbiol. 1997; 35: 537-543.

60. Trevejo RT, Krause PJ, Sikand VK, Schriever ME, Ryan R, Lepore T, et al. Evaluation of two-test serodiagnostic method for early Lyme disease in clinical practice. J Infect Dis. 1999; 179: 931-936.

61. Nowakowski J, Schwartz I, Liveris D, Wang G, Aguero-Rosenfeld ME, Girao G, et al. Laboratory diagnostic techniques for patients with early Lyme disease associated with erythema migrans: a comparison of different techniques. Clin Infect Dis. 2001; 33: 2023-2027.

62. Wojciechowska-Koszko I, Maźczyńska I, Szych Z, Giedys-Kalemba S. Serodiagnosis of Borrelia: indirect immunofluorescence assay, enzyme-linked immunosorbasent assay and immunoblotting. Arch Immunol Ther Exp 2011; 59: 69-77.

63. Chmielewska-Badora J, Cisak E, Wojcik-Fatia A, Zwołińska J, Buczak A, Dutkiewicz J. Correlation of tests for detection of Borrelia burgdorferi sensu lato infection in patients with diagnosed borreliosis. Ann Agric Environ Med 2006; 13: 307–311.

64. Dresasler F, Whalen JA, Reinhardt BN, Steere AC. Western blotting in the serodiagnosis of Lyme disease. J Infect Dis. 1993; 167: 392-400.

65. Hilton E, Devoli J, Sood S. Recommendation to include OspA and OspB in the new immunoblotting criteria for serodiagnosis of Lyme disease. J Clin Microbiol. 1996; 34: 1353-1354.

66. Cook MJ, Purki BK. Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy. Int J Gen Med. 2016; 9: 427-490.

67. Stricker RB, Johnson L. Gender bias in chronic Lyme disease. J Womens Health (Larchmt). 2009; 18: 1717-1718.

68. Stricker RB, Johnson L. Circular reasoning in CDC Lyme disease test review. Pubmed Commons comment on: Moore A, Nelson C, Molins C, Maed P, Schriever M. Current guidelines, common clinical pitfalls, and future directions for laboratory diagnosis of Lyme disease, United States. Emerg Infect Dis. 2016; 22: 1169-1177.

69. Oksi J, Ukila J, Marjamäki M, Nikoskelainen J, Viljanen MK. Antibodies against whole sonicated Borrelia burgdorferi spirochetes, 41-kilodalton flagellin, and P39 protein in patients with PCR- or culture-proven late Lyme borreliosis. J Clin Microbiol. 1995; 3: 2260-2264.

70. Chmielewski T, Fiett J, Gniadkowski M, Tylewska-Wierzbanowska S. Improvement in the laboratory recognition of Lyme borreliosis with the combination of culture and PCR methods. Mol Diagn. 2003; 7: 155-162.

71. Hastey CJ, Elsner RA, Barthold SW, Baumgarth N. Delays and diversions mark the development of B cell responses to Borrelia burgdorferi infection. J Immunol 2012; 188: 5612-5622.

72. Steere, AC, Hardin JA, Ruddy S, Murmaw JG, Malavista SE. Lyme arthritis: correlation of serum and cyroglobulin IgM with activity, and serum IgG with remission. Arthritis Rheum. 1979; 22: 471-483.

73. Ma B, Christen B, Leung D, Vigo-Pelfrey C. Serodiagnosis of Lyme borreliosis by Western immunoblot: Reactivity of various significant antibodies against Borrelia burgdorferi. J Clin Microbiol. 1992; 30: 370-376.

74. Craft J, Fischer DK, Shimamoto GT, Steere AC. Antigens of Borrelia burgdorferi recognized during Lyme disease: appearance of a new immunoglobulin M response and expansion of the immunoglobulin G response late in the illness. J Clin Invest. 1986; 78: 934-939.

75. Kailash RA, McHugh G, Granquist J, Shea B, Ruthazer R, Steere AC. Persistence of immunoglobulin M or immunoglobulin G antibody responses to Borrelia burgdorferi 10–20 years after active Lyme disease. Clin Infect Dis. 2001; 33: 790-795.

76. Racine R, McLaughlin M, Jones DD, Wittmer ST, MacNamara KC, Woodland DL, et al. IgM production by bone marrow plasmablasts contributes to long-term protection against intracellular bacterial infection. J Immunol. 2011; 186: 1011-1021.

77. Stricker RB, Winger EE. Decreased CD57 lymphocyte subset in patients with chronic Lyme disease. Immunol Lett. 2001; 76: 43–48.

78. Stricker RB, Savely VR, Motanya NC, Giclas PC. Complement split products C3a and C4a in chronic Lyme disease. Scand J Immunol. 2009; 69: 64–69.

79. Soloski MJ, Crowder LA, Lahey LJ, Wagner CA, Robinson WH, Aucott JN. Serum inflammatory mediators as markers of human Lyme disease activity. PLoS One. 2014; 9: e93243.

80. Berger BW. Dermatologic manifestations of Lyme disease. Rev Infect Dis. 1989; 11: S1475-S1481.

81. Bingham PM, Galetta SL, Athreya B, Sladky J. Neurologic manifestations in children with Lyme disease. Pediatrics. 1995; 96: 1053-1056.

82. Stricker RB, Phillips SE. Lyme disease without erythema migrans: cause for concern. Am J Med. 2003; 115: 72.

83. Klempern MS, Hu LT, Evans J, Schmid CH, Johnson GM, Trevino RP, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001; 345: 85-92.

84. Stricker RB. Counterpoint: long-term antibiotic therapy improves persistent symptoms associated with Lyme disease. Clin Infect Dis 2007; 45: 149–157.

85. Caïms V, Godwin J. Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. Int J Epidemiol 2005; 34: 1340–1345.

86. Aucott JN, Crowder LA, Kortte KB. Development of a foundation for a case definition of post-treatment Lyme disease syndrome. Int J Infect Dis; 2013; 17: e443-e449.

87. Aucott JN, Rebman AW, Crowder LA, Kortte KB. Post-treatment Lyme disease syndrome symptomatology and the impact on life functioning: is there something there? Qual Life Res. 2013; 22: 75-84.

88. Fallon BA, Levin ES, Schweitzer PJ, Hardesty D. Inflammation and central nervous system Lyme disease. Neurobiol Dis. 2010; 37: 534-541.

89. Embers ME, Ramamorthy R, Philipp MT. Survival strategies of Borrelia burgdorferi, the etiologic agent of Lyme disease. Microbes Infect. 2004; 6: 312-318.

90. CabelloF, Godfrey HP, Newman SA. Hidden in plain sight: Borrelia burgdorferi and the extracellular matrix. Trends Microbiol. 2007; 15: 350-354.

91. Szczpanski A, Benach JL. Lyme borreliosis: host responses to Borrelia burgdorferi. Microbiol Rev. 1991; 55: 326: 761-762.

92. Mahmood AA. The challenge of intracellular pathogens. N Engl J Med. 1992; 326: 761-762.

93. Sapi E, Bastian SL, Mpoyn CM, Scott S, Rattelle A, Pabbarati N, et al. Characterization of biofilm formation by Borrelia burgdorferi in vitro. PLoS One. 2012; 7: e48277.

94. Zhang JR, Hardham JM, Barbour AG, Norris SJ. Antigenic variation in Lyme disease borreliae by promiscuous recombination of VMP-like sequence cassettes. Cell. 1997; 89: 275-285.

95. Coutte L, Botkin DJ, Gao L, Norris SJ. Detailed analysis of sequence changes occurring during VlsE antigenic variation in the mouse model of Borrelia burgdorferi infection. PLoS Pathog. 2009; 5: e1000293.

96. Liang FT, Jacobs MB, Bowers LC, Philipp MT. An immune evasion strategy based on plasmidencoded chimeric flagellin proteins. J Immunol. 1993; 151: 312-318.

97. Barbour AG, Restrepo BI. Antigenic variation in vector-borne pathogens. Emerg Infect Dis. 2000; 6: 449-457.
113. Stricker RB. Manuscript submitted.

111. Al-Robaiy S, Dihazi H, Kacza JE, Seeeger J, Schiller J, Huster D, et al. Metamorphosis of Borrelia burgdorferi organisms-RNA, lipid and protein composition in context with the spirochetes’ shape. J Basic Microbiol. 2010; 50: 55-517.

110. Duray PH, Yin SR, Ito Y, Bezrukov L, Cox C, Cho MS, et al. Invasion of human tissue ex vivo by Borrelia burgdorferi. J Infect Dis. 2005; 191: 1747-1754.

109. Kersten A, Poitschek C, Rauch S, Aberer E. Effects of penicillin, ceftriaxone and doxycycline on morphology of Borrelia burgdorferi. Antimicrob Agents Chemother. 1995; 39: 1127-1133.

108. Alban PS, Johnson PW, Nelson DR. Serum-starvation-induced changes in protein synthesis and morphology of Borrelia burgdorferi. Microbiology. 2000; 146: 119-127.

107. Kraiczky P, Hellwage J, Skerka C, Becker H, Hirschfink M, Simon MM, et al. Complement resistance of Borrelia burgdorferi correlates with the expression of BcCRASP-1, a novel linear plasmid-encoded surface protein that interacts with human factor H and FHL-1 and is unrelated to Erp proteins. J Biol Chem. 2004; 279: 2421-2429.

106. Kumpainen I, Poistis K, Rauch S, Aberer E. Induction of immune responses in uninfected humans and rhesus monkeys. Infect Immun 1998; 66: 2691-2697.

105. Meriläinen L, Brander H, Herranen A, Schwarzbach A, Gilbert L. Pleomorphic spirochetes in Borrelia burgdorferi persisters in vitro: eradication achieved by using daptomycin, cefepim and doxycycline. PLoS One. 2015; 10: e0117207.

104. Pound MW, May DB. Proposed mechanisms and preventative options of Jarisch-Herxheimer reaction to treatment with antibiotics against tumor necrosis factor alpha. N Engl J Med. 1996; 335: 311-315.

103. Maloy AL, Black RD, Segurola RJ. Lyme disease complicated by the Jarisch-Herxheimer reaction. Emerg Med. 1998; 16: 437-438.

102. Phillips SE, Burrascano JJ, Harris NS, Johnson L, Smith PV, Stricker RB. Chronic infection in the blood-fed tick Ixodes scapularis: Implications for Lyme disease transmission. J Med Entomol. 2005; 42: 1439-1444.

101. Stricker RB, Johnson L. Spirochetal ‘debris’ versus persistent infection in BSK-H medium. Infection. 1998; 26: 144-150.

100. Brorson O, Brorson SH. Transformation of cystic forms to normal mobile spirochetes. Infection. 1995; 23: 240-246.

99. Schwartz TG, Piesman J. Temporal changes in outer surface proteins A and C of the Lyme disease-associated spirochete, Borrelia burgdorferi, during the chain of infection in ticks and mice. J Clin Microbiol. 2000; 38: 382-388.
140. Thompson C, Spiellman A, Krause P. Coinfecting deer-associated zoonoses: Lyme disease, babesiosis, and ehrlichiosis. Clin Infect Dis. 2001; 33:676–85.

141. Biggs HM, Behravesh CB, Bradley KK, Dahlgren FS, Drexler NA, Dumler JS, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain Spotted Fever and other spotted fever group Rickettsioses, Ehrlichioses, and Anaplasmosis - United States. MMWR Recomm Rep. 2016; 65: 1–44.

142. Dantas-Torres F, Chomel BB, Otranto D. Ticks and tick-borne diseases: a One Health perspective. Trends in Parasitology. 2012; 28: 437-46.

143. Maggi RG, Mozayeni BR, Pultorak EL, Hegarty BC, Bradley JM, Correa M, et al. Bartonella spp. bacteremia and rheumatic symptoms in patients from Lyme disease–endemic region. Emerg Infect Dis. 2012; 18: 783-791.

144. Podsiad E, Chmielowski YT, Tylewska-Wierzbanska S. Bartonella henselae and Borrelia burgdorferi infections of the central nervous system. Ann NY Acad Sci. 2003; 990: 404–406.

145. Thomas V, Anguita J, Barthold SW, Fikrig E. Coinfection with Borrelia burgdorferi and the agent of human granulocytic ehrlichiosis alters murine immune responses, pathogen burden, and severity of Lyme arthritis. Infect Immun. 2001; 69: 3359–3371.

146. Zeidner NS, Dolan MC, Massung R, Piesman J, Fish D. Coinfection with Borrelia burgdorferi and the agent of human granulocytic ehrlichiosis suppresses IL-2 and IFN gamma production and promotes an IL-4 response in C3H/HeJ mice. Parasite Immunol. 2000; 22: 581–588.

147. Moro MH, Zegarra-Moro OL, Bjornsson J, Hofmeister EK, Bruinsma E, Germer JJ, Persing DH. Increased arthritis severity in mice coinfected with Borrelia burgdorferi and Babesia microti. J Infect Dis. 2002; 186: 428–431.

148. Cameron D. Severity of Lyme disease with persistent symptoms. Insights from a double-blind placebo-controlled clinical trial. Minerva Med. 2008;99(5):489-96.

149. Johnson L, Wilcox S, Mankoff J, Stricker RB. Severity of chronic Lyme disease compared to other chronic conditions: a quality of life survey. Peer J. 2014; 2: e322.

150. Adrion ER, Aucott JN, Lemke KW, Weiner JP. Health care costs, utilization and patterns of care following Lyme disease. PLoS ONE. 2015; 10: e0116767.

151. Stricker RB, Johnson L. Lyme disease: the promise of Big Data, companion diagnostics and precision medicine. Infect Drug Resist. 2016; 9: 215-219.

152. van den Wijngaard CC, Hofhuis A, Wong A, Harms MG, de Wit GA, Lugnér AK, et al. The cost of Lyme borreliosis. Eur J Public Health 2017 okw269. doi: 10.1093/eurpub/ckw269.

153. Cassarino DS, Quezado MM, Ghatak NR, Duray PH. Lyme-associated parkinsonism: a neuropathologic case study and review of the literature. Arch Pathol Lab Med. 2003; 127: 1204-1206.

154. Middelvenen MJ, Stricker RB. Morgellons disease: a filamentous borrelial dermatitis. Int J Gen Med. 2016; 9: 349-354.

155. American Medical Association. Code of Medical Ethics. 2017.

156. Cameron DJ. Clinical trials validate the severity of persistent Lyme disease symptoms. Med Hypotheses. 2009; 72: 153-156.

157. Cameron DJ. Consequences of treatment delay in Lyme disease. J Eval Clin Pract. 2007; 13: 470-472.

158. Kienle GS, Kiene H. Clinical judgment and the medical profession. J Eval Clin Pract. 2011; 17: 621–627.