

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 (Bacon *et al.*, 2008; CDC, 2017; Sykes and Makiello, 2017; Wormser *et al.*, 2006; Cameron *et al.*, 2014). 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 (CDC, 2017; Sykes and Makiello, 2017). 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 (Cameron *et al.*, 2014). 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 (Klempner *et al.*, 1993; Georgilis *et al.*, 1992; Snyderman *et al.*, 1986; Häupl *et al.*, 1993; Girschick *et al.*, 1996; Valesova *et al.*, 1989; Nanagara *et al.*, 1996; Aberer *et al.*, 1996; Stanek *et al.*, 1990; de Koning *et al.*,

1989; Livengood and Gilmore, 2006; Ma *et al.*, 1991; Dorward *et al.*, 1997).

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 (Cameron *et al.*, 2014; Szer *et al.*, 1991; Borgermans *et al.*, 2014; Oksi *et al.*, 1999; Fallon *et al.*, 2018; Miklossy *et al.*, 2012; Donta, 2003; 1997). 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.* (2013) 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 (USDHHS, 2010a; Hwang *et al.*,

2001; Warshaw, 2006; Friedman and Jiang, 2008; Anderson, 2017; USDHHS, 2010b) and some researchers have suggested that the medical condition needs to be permanent to qualify (Bernstein *et al.*, 2003; McKenna and Collins, 2010). 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” (Pressler *et al.*, 2011; Behar *et al.*, 2014). In the case of TBDs, this process often becomes established and persists after 3-6 months of untreated or inadequately treated infection (Cameron *et al.*, 2014; Donta, 2003; 1997). 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 study 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 (Wormser *et al.*, 2006; Cameron *et al.*, 2014). The European vector of Lyme disease is *I. ricinus* and the Eurasian vector is *I. persulcatus* (Sykes and Makiello, 2017; Wormser *et al.*, 2006; Cameron *et al.*, 2014). *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 (MDH, 2017; Kilpatrick *et al.*, 2017). *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 (MDH, 2017; Kilpatrick *et al.*, 2017). Ticks may also be found in backyard gardens and on wooden structures (Eisen *et al.*, 2009). Reservoir hosts vary by region and may include mice, chipmunks, shrews, squirrels and other small mammals; humans and domesticated animals are incidental hosts (Rudenko *et al.*, 2011; Oliver *et al.*, 2006). 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 (Bouchard *et al.*, 2013; Elias *et al.*, 2011; Hubálek, 2004; Scott *et al.*, 2014).

Microbiology

CLD may be caused by any of the known pathogenic *Borrelia* genospecies and associated TBD pathogens including *Babesia*, *Anaplasma*, *Ehrlichia*, *Rickettsia*, *Powassan* virus and possibly *Bartonella*. In the USA, Lyme disease is primarily associated with *B. burgdorferi sensu stricto* (*Bbss*), while in Europe, *B. afzelii*, *B. garinii* and *Bbss* are found in the majority of cases (Sykes and Makiello, 2017; Wormser *et al.*, 2006; Cameron *et al.*, 2014). 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 (Sudhindra *et al.*, 2016; Cutler *et al.*, 2017; Golovchenko *et al.*, 2016; Margos *et al.*, 2014; Mattila *et al.*, 2007; Rudenko *et al.*, 2009). Genospecies of *Borrelia* and strains within a given genospecies differ in their clinical presentations, antigenic profiles and response to host immunity (Tijssse-Klasen *et al.*, 2013; Wang *et al.*, 1999). 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 ((Tijssse-Klasen *et al.*, 2013; Wang *et al.*, 1999)). 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” (Bacon *et al.*, 2008). 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 (Coulter *et al.*, 2005; Wormser *et al.*, 2008; Engstrom *et al.*, 1995; Ledue *et al.*, 1996; Bacon *et al.*, 2003; Bakken *et al.*, 1997; Trevejo *et al.*, 1999; Nowakowski *et al.*, 2001; Wojciechowska-Koszko *et al.*, 2011; Chmielewska-Badora *et al.*, 2006). 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 (Dressler *et al.*, 1993; Hilton *et al.*, 1996;

Cook and Puri, 2016; Stricker and Johnson, 2009). The allegedly high sensitivity of two-tiered testing in late Lyme disease is based on circular reasoning, as discussed in detail elsewhere (Stricker and Johnson, 2016).

Seronegativity is well documented in late Lyme disease (Lawrence *et al.*, 1995; Oksi *et al.*, 1995; Chmielewski *et al.*, 2003). In a study of 41 patients with active Bb infection shown by positive culture and/or PCR, 63.5% did not have reactive Lyme serologies despite the fact that 54% had been symptomatic for over a year (Oksi *et al.*, 1995). The authors concluded that “antibodies to *B. burgdorferi* often are present in only low levels or are even absent in culture- or PCR-positive patients” who have been suffering for years from symptoms of Lyme disease. In a second study of 32 patients hospitalized for late Lyme disease whose disease activity was confirmed by positive PCR, 56.3% were seronegative (Chmielewski *et al.*, 2003).

A further serological complication relates to interpretation of IgM seropositivity in the setting of CLD. Animal models and human studies support the presence of an IgM response in chronic as well as acute Bb infection (Hastey *et al.*, 2012; Steere *et al.*, 1979; Ma *et al.*, 1992; Craft *et al.*, 1986; Kalish *et al.*, 2001). In the murine model, Bb has been shown to infect lymph nodes and induce sustained proliferation of B-cells that secrete Bb-specific IgM (Chmielewski *et al.*, 2003). Hastey *et al.* (2012) describe a “B-cell response that is dominated by IgM secreting cells, both induced early in the lymph nodes and also found later in the bone marrow.” Not only do their findings support persistence of an IgM response in chronic disease, but their data “provide strong evidence for the diversion and delay of B-cell responses by Bb, which might help Bb to establish and maintain persistence.” Likewise in humans, according to Steere and colleagues, “The amount of IgM generally rose during exacerbations and fell during remissions. Thus, IgM was an important correlate of clinical disease activity” (Steere *et al.*, 1979). Persistent IgM seroreactivity has been described in other infectious diseases (Racine *et al.*, 2011) and appears to be a significant marker of CLD.

Companion diagnostic testing may be useful for the detection and clinical monitoring of CLD. Examples of TBD-related companion diagnostics include CD57 natural killer cell levels, complement C4a changes and cytokine/chemokine alterations (Stricker and Winger, 2001; Stricker *et al.*, 2009; Soloski *et al.*, 2014). The utility of this 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 (Berger, 1989). Thus, while 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 (Kilpatrick *et al.*, 2017; Eisen *et al.*, 2009). 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 (Bingham *et al.*, 1995; Stricker and Phillips, 2003). The CDC found that patients lacked an EM rash in 30% of cases that were diagnosed using the surveillance case definition (Bacon *et al.*, 2008). 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 < four 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 (Klempner *et al.*, 2001; Stricker, 2007; Cairns and Godwin, 2005; Aucott *et al.*, 2013a; 2013b).

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 (Fallon *et al.*, 2010; Embers *et al.*, 2004; Cabello *et al.*, 2007;

Szczpanski and Benach, 1991; Hodzic *et al.*, 2003; Mahmoud, 2012; Sapi *et al.*, 2012; Zhang *et al.*, 1997; Coutte *et al.*, 2009). 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 (Fallon *et al.*, 2010; Embers *et al.*, 2004; Cabello *et al.*, 2007; Szczpanski and Benach, 1991; Hodzic *et al.*, 2003; Mahmoud, 2012; Sapi *et al.*, 2012; Zhang *et al.*, 1997; Coutte *et al.*, 2009); (2) alterations in outer surface protein (Osp) profiles of pathogens through antigenic variation (Zhang *et al.*, 1997; Coutte *et al.*, 2009; Liang *et al.*, 2002; Barbour and Restrepo, 2000; Schwan and Piesman, 2000) and alteration in pathogen morphology (including cell-wall deficient forms, spherocytes, round bodies and biofilm aggregates) (Brorson and Brorson, 1997; Brorson and Brorson, 1998; Miklossy *et al.*, 2008; Mursic *et al.*, 1996; Al-Robaigy *et al.*, 2010; Duray *et al.*, 2005; Kersten *et al.*, 1995; Alban *et al.*, 2000); (3) immune modulation via complement interference, neutrophil and dendritic cell dysfunction and cytokine/chemokine alterations (Kraiczy *et al.*, 2004; Pausa *et al.*, 2003; Kraiczy *et al.*, 2002; Hartiala *et al.*, 2008; Hartiala *et al.*, 2007; Meriläinen *et al.*, 2016; Lazarus *et al.*, 2008; Giambarolemei *et al.*, 1998); and (4) generation of antibiotic-tolerant “persister cells” in some pathogen populations (Sharma *et al.*, 2015; Feng *et al.*, 2015; 2014).

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 (Cruz *et al.*, 2015; Kursawe, 2002; Fallon *et al.*, 1992; Liegner, 2015; Binalsheikh *et al.*, 2012). The wide spectrum of clinical features can range from an EM rash to severe arthritis, carditis or neuropsychiatric symptoms (Wormser *et al.*, 2006; Cameron *et al.*, 2014). Another clinical feature often associated with this condition is the Jarisch-Herxheimer reaction whereby symptoms increase after exposure to antimicrobials (Bryceson *et al.*, 1972; Vaughan *et al.*, 1994; Zifko *et al.*, 1994; See *et al.*, 2005; Pound and May, 2005; Maloy *et al.*, 1998; Fekade *et al.*, 1996; Butler, 2017). This is a phenomenon associated with the treatment of spirochetal diseases such as syphilis, louse-borne relapsing fever, leptospirosis and Lyme disease (Bryceson *et al.*, 1972; Vaughan *et al.*, 1994; Zifko *et al.*, 1994; See *et al.*, 2005; Pound and May, 2005; Maloy *et al.*, 1998; Fekade *et al.*, 1996; Butler, 2017). 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 (Butler, 2017). 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 and colleagues in the USA (Steere *et al.*, 1987; Szer *et al.*, 1991). Prior to recognition of the importance of antimicrobial therapy, untreated patients with EM rash displayed the following clinical characteristics 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 (Steere *et al.*, 1987). Further characteristics of CLD-U patients have been described by Wormser *et al.* (2006) in the IDSA Lyme guidelines. 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 (Bacon *et al.*, 2008; Wormser *et al.*, 2006; Cameron *et al.*, 2014).

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 (Phillips *et al.*, 2005; Stricker and Johnson, 2012). 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” (Wormser *et al.*, 2006). 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.

Table 1: Untreated Chronic Lyme Disease (CLD-U)

Symptom/sign	No. of patients	Category
Chest Pain	1	Cardiac
Fibrillation	1	Cardiac
Flutter	1	Cardiac
Murmur	1	Cardiac
Myocardial Infarction	1	Cardiac
Myocarditis	1	Cardiac
Myopericarditis	1	Cardiac
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
Periorbital Edema	1	Musculoskeletal
Encephalomyelitis	1	Neurologic
Paraparesis	1	Neurologic
Encephalopathy	1	Neurologic
Neuropathy	2	Neurologic
Optic Neuritis	2	Neurologic
Transient Ischemic Attack	1	Neurologic
Blurred Vision	2	Neurologic
Eye Pain	1	Neurologic
Facial Pain	1	Neurologic
Fatigue	2	Neurologic
Headaches	3	Neurologic
Hypesthesia	1	Neurologic
Memory Difficulties	1	Neurologic
Photophobia	1	Neurologic
Progressive Visual Loss	2	Neurologic
Ptosis	1	Neurologic
Radicular Pain	3	Neurologic
Restriction of Visual Field	1	Neurologic
Tinnitus	1	Neurologic
Vertigo	1	Neurologic
Total: 37	Total: 59	(16 Studies)
Symptom/Sign Category		
Musculoskeletal (%)	23/59 (39)	
Neuropsychiatric (%)	29/59 (49)	
Cardiovascular (%)	7/59 (12)	

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	Neurologic
Parkinsonism	1	Neurologic
Depressed Corneal Reflexes	1	Neurologic
Hemiparesis	1	Neurologic
Recurrent encephalomyeloradiculopathy	1	Neurologic
Trigeminal Sensory Neuropathy	1	Neurologic
Blunted Affect	1	Neurologic
Cognitive Dysfunction	3	Neurologic
Cogwheel Rigidity	1	Neurologic
Confusion	1	Neurologic
Decreased Central Vision	1	Neurologic
Decreased Verbal Fluency	1	Neurologic
Depression	1	Neurologic
Difficulty Naming Objects	1	Neurologic
Disorientation	2	Neurologic
Drooling	1	Neurologic
Fatigue	4	Neurologic
Fullness in head	1	Neurologic
Headaches	3	Neurologic
Hypalgesia	1	Neurologic
Hypesthesia	2	Neurologic
Impaired Judgment	1	Neurologic
Impaired Swallowing	1	Neurologic
Memory Difficulties	3	Neurologic
Numbness	2	Neurologic
Paresthesias	3	Neurologic
Perseveration	1	Neurologic
Poor Concentration	2	Neurologic
Poor Initiation	1	Neurologic
Radicular Pain	1	Neurologic
Tinnitus	2	Neurologic
Tremors	1	Neurologic
Vertigo	1	Neurologic
Total: 47	Total: 73	(13 Studies)
Symptom/Sign Category		
Musculoskeletal (%)	24/73 (33)	
Neuropsychiatric (%)	49/73 (67)	
Cardiovascular (%)	0/73 (0)	

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 (Table 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 (Gschnait *et al.*, 1982). However the number of studies with stringent documentation of persistent Bb infection was 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 types of bacteria and at least 26 viruses (Zhang *et al.*, 2014; Tokarz *et al.*, 2014). 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 (Hunfeld *et al.*, 2008; Curcio *et al.*, 2016; Thompson *et al.*, 2001; Biggs *et al.*, 2016; Dantas-Torres *et al.*, 2012). Additionally, the evidence supporting tickborne *Bartonella* infection is growing (Maggi *et al.*, 2012; Podsiad *et al.*, 2003). The interplay of other infectious agents with Bb may complicate the clinical presentation of Lyme disease and prolong the duration of infection, as noted in animal models (Thomas *et al.*, 2001; Zeidner *et al.*, 2000; Moro *et al.*, 2002). 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 (Cameron, 2008). Using a CDC metric of health-related QoL, a second survey of more than 5,000 respondents with CLD supported this analysis, revealing that 71.6% rated their health as fair or poor. The functionality scores of CLD patients were worse than those of other chronic diseases including congestive heart failure, fibromyalgia, post-stroke syndrome, post-myocardial infarction, diabetes and multiple sclerosis (Johnson *et al.*, 2014).

Further support for the adverse health impact of CLD was recently provided by Adrion *et al.* (2015) 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 (Stricker and Johnson, 2016; van den Wijngaard *et al.*, 2017). 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 (Cassarino *et al.*, 2003).

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 (Cassarino *et al.*, 2003; Middelveen and Stricker, 2016). 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 (Cameron, 2008; Johnson *et al.*, 2014; Adrion *et al.*, 2015; Stricker and Johnson, 2016; van den Wijngaard *et al.*, 2017). 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 (AMA, 2017). As previously described by Johnson *et al.* (2014) and Cameron (2009; 2007) 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” (Kienle and Kiene, 2011). 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) (Cameron *et al.*, 2014).

Proposed Diagnostic Criteria for CLD

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

Table 3. Proposed Diagnostic Criteria for CLD

The four levels of diagnostic criteria are as follows:

1. Required criteria
2. Strongly supportive criteria (but not required)
3. Supportive criteria
4. Additional criteria

I. Required criteria

1. Presence of clinical symptoms and/or signs consistent with Bb infection and/or associated TBDs, as described in Table 1 and 2, that adversely impact patient quality of life.
2. Symptom duration greater than six months, either without antibiotic treatment (CLD-U)* or following a limited course of antibiotic treatment for Lyme disease (CLD-T)**.
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.

II. Strongly supportive criteria

1. Positive culture, molecular testing, or some other technology that directly identifies the presence of Bb spirochetes and/or associated TBD pathogens.†
2. Positive serological testing.†
 - a. Fulfills CDC surveillance criteria for Bb-related Western blot testing (Bacon *et al.*, 2008).
 - 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) (Cook and Puri, 2016; Stricker and Johnson, 2009; Stricker and Johnson, 2016; Lawrence *et al.*, 1995; Oksi *et al.*, 1995; Chmielewski *et al.*, 2003). Note that this could be either IgG or IgM seroreactivity (Hastey *et al.*, 2012; Steere *et al.*, 1979; Ma *et al.*, 1992; Craft *et al.*, 1986; Kalish *et al.*, 2001).
 - c. Seropositivity for Bb-associated TBD pathogens.

III. Supportive criteria

1. History of EM rash. Although this clinical sign is diagnostic of Lyme disease, absence of the rash does not rule out Bb infection.
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 areas

IV. Additional criteria

Response to antibiotic intervention

- a. Positive and sustained clinical response to appropriately directed antimicrobials
- b. Development of a Jarisch-Herxheimer reaction (Bryceson *et al.*, 1972; Vaughan *et al.*, 1994; Zifko *et al.*, 1994; See *et al.*, 2005; Pound and May, 2005; Maloy *et al.*, 1998; Fekade *et al.*, 1996; Butler, 2017).

*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 (Cameron *et al.*, 2014)

**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 (Wormser *et al.*, 2006).

†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.

Conclusion

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 (Cameron *et al.*, 2014; Liegner, 2015). 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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Disclosures

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Author's Contributions

Raphael B. Stricker: Conceived the study, researched the data, reviewed the tables and wrote the manuscript.

Melissa C. Fesler: Researched the data, constructed the tables and edited the manuscript.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and there are no ethical issues involved.

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Appendix A

Peer-Reviewed Evidence of Persistence of Lyme Disease Spirochete *Borrelia burgdorferi* and Other Tickborne Diseases

The following is a list of over 700 peer-reviewed articles that support the evidence for persistence of Lyme and other tickborne diseases. It is organized into different categories—general, neuropsychiatric, dementia and congenital/sexual transmission.

General: Persistence of *Borrelia burgdorferi* and Other Tickborne Diseases

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2. Aberer E, Klade H. Cutaneous manifestations of Lyme borreliosis. *Infection* 1991; 19: 284-286. [chronic Lyme borreliosis].
3. Aberer E, Breier F, Stanek G, and Schmidt B. Success and failure in the treatment of acrodermatitis chronica atrophicans skin rash. *Infection* 1996; 24: 85-87.
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6. Akin E, McHugh GI, Flavell RA, Fikrig E, Steere AC. The immunoglobulin G (IgG) antibody response to OspA and OspB correlates with severe and prolonged Lyme arthritis and the IgG response to P35 with mild and brief arthritis. *Infect Immun* 1999; 67: 173-181.
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17. Barthold SW, Hodzic E, Imai DM, Feng S, Yang X, Luft BJ. Ineffectiveness of tigecycline against persistent *Borrelia burgdorferi*. *Antimicrob Agents Chemother* 2010; 54(2): 643-651.
18. Barthold SW. Global challenges in diagnosing and managing Lyme disease—closing knowledge gaps. Testimony before House Committee on Foreign Affairs, United States Congress, 17 July 2012. Transcript available at: <http://archives.republicans.foreignaffairs.house.gov/112/75161.pdf>
19. Battafarano DF, Combs JA, Enzenauer RJ, Fitzpatrick JE. Chronic septic arthritis caused by *Borrelia burgdorferi*. *Clin Orthop* 1993;297: 238-241.
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Congenital/Sexual Transmission of Lyme/Tickborne Diseases

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SOURCE: ILADS website, http://www.ilads.org/ilads_news/2017/list-of-700-articles-citing-chronic-infection-associated-with-tick-borne-disease-compiled-by-dr-robert-bransfield/

Appendix B

Studies Used for Identification of Symptoms and Signs in CLD*

I. CLD-U

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* Some studies had both CLD-U and CLD-T patients.