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; Snydman 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.,...
and dispersal and migratory birds may transport ticks to
2006). Deer play an important role in tick reproduction
incidental hosts (Rudenko
2009).
should not be withheld for individuals presenting with all
define CLD as persistent TBD infection of at least six
(Cameron
2010). 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. kurtzehachii, B. andersonii, 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;
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 Bronson, 1998; Miklossy et al., 2008; Mursie et al., 1996; Al-Robaiy 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; Kraiczky et al., 2002; Hartia et al., 2008; Hartia et al., 2007; Meriläinen et al., 2016; Lazarus et al., 2008; Giambalvo 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 wherein 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>
<thead>
<tr>
<th>Table 1: Untreated Chronic Lyme Disease (CLD-U)</th>
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<tbody>
<tr>
<td><strong>Symptom/sign</strong></td>
</tr>
<tr>
<td>Chest Pain</td>
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<tr>
<td>Fibrillation</td>
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<tr>
<td>Flutter</td>
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<tr>
<td>Murmur</td>
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<tr>
<td>Myocardial Infarction</td>
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<tr>
<td>Myocarditis</td>
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<tr>
<td>Myopericarditis</td>
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<tr>
<td>Muscle Atrophy</td>
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<tr>
<td>Synovitis</td>
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<tr>
<td>Tenosynovitis</td>
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<tr>
<td>Arthralgia (joint pain)</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Dacltylitis</td>
</tr>
<tr>
<td>Joint Warmth</td>
</tr>
<tr>
<td>Muscle Weakness</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
</tr>
<tr>
<td>Periorbital Edema</td>
</tr>
<tr>
<td>Encephalomyelitis</td>
</tr>
<tr>
<td>Paraparesis</td>
</tr>
<tr>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Neuropathy</td>
</tr>
<tr>
<td>Optic Neuritis</td>
</tr>
<tr>
<td>Transient Ischemic Attack</td>
</tr>
<tr>
<td>Blurred Vision</td>
</tr>
<tr>
<td>Eye Pain</td>
</tr>
<tr>
<td>Facial Pain</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Headaches</td>
</tr>
<tr>
<td>Hypesthesia</td>
</tr>
<tr>
<td>Memory Difficulties</td>
</tr>
<tr>
<td>Photophobia</td>
</tr>
<tr>
<td>Progressive Visual Loss</td>
</tr>
<tr>
<td>Ptosis</td>
</tr>
<tr>
<td>Radicular Pain</td>
</tr>
<tr>
<td>Restriction of Visual Field</td>
</tr>
<tr>
<td>Tinnitus</td>
</tr>
<tr>
<td>Vertigo</td>
</tr>
<tr>
<td><strong>Total:</strong> 37</td>
</tr>
</tbody>
</table>

**Table 2: Chronic Lyme Disease Following Limited Antibiotic Treatment (CLD-T)**

<table>
<thead>
<tr>
<th><strong>Symptom/sign</strong></th>
<th><strong>No. of patients</strong></th>
<th><strong>Category</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle Atrophy</td>
<td>1</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>1</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Meningismus</td>
<td>1</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Synovitis</td>
<td>1</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>1</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Arthralgia (joint pain)</td>
<td>7</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Migratory Pain</td>
<td>1</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Muscle Stiffness</td>
<td>1</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Muscle Weakness</td>
<td>1</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>1</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Torticollis</td>
<td>1</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Trigger Finger</td>
<td>1</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Dementia</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Depressed Corneal Reflexes</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Recurrent</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>encephalomyeloradiculopathy</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Trigeminal Sensory Neuropathy</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Fullness in head</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Decreased Central Vision</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Increased Central Vision</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Decreased Verbal Fluency</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Difficulty Naming Objects</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Fullness in head</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Headaches</td>
<td>3</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Hypalgesia</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Hypesthesia</td>
<td>2</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Impaired Judgment</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Impaired Swallowing</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Memory Difficulties</td>
<td>3</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Numbness</td>
<td>2</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>3</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Perseveration</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Poor Concentration</td>
<td>2</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Poor Initiation</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Radicular Pain</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>2</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Tremors</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1</td>
<td>Neurologic</td>
</tr>
<tr>
<td><strong>Total:</strong> 47</td>
<td><strong>Total:</strong> 73</td>
<td>(13 Studies)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom/Sign Category</th>
<th><strong>No. of patients</strong></th>
<th><strong>Category</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal (%)</td>
<td>24/73 (33)</td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric (%)</td>
<td>49/73 (67)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (%)</td>
<td>0/73 (0)</td>
<td></td>
</tr>
</tbody>
</table>
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/Anaplasmia, 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>
<thead>
<tr>
<th>Table 3. Proposed Diagnostic Criteria for CLD</th>
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<tr>
<td>The four levels of diagnostic criteria are as follows:</td>
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<tr>
<td>1. Required criteria</td>
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<td>2. Strongly supportive criteria (but not required)</td>
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<tr>
<td>3. Supportive criteria</td>
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<tr>
<td>4. Additional criteria</td>
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</tbody>
</table>

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.†
   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; Zitko et al., 1994; Sec 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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DOI: 10.1099/00221287-146-1-119


DOI: 10.1002/jobm.201000074


DOI: 10.1016/j.ijid.2013.01.008


DOI: 10.1086/374395


Golovchenko, M., M. Vancová, K. Clark, J.H. Oliver Jr and L. Grubhoffer, 2016. A divergent spirochete strain isolated from a resident of the southeastern United States was identified by multilocus sequence typing as *Borrelia bissettii*. Parasit. Vectors,


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

53. Chmielewski T, Tylewlska-Wierzhanowska S. Inhibition of fibroblast apoptosis by Borrelia afzelii, Coxiella burnetii and Bartonella henselae. Poll Microbiol 2011; 60(3); 269-272.


123. Hamlen R. Tick-borne infections--a growing public health threat to school-age children. Prevention steps that school personnel can take. NASN School Nurse 2012(Mar); 27(2): 94-100.


234. Preac-Mursic V, Marget W, Busch U, Rigler DP, Hagl S. Kill kinetics of Borrelia burgdorferi and bacterial findings in relation to the treatment of Lyme borreliosis. Infection 1996; 24(1): 9-16. [Bb was isolated by culture in five patients, four of whom had previously tested antibody-negative.]


312. Yrjänäinen H, Hytönen J, Söderström KO, Oksi J, Hartiala K, Viljanen MK. Persistent joint swelling and Borrelia-specific antibodies in Borrelia garinii-infected mice after eradication of vegetative spirochetes with antibiotic treatment. Microbes Infect 2006; 8: 2044-2051. [persistence if Bb in mice]

Neuropsychiatric Symptoms and Lyme/Tickborne Diseases

1. Aalto A, Sjowall J, Davidsson L, Forsberg P, Smedby O. Brain magnetic resonance imaging does not contribute to the diagnosis of chronic neuroborreliosis. Acta Radiol 2007; 48: 755-762. [white matter hyperintensities or basal ganglia lesions].
62. Dupuis MJ. Multiple neurologic manifestations of Borrelia burgdorferi infection. Rev Neurol (Paris) 1988;144(12):765-75


91. Fritzsche M. Seasonal correlation of sporadic schizophrenia to Ixodes ticks and Lyme borreliosis. Int J Health Geogr. 2002; 1:2


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Dementia and Lyme/Tickborne Diseases


33. Miklossy J. Chronic or late Lyme neuroborreliosis: analysis of evidence compared to chronic or late neurosyphilis. Open Neurol J 2012;6: 146-157.


47. Miklossy J. Chronic or late Lyme neuroborreliosis: analysis of evidence compared to chronic or late neurosyphilis. Open Neurol J 2012;6: 146-57.


Congenital/Sexual Transmission of Lyme/Tickborne Diseases


Appendix B

Studies Used for Identification of Symptoms and Signs in CLD*

I. CLD-U


II. CLD-T


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