Challenges to the Accurate and Appropriate Diagnosis of Lyme Disease

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Challenges to the Accurate and Appropriate Diagnosis of Lyme Disease

Abstract

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Abstract

Purposes: The purposes of this review are to highlight the prevalence and pathology of Lyme Disease in the United States, to explore the challenges presented to clinicians in appropriately diagnosing Lyme Disease, and to examine the most accurate and efficient methods of approaching the diagnosis of Lyme Disease.

Data Sources: This literature review was compiled by reviewing scientific literature regarding Lyme Disease, transmission, disease pathology, diagnostic recommendations, and both quantitative and qualitative studies.

Conclusions: Lyme Disease is the most common vector-borne illness in the United States, infecting nearly 40,000 individuals and costing approximately $500 million per year. Most often manifested by the classic *erythema migrans* rash, disseminated infection occurs in up to 60% of untreated patients, leading to articular, neurologic, and cardiac complications. Diagnostic CDC recommendations include either a distinguishable
*erythema migrans*, or at least one disseminated manifestation in addition to two-part laboratory confirmation. Inconsistent diagnostic practices, concurrent infections, unreliable laboratory tests, and difficult, nonspecific illness presentation all contribute to the diagnostic challenge.

**Implications for Practice:** Education for health care providers, development of consistent diagnostic criteria, further research and development of more accurate laboratory tests, and public prevention education are imperative in the approach to this challenging diagnosis.

*Key Words:* Lyme Disease; diagnosis; vector-borne; ELISA; Western immunoblot; disseminated; chronic Lyme Disease.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>iii</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>THEORETICAL FRAMEWORK</td>
<td>3</td>
</tr>
<tr>
<td>LITERATURE REVIEW</td>
<td></td>
</tr>
<tr>
<td>METHODS</td>
<td>4</td>
</tr>
<tr>
<td>THE CLINICIAN’S APPROACH TO DIAGNOSIS</td>
<td>4</td>
</tr>
<tr>
<td>THE DIFFICULTIES IMPEDING ACCURATE DIAGNOSIS</td>
<td>6</td>
</tr>
<tr>
<td>THE EXPERIENCE OF DIAGNOSIS</td>
<td>7</td>
</tr>
<tr>
<td>THE CURRENT RESEARCH REGARDING DIAGNOSIS</td>
<td>8</td>
</tr>
<tr>
<td>SYNTHESIS</td>
<td>9</td>
</tr>
<tr>
<td>IMPLICATIONS FOR PRACTICE</td>
<td>10</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>12</td>
</tr>
<tr>
<td>APPENDIX</td>
<td></td>
</tr>
<tr>
<td>FIGURES</td>
<td>14</td>
</tr>
</tbody>
</table>
Challenges to the Accurate and Appropriate Diagnosis of Lyme Disease

As the most common vector-borne illness in the United States, Lyme disease (LD) has been both an important, emerging infection and a controversial clinical diagnosis for the past three decades. Reported in all 50 states, this tick-borne bacterial infection is endemic in the regions of New England and the Great Lakes (Table 1), accounting for a majority of the 30,000-37,000 cases that were reported to the Centers for Disease Control and Prevention (CDC) in the year 2009 (CDC, 2009) (Table 2). Being a multisystem disorder, the tick-borne spirochete *Borrelia burgdorferi* can affect many physiologic systems, including the joints, the nervous system, and the heart. As a result, LD imposes a huge economic burden on society, estimated in 1998 to cost approximately $2.5 billion over 5 years in the United States alone (Foster, 2002). Although appropriate diagnosis is therefore critical, clinicians must form their differential diagnosis from difficult and nonspecific clinical presentations in the absence of reliable and readily available serological testing (Seybold, Reiser, & Schlenk, 2008).

Unfortunately, clinical presentation of LD has proven perplexing to healthcare providers for nearly a century. “In the early 1900s, physicians in Europe discovered a disease pattern characterized by an erythematous, migrating rash called *erythema migrans* that was associated with the bite of ticks” (Bratton, Whiteside, Hovan, Engle, & Edwards, 2008, p.566). By the 1940s, it had become associated with a systemic illness and spirochete-like bacteria were isolated. In the 1970s, an unusual rash and associated arthritis was identified in children from the region of Lyme, Connecticut, announcing the presence of LD across the Atlantic. Thus it received the name *Lyme Disease*. Surveillance for LD by the CDC began in 1982, and it became a nationally reportable disease in 1991 (Bratton, et al., 2008).

Since that time, the causative agent of LD has been identified as members of the *B. burgdorferi* sensu lato complex, found worldwide in the form of eleven different species. Three of these species are found in North America, of which the *B. burgdorferi* sensu stricto is the only species known to cause human infection in the United States. The *B. burgdorferi* is a helically
shaped, spirochete bacterium with multiple endoflagella that allow it to be very motile in its environment (Aguero-Rosenfeld, Wang, Schwartz, & Wormser, 2005). These cells are known to exist in non-dividing or very slowly dividing forms, resulting in unclear and lengthy culturing attempts in the laboratory environment (Lee, et al., 2010). The *Ixodes scapularis*, the deer tick, carries the *B. burgdorferi* in the New England and Great Lakes regions, and the *I. pacificus* is the primary vector for the bacteria on the West Coast. Following tick bite and adhesion, transmission rates of infection to humans increases markedly after approximately 24 hours, with the highest incidence of infection occurring from April to November (Bratton, et al., 2008). Left untreated, infection may disseminate from an initial localized rash, most commonly manifesting itself in the damaging complications of inflammation to the joints, nervous system, and heart (Stanek & Strle, 2003). Long-term implications of untreated LD are suspected to stimulate the immune system in such a way as to result in possible chronic inflammatory states and autoimmune processes (Nau, Christen, & Eiffert, 2009).

Therefore, clinical features and length of presentation form the basis for classification of LD as early localized (EL), early disseminated (ED), late disseminated (LD), and chronic or post-Lyme syndrome (Bratton, Whiteside, Hovan, Engle, & Edwards, 2008). To further complicate the issue, the literature displays some diversity of opinions regarding these stages and their classification. As a result, the presentation of LD creates diagnostic challenges for primary care providers (PCPs), rheumatologists, dermatologists, cardiologists, neurologists, and even psychiatrists. According to Foster (2002), LD is most often encountered and diagnosed by PCPs (2002). LD is also a major focus in public health. Its importance is recognized by the CDC, which “awards more than $3.5 million per year for new research on Lyme Disease” (Bratton, et. al. 2008). This makes LD a concern for individuals, for specific communities, for society at large, and for clinicians. The problem and challenge to the nurse practitioner is “how do we as healthcare providers accurately and appropriately diagnose or rule out the diagnosis of LD?” The
purpose of this paper is to report results of a literature review exploring the difficulties presented to clinicians and patients during the diagnostic experience of LD.

Theoretical Framework

The Agent-Host-Environment Model is an ecological model that was originally developed by Leavell and Clark in 1965 to describe the health of a community. However, this model is used primarily to examine the cause of disease in individuals and to predict illness by interpreting levels of health and illness as a dynamic relationship between the agent, the host, and the environment.

The agent is the internal or external environmental factor that must be present or absent for an illness to occur. This potentially biological, chemical, physical, mechanical, or psychosocial agent has a direct relationship with both the host and the environment in an interactive, dynamic triangle. The host is a living organism or being that is susceptible to being infected or affected by the agent, but that susceptibility may be influenced by family history, age, sex, and lifestyle. Finally, the physical and social environment is everything external to the host that may make illness more or less likely. In summary, the etiology of both health and illness can be interpreted as an imbalance or disruption of the dynamic triangular relationship between these three factors (Leavell & Clark, 1965).

This classic model formed the foundation for the development of preventative medicine and public health models when it was first proposed in the 1960s, and despite its deficiencies in acknowledging the breadth of genetics to the development of disease (Acheson, 1986), it continues to be used today (Zastrow, 2011). Chosen for its applicability to the diagnosis of LD, the Agent-Host-Environment Model provides a framework from which clinicians can predict and describe patterns of LD. The relationships between community environments, the *borrelia burgdorferi* agent, and the hosts of tick and human and the mode of transmission are all essential if a provider is to successfully approach the challenges in detecting and diagnosing LD.
Literature Review

Methods

To explore the literature, the key words “lyme”, and “diagnosis” were used to search the CINAHL database for multi-disciplinary articles published between January 1, 2000, through March 15, 2011. Additional modifiers of “Lyme disease” and “Chronic Lyme disease” were also used to expand the search. The PubMed database was also searched using the key phrase “lyme disease diagnosis”, identifying articles published between January 1, 2000 through March 15, 2011. Criteria were developed during the literature review by identifying themes related to diagnosis of LD and associated challenges. After reviewing over 50 articles and studies, the search was narrowed down to 9 articles that met the following criteria: the clinician’s approach to diagnosis, the difficulties impeding accurate diagnosis, the experience of diagnosis, and the current research regarding diagnosis.

The Clinician’s Approach to Diagnosis

Bratton, Whiteside, Hovan, Engle, and Edwards (2008) conducted a literature review searching the PubMed and MEDLINE databases for the purpose of reviewing the clinical presentation, risk factors, treatment, and prophylaxis of LD. They found that “the diagnosis of LD is based on clinical features in a person who has traveled to or lives in an endemic area” (p. 568). The *erythema migrans* is the most important clinical sign, appearing as an erythematous, enlarging lesion often with central clearing, days to weeks after the infectious tick bite. It may be accompanied by a low-grade fever and mild systemic symptoms. Disseminated infection occurs later in 60% of untreated patients, and manifests itself in a variety of physiologic systems. In 60% of infected patients, migratory joint or muscle pain is present, and in 15% of cases neurologic manifestations of meningitis, paralysis of the facial cranial nerve, radicular neuropathies, and psychological changes are noted. Temporary atrioventricular blocks of varying degree are also found in 8% of infected patients. Confirmatory common laboratory testing is usually not helpful, although cerebrospinal fluid lymphocytic pleocytosis may be present alongside neurologic
manifestations. Serological tests can be supportive, but are unfortunately prone to false-negative and false-positive results. Despite the often inaccurate findings, the CDC does recommend an enzyme-linked immunosorbent assay (ELISA) followed by the more specific Western immunoblot test, when attempted confirmation is necessary. The search and review of multiple articles from different databases contributed to a very thorough description of the advantages, and disadvantages of various diagnostic methods.

Foster (2002) also conducted a literature review in order to provide a professional review and update for PCPs regarding the transmission, diagnosis, management, and prevention of LD. She quotes CDC surveillance criteria and describes the two basic pathways to the clinical diagnosis of LD. Either a PCP must be able to diagnose erythema migrans > 5cm in diameter, or at least one disseminated manifestation must be present in addition to laboratory confirmation. Therefore, early LD can be diagnosed by clinical manifestations without laboratory confirmation, but late LD diagnosis requires laboratory confirmation. Early symptoms coinciding with the erythema migrans rash can include mild fever, fatigue, myalgia, arthralgia, and headache, but notably without any associated gastrointestinal complaints. The most common disseminated neurologic, cardiac, and joint symptoms can manifest themselves as early as a few weeks following infection to months and years later following a clinically silent period. This characteristic is just one of the many similarities that LD shares with syphilis, another spirochete-caused disease. Laboratory confirmation by a two-step testing approach is recommended. First-step assays include ELISA, immunofluorescence antibody (IFA), or immunodot techniques for detection of IgG, IgM, or antibodies. Positive or equivocal results must be confirmed by a Western blot IgG or IgM. Accurate timing is required for accurate results, as the antibodies, IgM, and IgG all peak at various periods following initial infection. The review of national guidelines and recommended treatment algorithms provided very clear and important implications for the improving education among PCPs regarding the diagnosis of LD.
The Difficulties Impeding Accurate Diagnosis

Terkeltaub (2000) describes an informative but informal review of the literature regarding “the changing infection patterns of tick-borne diseases and how these changes are affecting clinical practice” (p. 34). One such emerging change is the growing population of ticks that harbor more than one pathogen. Ehrlichiosis is an intracellular rickettsial disease that presents with fever, myalgias, leucopenia, and elevated liver enzymes, thereby differentiating it from LD. Babesiosis is a quickly spreading malaria-like parasitic disease. Either of these two pathogens experienced concurrent with LD will usually cause a much more serious and atypical clinical presentation than LD alone. Despite these complications, the diagnosis of LD depends on the clinical presentation. The ELISA, Western blot, and PCR are the mainstay diagnostic studies used to confirm diagnosis of LD. However, not only are the laboratories that perform these studies limited to a few specialized medical centers, but also the ELISA frequently produces false positives and can be inaccurate if autoimmune diseases are present. Numerous positive ELISA tests with negative Western blots results in a conundrum that is compounded by the 60-80% of LD patients with no definitive laboratory proof of disease. Terkeltaub concludes that many patients are subsequently diagnosed incorrectly with LD due to the nonspecific presentation and lack of reliable serological testing. The misdiagnosed include a number of probable fibromyalgia patients. Being an overview, this article strongly presented a broad context for considering multiple laboratorial and psychosocial factors that may impede upon a clear and accurate diagnosis of Lyme.

Wormser and Shapiro (2009) conducted a cross-sectional study and literature review examining the relationship between gender, LD diagnosis, and post-LD syndrome. The purpose of the review was to explore the validity of post-LD syndrome or the “chronic LD” diagnosis by studying gender differences between LD patients and so-called chronic LD patients. If the proportions of men to women were the same for both, the post-LD syndrome patients may indeed be experiencing a chronic result from the \textit{B. burgdoferi} infection that caused initial LD. If the
proportions were significantly different, the post-LD syndrome may be completely unrelated to LD and an invalid diagnosis. The findings revealed that females were more likely to be treated for post-LD syndrome and many were misdiagnosed, experiencing fibromyalgia, chronic fatigue syndrome, or depression instead. Therefore, the authors concluded that the diagnosis of post-LD syndrome is invalid. Despite the explicit review and description of the study’s intentions, methods, and results, the emphatically stated conclusions were only mildly substantiated.

Nau, Christen, and Eiffert (2009) wrote an article intended to educate European medical professionals about the current understandings and controversies regarding the diagnosis of LD. The challenges that they discuss include variation among the *Borellia* species, difficulties obtaining laboratory confirmation, overdiagnosis, and seemingly chronic symptomology. Although healthcare providers in the United States often do not have to be concerned about the variety of causative agents and presentations of LD found in Europe and Asia, laboratory testing of limited sensitivity and specificity, such as the PCR, provide an obstacle to confirmation. Diagnosis is often entirely clinical. As a result, worried patients with vague symptoms have been found to be overdiagnosed with LD by their healthcare providers. Finally, the vast number of patients who complain of vague symptoms following an apparent resolution of LD present a clinical controversy. Some clinicians have treated these patients in the name of “chronic LD” with a prolonged antibiotic treatment up to many months long. Controlled studies do not support this prolonged antibiotic treatment, as placebos have a high rate of effect as well. New research, however, has proposed that LD can trigger chronic inflammation and an autoimmune reaction of the rheumatic type that could be causing many of the so called “post-LD syndrome” complaints.

**The Experience of Diagnosis**

Drew and Hewitt (2006) conducted a qualitative, phenomenological study interviewing a sample of 10 individuals diagnosed with LD to investigate the diagnostic experience. Particularly localized in the Northeastern, Mid-Atlantic, and upper Midwest regions, in addition to several Californian counties, LD prevalence has continued to increase nearly every year since national
surveillance began. In addition, the CDC relies on voluntary reporting alone, which historically equates to underreporting (CDC, 2004). Therefore, in contrast to prior authors’ conclusions, reported LD cases are suspected to account for only 7-10% of actual cases (Jossi, 2001). Lack of standard diagnostic and reporting practices among the states may contribute to the underreporting of LD, in addition to the great variance in diagnostic criteria and lack of definitive serologic testing. According to Donta (2002), more than 75% of patients with chronic LD have negative ELISA results and positive Western blot results, and many other patients are tested before the antibodies can even mount a response and be detected. Chronic LD can then develop, despite initial treatment, resulting in multisystem disorders such as fibromyalgia and chronic fatigue. The challenges in diagnosis were revealed in patient interviews. Six themes emerged as patients expressed frustration with the long road to diagnosis, the unfortunate necessity of self-advocacy, the financial burden, and feelings of validation and hopefulness with the diagnosis. Clearly, the diagnosis of LD not only presents challenges to the clinician, but to the patients and their families as well.

Weintraub (2008) qualitatively describes her personal and family experience with LD and the diagnostic process, focusing on the neurologic and psychiatric implications of LD. Based upon the similarities between the spirochete-caused LD and syphilis, testimonials of children and adults were produced describing profound psychiatric and neurologic decline following acute LD. The neuropsychiatric changes were reported to be dramatically improved only with prolonged antibiotic treatment for chronic LD. Weintraub concluded that the road to diagnosis with LD was frustratingly long due to multiple divisive controversies and misunderstandings, and was especially confusing when patients presented with resulting encephalopathy and neuropsychiatric fallout.

**The Current Research Regarding Diagnosis**

Aguero-Rosenfeld, Wang, Schwartz, and Wormser (2005) published a comprehensive literature review assessing the development and application of current laboratory tests in addition
to a discussion of continuing diagnostic developments specifically for LD. They describe the different approaches that have been used in clinical laboratories to test for the *B. burgdorferi* bacteria from patient samples - culture, microscope-based assays, and detection of the bacterium specific proteins, nucleic acids, or antibodies. Culture is found to the best confirmation of active infection; however, it is often impractical due to the facts that the required liquid medium for culturing these slow growing bacteria has historically been in short supply, and cultures can take up to 12 weeks of incubation. Polymerase chain reaction (PCR) assays lack sensitivity in cerebrospinal fluid (CSF) and blood cultures. Therefore, immunoassays detecting serum antibodies, including the immunofluorescent assay (IFA), ELISA, and Western immunoblot tests, are the most common methods used. Yet, their deficiencies in sensitivity and specificity have led researchers to explore new methods. One of these methods is the peptide-based ELISA test evaluating the C6 peptide, which reveals a test that exhibits high sensitivity in all stages of LD and competitive specificity.

Mogilyansky, Loa, Adelson, Mordechai, and Tilton (2004) conducted a study to examine the comparative specificity and sensitivity of 3 available Western immunoblot tests and 1 C6 ELISA test. After carefully applying these clinical laboratory tests to serum and plasma specimens, they found that the C6 ELISA is a more sensitive antibody test than the Western immunoblot. Responding to IgG and IgM isotypes even in early disease, it also exhibited high specificity with a short laboratory reaction time of approximately 1 hour. In confirmation of specificity, patients identified with over 12 different diseases such as systemic lupus erythematosus, rheumatoid arthritis, and other spirochetal diseases, were tested as negative by the C6 ELISA. These results led to a proposal that the C6 ELISA testing may be a viable option in the future for replacing the current two-tiered system currently advocated by the CDC.

**Synthesis**

LD is most often approached and diagnosed by clinicians based upon the clinical presentation, which can often present as nonspecific and seemingly random complaints. In
compliance with the national recommendations for confirmation, serological testing in the two-tiered approach should be ordered, despite its apparent deficits in regards to sensitivity and specificity. The diagnostic process is complicated and impeded by polarized controversy in both the clinical and academic healthcare community. Potential exists to inaccurately diagnose fibromyalgia, chronic fatigue, or depression as LD, but the challenges are compounded by the concurrent potential to miss accurate diagnoses of LD, result in progression to serious complications. Therefore, the exploration of C6 ELISA testing for LD could be a critical development in the future of the clinician’s approach to LD. Clearly however, these challenges facing clinicians are shared by their patients and their families, for whom the diagnostic experience can be a very long, frustrating, and financially draining process.

Implications for Practice

As stated, this paper presented an analysis of the LD literature with the purpose of examining the challenges healthcare providers encounter in accurately and appropriately diagnosing or ruling out the diagnosis of LD. The triangular relationships between the B. burgdorferi bacteria, its transmission and infection of humans, and the environment conducive to infection have been briefly explored. Four implications for practice are proposed. First, providers and clinicians need to be educated regarding LD, its clinical manifestations, its prevalence or potential prevalence in their community, and the current evidence based recommendations for accurate and appropriate diagnosis. In the absence of any widespread understanding of clinical presentation and adequate diagnostic workup for LD, the confusion and controversy will most likely not be resolved in the near future. Second, the diagnostic workup for LD ought to be clearly outlined. From this review, the tentative approach appears to be based upon clinical presentation, followed by a two-step process of serological testing, and additional cerebrospinal fluid analysis, if neurological implications are suspected. Insufficient research and data to support such an outline prompts the third proposal to encourage further research. Further research involving large samples of the population should decidedly assess the accuracy of the current,
available testing procedures. Not only this, but future research ought to be aimed at discovering highly specific and more easily available diagnostic tests, and perhaps, continued development toward availability of the C6 ELISA testing. Highly sensitive and specific diagnostic tests are imperative to approaching the challenges of appropriate and accurate diagnosis of LD.

Finally, continuing education to the public is necessary for prevention of this tick-borne illness, and, in the absence of prevention, early detection, and decisive management. Education ought to be directed toward patients located within or traveling through the regions where LD is reported in endemic proportions, as well as those who live, work, or recreate in wooded areas across the country. Patients must be informed regarding preventative measures, including avoiding tall grasses and woodlands if possible; wearing long sleeved, light-colored clothing so that ticks can be more easily seen; and applying insect repellants containing DEET. Instructions regarding careful skin inspections and proper, timely tick removal using only tweezers should also be disseminated. Because of the importance of early detection, information should also be provided to patients at high risk describing characteristic early symptoms of LD. From the primary care provider's clinic, to the emergency room, to the public health office – LD is an illness that we must understand and approach with a commitment to accurate and appropriate prevention, detection, and diagnosis.

Conclusion

Despite the challenges and controversies surrounding the diagnosis of LD, two facts are clear – this is the most common vector-borne illness in the United States and it can have serious and far-reaching consequences. Proper, timely, and accurate diagnosis of this serious public health issue is imperative for optimal patient outcomes (Seybold, et. al. 2008). Clearly then, the proper, timely, and accurate diagnosis of LD is a critical challenge that we as clinicians must intentionally strive to overcome. Education, clarity of diagnostic procedures, and further research are therefore just the beginning toward providing a higher quality of patient care by improving the proper diagnosis of Lyme disease.
References


APPENDIX

LIST OF FIGURES

1. Reported Cases of Lyme Disease – United States, 2009 .................. 15
2. Reported Cases of Lyme Disease by Year ...................................... 16
Figure 1  Reported Cases of Lyme Disease – United States, 2009 (CDC, 2010)

Reported Cases of Lyme Disease -- United States, 2009

1 dot placed randomly within county of residence for each confirmed case
Figure 2  Reported Cases of Lyme Disease by Year, United States, 1995-2009 (CDC, 2010)