

Lyme Disease: In the "Lime Light" for Over 25 Years

Kenisha J Evans^{1,*}, Eric Ayers¹, Cassandra E. Stinson¹, Arren E Simpson¹, Delisa Quayson¹,

¹Wayne State University School of Medicine

Abstract

Lyme disease has been a topic of debate practically since its discovery in the 1970's. The hot topic is whether or not long-term antibiotics should be used for Lyme disease patients with persistent symptoms. The source of such a long-running debate stems from the difference in opinions over the cause of long-term, persistent symptoms after treatment in some patients. Toward its end, Medicine has finally begun to embrace the existence of Chronic Lyme Disease, but changes still need to be made in the future.

Corresponding author: Kenisha J Evans, Wayne State University School of Medicine Address: 540 E. Canfield St. Detroit, MI 48201, Email: keevan@med.wayne.edu

Keywords: Lyme disease, Ixodes ricinus complex, juvenile rheumatoid arthritis

Received: Apr 03, 2018

Accepted: May 28, 2019

Published: Jun 13, 2019

Editor: ANGELA Pia Cazzolla, professor for the Master degree of Dentistry and for the in Pediat Vocational Masters Degree ric Dentistry and Dental Traumatology at University of Foggia, Italy.

Introduction

Lyme disease, also known as Lyme Borreliosis, is caused by *Borrelia burgdorferi sensu lato*, a spirochete that is transmitted by ticks of the *Ixodes ricinus* complex [1,2]. This disease was first discovered in Lyme, Connecticut, a small town in eastern Connecticut. Beginning in 1972, a cluster of children had developed what appeared to be juvenile rheumatoid arthritis. Investigators discovered most of these children lived or played in wooded areas with the peak incidence of new cases coincide with tick season, summer and early fall. Additionally, many of the children reported having a unique characteristic annular rash prior to the onset of arthritic symptoms and some even recalled having a tick bite at the same location that the rash had developed³. Although the exact cause still had not been identified, the investigators termed these constellation of symptoms, Lyme disease [3].

It was not until 1977, Allen Steere, a rheumatologist at Yale, affirmed Lyme disease as its own entity [4]. In a prospective study Dr. Steere and a team of researchers evaluated 48 patients with erythema chronicum migrans as its initial marker for the subsequent development of Lyme arthritis. They discovered serum cryoprecipitates associated with the disease clinical activity involving skin and joints [5]. The term erythema chronicum migrans had originally been used by European researchers in the early 1900's, in their evaluation of a similar pattern annular skin rash. Nevertheless, in 1981, it was Willy Burgdorfer and his colleague, Alan Barbour, who were studying spirochetes (spiral- shaped bacteria) from deer ticks, who discovered

the same spirochete that caused both erythema migrans and Lyme disease.

Since that time, to present date, much research has been done and a lot has been discovered about Lyme disease. However, there is a large part that is still unknown, which has caused confusion and controversy regarding the diagnosis and treatment of this disease.

Epidemiology

According to Infectious Diseases Society of America (IDSA), Lyme disease is the most commonly reported vector-borne illness in the United States (U. S.). In 2015, the Center for Disease Control (CDC) reported the majority of Lyme cases were concentrated in the upper Midwestern and Northeastern, however the disease has migrated to other regions of the U. S. In some southern areas of the U. S., a number of cases have been documented of erythema migrans- like lesions [6]. However there is a relatively lower incidence

observed in Northwest regions due to difference in feeding habits of the primary tick vectors. These vectors maintain an enzootic transmission but rarely feed on human [7]. (Figure 1).

Reported Cases, 2015

"Though Lyme disease cases have been reported in nearly every state, cases are reported from the infected person's county of residence, not the place where they were infected"[6].

The national incidence rate was 7.9 cases per 100,000 persons in 2015, and "96% of confirmed Lyme disease cases were reported in 14 states" [6]:

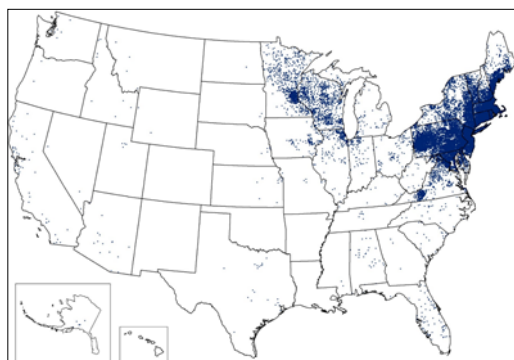


Figure 1.

- Connecticut
- Minnesota
- Rhode Island
- Delaware
- New Hampshire
- Vermont
- Maine
- New Jersey
- Virginia
- Maryland
- New York
- Wisconsin
- Massachusetts
- Pennsylvania

In a 2015 review article entitled "Lyme neuroborreliosis," the authors reported the incidence of cases are 10 times higher than national surveillance per recent retrospective analyses from health insurance data. This data yielded annual rates of incidence for Lyme disease of 100-300 cases per 100,000 persons in US and Germany [8]. The review also states that the prevalence of Lyme Disease cases has increased substantially in the past two decades [8].

Nevertheless, there are many factors that contribute to this epidemiologic transmission dynamics of *Borrelia burgdorferi sensu lato*. These factors include conditions that favor tick survival, the density and

infection rate of local vectors, the abundance and infectivity of reservoir hosts, and the likelihood and duration of human exposure to tick vectors [3].

Presentation

Tick Bite Without Symptoms

People who are exposed to endemic areas will sometimes notice a tick on their skin. It is important to properly remove the tick as promptly as possible. According to the CDC, it takes up to 36 to 48 hours to transmit the bacterium [6]. It is recommended to remove the tick by using fine-tipped tweezers to grab the tick at the skin surface and steadily pull upward. If any mouth parts remain, remove them with tweezers. Thoroughly clean the area with rubbing alcohol, iodine scrub, or soap and water. Dispose of the tick by submerging it in alcohol or flushing it down the toilet [6].

Stage 1: Early Localized Infection

The person may also experience flu-like symptoms such as fever, chills, headache, stiff neck, fatigue, and body aches and pains within days to weeks [9]. (Figure 2).

After injecting into human skin, the spirochete may migrate outward producing an annular or spread hematogenously or through the lymphatics to other organs. An infection begins with the characteristic expanding erythema migrans (EM) as previously described by the Europeans in the early 1900's. Erythema migrans initially develops as a small red spot macule or papule isolated to the site of the tick bite but enlarges within one to two weeks. During this incubation



Figure 2.

period EM center becomes erythematous and indurated and even vesicular [1]. It can be one solid red oval or have the classic "bull's eye" appearance. On the other hand, most patient may not remember a preceding tick bite due to the size of the nymphal Ixodes richness complex ticks [1].

Stage 2: Early Disseminated Infection

Infection with *B. burgdorferi sensu* may not become symptomatic until its progression to Stage 2 and 3. Typically, stage 2 occurs within 3 to 10 weeks of inoculation and characterized as disseminated infections via hematogenous spread. Patients may develop multiple erythema migrans, with severe headaches and mild stiff neck, meningitis, cranial nerve VII palsy, carditis, AV block, migratory musculoskeletal pain and borrelia lymphocytoma. Borrelia Lymphocytoma is an uncommon presentation of early lyme disseminated infection that has only been reported in Europe. It is a bluish-red nodular lesion that appears most commonly on the ears in children and the nipple in adults but may also appear on the nose, extremities, and scrotum [1,10,11,12.]

All signs and symptoms of stage 2 are intermittent and often changing. Some patients with untreated symptoms may become less severe and even have disappearance of symptoms within weeks of staging [1]. Harrison's Principles of Internal Medicine, reports about 15% of patient present with nonspecific systemic symptoms at stage 2 and another 15% may develop frank neurologic abnormalities such as meningitis, peripheral neuropathy cerebellar ataxia, sensory or motor radiculoneuropathy.

Stage 3: Late Disseminated Infection

After month to years of proceeding Ixodes complex tick infection, patients untreated are classified as stage 3. There is usually a period of latency [1,10,11,12]. Persistent arthritis is the hallmark of this stage. Patients may experience patterns of intermittent attacks of oligoarticular arthritis particularly in large joint like the knees. However, patients may also develop encephalitis or acrodermatitis chronica atrophicans (ACA) [8]. ACA typically affects elderly woman who presents with solitary macular or annular erythemas often located in or near intertriginous areas such as the groin, axilla or popliteal

fossa [13]. Lymphadenopathy may also be present [1,10,11,12].

Chronic Lyme Disease

In some Lyme disease patients, symptoms persist for years even after appropriate treatment. Chronic infection leads to persistent musculoskeletal, neurologic and cardiac symptoms that are the hallmark of chronic lyme disease. The nature of such chronic condition and its therapeutic management is of much debate.

Treatment

According to the IDSA's 2006 guidelines the antibiotic, route of administration, and duration are all determined by the patient's clinical manifestations and stage. Table 1 and Table 2 summarize the IDSA's 2006 treatment guidelines for Lyme disease.

The Controversy

The CDC defines the persistent symptoms of fatigue, pain, or joint and muscle aches, lasting greater than 6 months in Lyme disease patient after proper treatment, as "Post-Treatment Lyme Disease Syndrome" (PTLDS) [6]. On the other hand, the IDSA refers to this consolation of symptoms as Post-Lyme Syndrome and argues that there is no concrete evidence that spirochetes persist in these patients. The IDSA propose that the chronic symptoms are due to an autoimmune response. Therefore they disagree with the use of long-term antibiotics for persistent symptoms of Lyme disease. In contrast, the International Lyme and Associated Diseases Society (ILADS) insist that the chronic symptoms are due to the persistence of spirochetes and define these symptoms as "chronic Lyme disease" (CLD). The ILADS conclude that the bacteria are undetected by traditional assay test. They contend that long term antibiotics should be used to combat Chronic Lyme Disease.

In 2006, the IDSA developed and released treatment guidelines, which advised against long-term antibiotic treatment. However the resultant guidelines failed to address persistent spirochetal infection in chronic Lyme disease patients, who often remain symptomatic after short-term antibiotic therapy [14]. These guidelines influenced medical practitioners' treatment decisions and had been used by

Table 1. Clinical presentation and therapy for the stages of Lyme Disease¹⁰.

Disease Stage	Clinical Manifestations	Treatment	Duration
Stage 1: Early localized	Erythema migrans	Oral Therapy	14-21 days
Stage 2: Early disseminated	Multiple erythema migrans	Oral Therapy	14-21 days
	Isolated cranial nerve palsy	Oral Therapy	14-21 days
	Meningoradiculoneuritis	Oral Therapy	14-28 days
	Meningitis	Intravenous or oral	14-21 days
	<i>Carditis</i>		
	-Ambulatory	Oral Therapy	14-21 days
	-Hospitalized	Intravenous followed by oral	14-21 days
	Borrelial lymphocytoma	Oral Therapy	14-21 days
Stage 3: Late	Arthritis	Oral Therapy	28 days
	Recurrent arthritis after oral therapy	Oral or intravenous	28 days or 14-28 days
	Encephalitis	Intravenous Therapy	14-28 days
	Acrodermatitis chronica atrophicans	Oral Therapy	14-28 days

Table 2. Adult and Pediatric treatment options, dosages, and routes of administration ^{1,10,11,12}.

	Treatment	Adult Dose	Pediatric Dose
Oral Therapy	Doxycycline (patients > 8 yr)	100 mg twice a day	4 mg/kg (up to 100 mg) twice a day
	Amoxicillin	500 mg three times a day	50 mg/kg (up to 500 mg) three times a day
	Cefuroxime axetil	500 mg twice a day	30 mg/kg (up to 500 mg) twice a day
Intravenous Therapy	Ceftriaxone	2 g once a day	50-75 mg/kg (up to 2 g) once a day
	Cefotaxime	2 g every 8 h	150-200 mg/kg (up to 2 g) every 8 h
	Penicillin G	18-24 million U/d divided every 4 h	200,000-400,000 mg/kg (up to 2 g) every 8 h

Table 3. Comparison of Infectious Diseases Society of America (IDSA) and International Lyme and Associated Diseases Society (ILADS) recommendations for Lyme disease treatment^{10,11,12}.

Treatment Focus	IDSA	ILADS
Treatment of a tick bite without symptoms of Lyme disease	Doxycycline 200 mg single dose	Doxycycline, 100 mg bid for 20 days
Erythema migrans	Doxycycline, amoxicillin, or cefuroxime for 14-21 days	Doxycycline, amoxicillin, or cefuroxime for 28-42 days or azithromycin for at least 21 days
"Persisting symptoms of Lyme disease"	No antibiotic therapy	Multiple agents (individually or in combination) are mentioned without specific doses or duration recommended

insurance companies as justification to deny coverage [15].

This severely diminishes the ability to obtain long-term antibiotic treatment for those patients who have persistent symptoms and who cannot afford to pay out-of-pocket.

In 2008, Richard Blumenthal, the Connecticut Attorney General initiated an investigation into the development of the 2006 IDSA disease treatment guidelines [16]. He accused the IDSA panel of undisclosed conflicts of interest of panel members and its chairman and disregarding the existence of chronic Lyme disease [15].

The New England Journal of Medicine (NEJM) and the American Academy of Neurology (AAN) provided "independent corroboration" that the 2006 guidelines were developed from evidence-based medicine [16]. However, it was later revealed that 11 members of the IDSA guidelines panel were authors of the NEJM article. The AAN had similar overlapping authorship [17]. Both the NEJM and the AAN failed to disclose this obvious conflict of interest.

The investigation was terminated and the IDSA did agree to an independent review of the 2006 guidelines [15]. The independent review by an expert panel was published in 2010. The panel unanimously supported the 2006 guidelines, stating, "No changes or revisions to the 2006 Lyme guidelines are necessary at this time". They also purported that long-term antibiotics

are "unproven and potentially dangerous" [17].

The 2006 IDSA's Lyme Disease treatment guidelines remain unchanged and appear validated. However, several states have enacted laws that allow licensed physicians to prescribe long-term antibiotics for therapeutic reasons for patients clinically diagnosed with Lyme disease. Additionally, Connecticut and Rhode Island have passed laws mandating insurance coverage when long-term antibiotic therapy is deemed medically necessary.

Furthermore, there is still a difference in recommended treatment for certain manifestations of Lyme Disease (Table 3).

Diagnosis

When the hallmark, bull's eye rash or erythema migrans is present during the early stage, the diagnosis is clinically based on history and physical exam and no blood test is required. When there is no erythema migrans rash, the diagnosis is still made clinically and a blood test can help confirm the diagnosis.

The CDC recommends a two-step process when testing blood [6]. These blood tests are most reliable about 2 weeks post-innoculation, as the body has had time to make antibodies. The following diagram shows the steps as laid out by the CDC [6]: (Figure 3).

The first test, an enzyme immunoassay, has high sensitivity, meaning however, there could be false positives and therefore must be confirmed by the

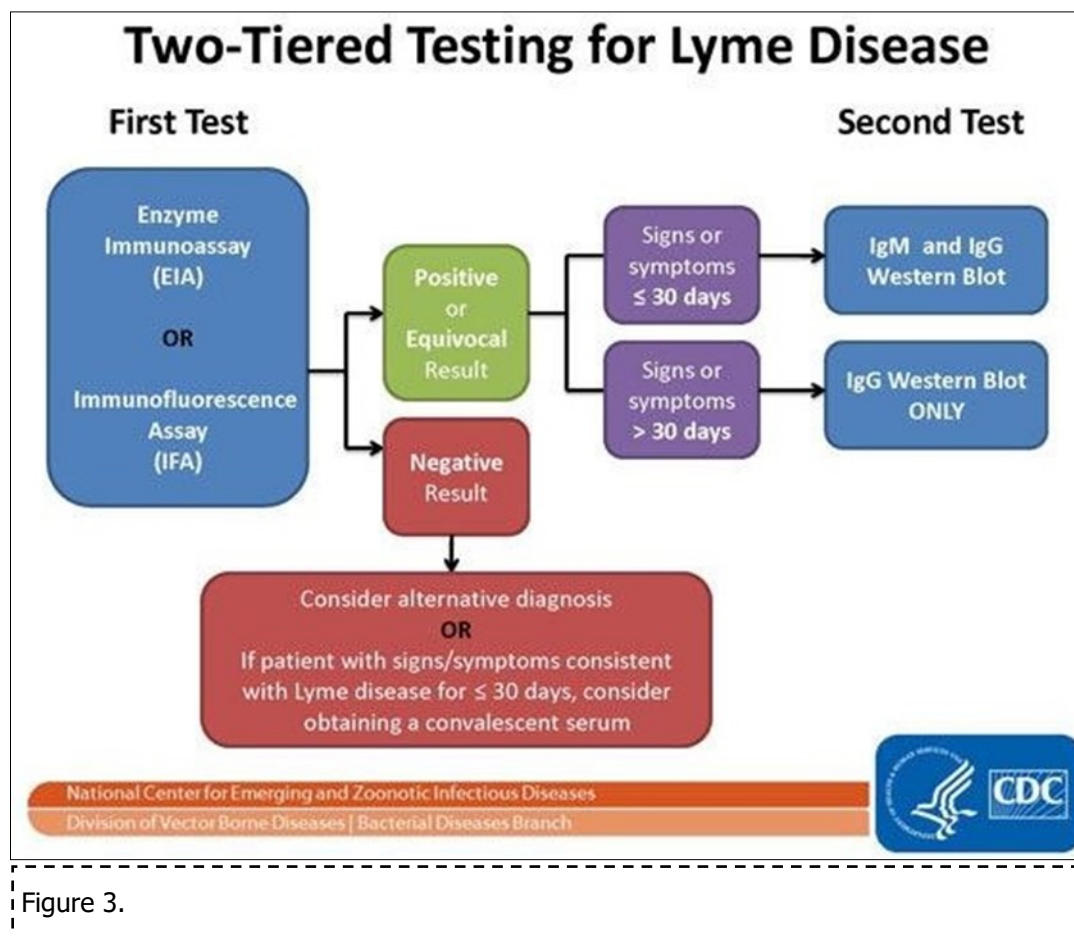


Figure 3.

second test. The second test, an immunoblot test, commonly called a “Western Blot” which has high specificity yet, this means there could be some false negatives. Theoretically when a highly sensitivity test is followed by a highly specific test, only a few true positives are excluded and rarely any false positives are included⁶. Nevertheless for specific laboratory case ascertainment, a positive *B. burgdorferi* culture plus a positive result from the two-tier testing is sufficient in the diagnosis of Lyme Disease for patient with symptoms onset less than 30 days [18].

Differential Diagnosis

Lyme disease is known as the “Great Imitator” because it has very nonspecific symptoms that can look like many other conditions. Patients of Lyme disease are frequently misdiagnosed with chronic fatigue syndrome, fibromyalgia, multiple sclerosis, and various psychiatric illnesses, including depression. Misdiagnosis with these other diseases may delay the correct diagnosis and treatment as the underlying infection progresses

unchecked [18].

As previously stated systemic symptoms of Lyme Disease can be nonspecific and look very much like the flu. Consequently this can make diagnosing Lyme disease very difficult in some patients. One major difference in the constellation symptoms characteristic to the flu, is that in early Lyme disease these symptoms are intermittent with a longer duration in comparison to the flu [1,2].

Finally, it is important to always consider other conditions as well as possible co- infections when Lyme disease is suspected. There are at least four known pathogens in addition to Lyme disease that is transmitted by the black-legged or the Ixodes ticks. The most common co-infections that occur with Lyme disease are Anaplasma

Phagocytophilum, which causes Human Granulocytic Anaplasmosis, previously known as Human Granulocytic Ehrlichiosis; and Babesia Microti, the primary cause of Babesiosis. These co-infections are an

emerging problem and may exacerbate clinical features of Lyme disease [19].

Prognosis

When treated early, Lyme disease is easily and rapidly cleared, preventing later stages of disease. However, these later stages of Lyme disease also respond well to treatment if therapy is commenced soon after the appearance of symptoms [1,2].

Although there continues to be percentage of patients infected with *Borrelia burgdorferi* who develop chronic Lyme Disease, most patients recover fully from this infection [1,2]. It is critical to identify chronic lyme disease patient as their conditions may be intermittent but debilitating.

Conclusion

No matter what side of the fence you stand, Post-Lyme Treatment Syndrome or Chronic Lyme Disease, one thing is abundantly clear, more research still needs to be done!

Though the course has been long and rocky, science and medicine have already taken a step in the right direction when it comes to diagnosing and treating patients with Lyme Disease. Over the next ten years, there should be advancements both academically and pharmacologically that will hopefully take Lyme disease out of the lime light and give much needed relief to those with Chronic Lyme Disease.

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