

Top Ten Lyme Disease-related Scientific Publications of 2013

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Epidemiology and Surveillance

CDC Estimates 300,000 US Cases of Lyme Disease Annually. Kuehn BM. JAMA. 2013 Sep 18;310 (11): 1110. Doi: 10.1001/jama.2013.278331

Background: Traditional CDC surveillance for Lyme disease relies on physician case reporting to their state departments of Health. The number of Lyme disease cases reported increased steadily over the years to around 30,000 cases a year, although significant under-reporting of cases was suspected due to unreliable diagnostics.

Findings: Data from multiple sources including medical insurance claims, clinical laboratories and national surveys cause the CDC to increase incidence 10-fold to about 300,000 new cases of Lyme disease each year.

Cautions: Distribution of cases across the United States is still not fully understood, including the impact of Southern Tick Associated Rash Illness (STARI) in southern states where lone star ticks and *Ixodes* are “different”.

Implications: Lyme disease is clearly a major public health problem. The growing magnitude of cases suggests that complications such as misdiagnosis and rare manifestations may be more prevalent than previously appreciated. False negative rates, even if small, can result in large numbers of misdiagnosed cases. Improved diagnostics are vitally needed.

Poleward Expansion of the White-Footed Mouse (*Peromyscus leucopus*) under Climate Change: Implications for the Spread of Lyme Disease. Roy-Dufresne E et al. PLOS ONE November 18, 2013

Background: Small mammals and birds, especially the white-footed mouse, are the reservoir host where *Borrelia burgdorferi*, the bacterial cause of Lyme disease, survive in the environment. Expansion of this animal reservoir may be related to the spread of Lyme disease into new environmental niches.

Findings: Mild and shorter winters are favoring the northern expansion of the white-footed mouse in Quebec Canada. In southern Quebec, the occurrence of *B. burgdorferi* is associated with high probability of the presence of the white-footed mouse.

Cautions: The expansion of Lyme disease depends on other factors including abundance of deer and relationship of human to their environment. The impact of climate change in southern states and warmer environments is unknown and may not explain the westward and southward expansion of Lyme disease in the Northeast and Mid-Atlantic states.

Implications: Climate change associated with the northern expansion of white-footed mice will likely increase the geographical range of *B. burgdorferi* and impact the public health in Canada and northern regions of the United States that have yet to be exposed to Lyme disease.

Clinical Illness

Three Sudden Cardiac Deaths Associated with Lyme Carditis – United States, November 2012 – July 2013. CDC MMWR 2013 Weekly/Vol. 62/No. 49. 993-996

Background: Lyme disease is a systemic, multi-system infection in which cardiac involvement may occur, typically 3 weeks into infection. Patient reported symptoms of cardiac illness are nonspecific and include lightheadedness, palpitations and rarely passing out. Cardiac illness may also be asymptomatic.

Findings: Three cases of sudden death due to cardiac Lyme disease were reported to the CDC. None of the cases had an erythema migrans skin lesion, but two of the three cases had nonspecific symptoms including musculoskeletal pain, malaise, shortness of breath and anxiety 1-2 weeks before death. Examination of heart tissues at CDC demonstrated diffuse mixed perivascular lymphocytic pancarditis. ELISA and IgM Western blot serology was positive for all three cases. No case had a (+) IgG Western Blot. Two of the cases were discovered by the tissue bank pathologist prior to organ donation.

Cautions: Results from case reports cannot be used to calculate the overall frequency of disease and so it is not known if this report represents a trend or emergence of more virulent strains of *Bb*.

Implications: Clinical series can provide important clues into disease manifestations. In this case the take home point is that nonspecific symptoms can be the presenting manifestation of a serious illness and that they need to be taken seriously and properly evaluated understanding the unique circumstances and risk factor present in the given case, including added vigilance in Lyme endemic regions.

The nonspecific nature of Lyme disease symptoms may lead to underdiagnosis of blood-borne disseminated infection. Infection of blood and tissues may represent a public health risk for transfusion and organ donation. Unrecognized cardiac disease may result in sudden death of individuals eligible for organ donation.

Chronic Lyme Disease

Development of a Foundation for a Case-definition of Post-Treatment Lyme Disease Syndrome. Aucott JN, Crowder LA, Kortte KB; Int J of Infectious Dis. 2013 June; 17 (6): e443-e449

Background: Chronic Lyme disease (CLD), as experienced in community-based healthcare settings, is a heterogeneous group of illnesses, with each patient having a unique and complex medical history, resulting in broad variation of symptoms and disease progression. Post-antibiotic Treatment Lyme Disease Syndrome (PTLDS) refers to a narrowly defined group of patients seen in research settings. One great difficulty in understanding CLD comes from the lack of definitions and controlled studies of PTLDS.

Findings: In a research setting, PTLDS can be defined and identified in a low risk group with ideally diagnosed and treated early Lyme disease. This group of patients is distinct with decreased health related function that is different from other treated Lyme patients and controls. An intermediate group of patients have persistent symptoms after treatment of Lyme disease, but maintain normal health related function.

Cautions: These finding may not be generalizable to Lyme disease patients who are diagnosed and treated at later stages of Lyme disease or have initial misdiagnosis and treatment.

Implications: This study shows that PTLDS patients can be defined by a combination of identifiable symptoms and measurable functional outcomes. PTLDS patients have an illness that is measurably different than the norm of the general population.

Immunology of Lyme Disease and PTLDS

Elevated Levels of IL-23 in a Subset of Patients with Post-Lyme Disease Symptoms

Following Erythema Migrans. StrleK, StupicaD, Drouin EE, Steere AC, Strle F, Clin Infect Dis 2013 Dec 4

Background: Chronic Lyme disease, as experienced in community-based healthcare settings, is a heterogeneous group of illnesses, with each patient having unique immune system exposures and responses. Post-antibiotic Treatment Lyme Disease Syndrome (PTLDS) refers to a narrowly defined group of patients seen in research settings. The causation of chronic Lyme disease and PTLDS remains controversial. Studies of PTLDS may begin to elucidate some of the pathophysiology involved in the heterogeneous diseases that make up CLD and syndromes such as fibromyalgia and chronic fatigue whose symptoms overlap with PTLDS.

Findings: PTLDS may be associated with immune system abnormalities that perpetuate symptoms after antibiotic therapy. Elevated IL-23 cytokine levels and certain autoantibodies were associated with PTLDS.

Cautions: These finding may not be generalizable to Lyme disease patients who are diagnosed and treated at later stages of Lyme disease or have initial misdiagnosis and treatment. The mechanism of illness in PTLDS may have limited applicability to those currently identified with CLD. Findings from patients in European Lyme disease may not be generalizable to North American Lyme disease. Determining whether spirochetal eradication has occurred was not fully or conclusively examined in this study.

Implications: Findings of ongoing immune activation in a subset of individuals with ideally diagnosed and treated Lyme disease opens the door to dissecting the pathophysiology of the objective physiology of this illness. Cytokines and other inflammatory signaling proteins may be candidates for future diagnostic tests for PTLDS.

Potential Immune Response Markers for Diagnosis of Lyme Disease

Cerebrospinal fluid CXCL13 in Lyme neuroborreliosis and asymptomatic HIV Infection.

Bremell D. et al. BMC Neurology 2013, 13:2-8

Background: The human immune system produces proteins to recruit immune cells to the sites of infection. Immune system autoantibodies and inflammatory proteins are used for diagnosis and monitoring response to therapy in other diseases such as Lupus and Rheumatoid arthritis.

Findings: This study looked in the cerebrospinal fluid (CSF) in patients with Lyme neuroborreliosis (LNB) for inflammatory proteins that signal infection to the human immune system. Patients with documented neurologic Lyme disease had very elevated levels of CXCL13 in CSF that rose early in the course of LNB and declined significantly with antibiotic therapy.

Cautions: Markers of immune responses may not be specific for Lyme disease (e.g. CSF CXCL13 is also elevated in neurologically asymptomatic HIV patients) and therefore may not make good diagnostic tests.

Implications: The host inflammatory response in Lyme disease may be used to discover new diagnostic tests for detecting infectious complications such as neurologic disease or chronic infection. The diagnostic value of CSF CXCL13 elevations for neurologic Lyme disease deserves further exploration. Other inflammatory markers may be discovered that can indicate other complications of *Bb* infection.

Tick-Borne Pathogens other than Lyme Disease

***Borrelia miyamotoi* Infection Presenting as Human Granulocytic Anaplasmosis: A case report.** Chowdri HR et al. Annals of Internal Medicine 2013 Jul 2;159 (1):21-7

Background: While *Borrelia burgdorferi*, the agent of Lyme disease, accounts for the vast majority of tick-borne infection, other borrelia species and other bacterial, viral and protozoal pathogens can cause tick-borne infection as well. In Europe the closely related species *B. garinii* and *B. afzelii* cause a significant percentage of Lyme disease cases. A newly identified human pathogen *Borrelia miyamotoi* causes a Lyme-like illness in Eurasia and N. America. It is known that all of the different tick-borne infections can present with nonspecific infectious symptoms such as myalgia, headache, and fever.

Findings: A new cause of tick-borne infectious disease called *B. miyamotoi* presents with an illness that is indistinguishable from other common tick-borne infections. This case report describes two patients initially suspected of having Anaplasmosis who were diagnosed using research laboratory PCR testing to have infection with *B. miyamotoi* instead.

Cautions: It is not known how common infection with *B. miyamotoi* is in the United States or what percentage of tick-borne infections or co-infections it may cause.

Implications: The ability of newly discovered tick-borne pathogens expands the range of diagnostic needs in patients with nonspecific febrile illness. The lack of commercially available diagnostic tests for *B. miyamotoi* limit the ability of clinicians to diagnosis this tick-borne pathogen. Empiric use of doxycycline in patients with febrile acute infections and risk factors for tick-borne pathogens may be a reasonable strategy for empiric treatment.

Changing epidemiology of Powassan encephalitis in North America suggests the emergence of the deer tick virus subtype. Khoury MY, Cargo J, Wormser G.; Expert Rev. Anti Infect Ther. 11 (10), 983-985. (2013)

Background: Different tick species occur across North America that are responsible for transmitting different tick-borne diseases. In general, tick-pathogen relationships are specific with the majority of any one disease causing pathogen being transmitted by only one tick species. For example, Anaplasma is transmitted by the deer tick, *Ixodes scapularis*, and Ehrlichia by the Lone Star Tick, *Amblyomma americanum*. However, one species of tick may transmit more than one co-infectious pathogen in a single bite (For example, a single deer tick bite can transmit *Bb*, Anaplasma, and Babesia.) The encephalitis causing Powassan virus is a pathogen known to be transmitted by *Ixodes cookie* ticks.

Findings: A new strain of Powassan virus has emerged that is transmitted from white-footed mice by *Ixodes scapularis* deer ticks. The new Powassan strain has been found mainly in Wisconsin, Minnesota and New York. Transmission of the virus is rapid, occurring as soon as 15 minutes after the beginning of a deer tick bite. Neurologic disease from Powassan virus is severe with 10-36% fatality rate and significant disability in many survivors of infection.

Cautions: It is not known what percentage of infections with Powassan virus are asymptomatic or whether infections due to the new strain of Powassan virus will increase in frequency.

Implications: The ability of a new strain of Powassan virus to adapt to a new tick vector dramatically expands its ability to impact larger at risk populations. *Ixodes scapularis* tick bites are much more common than *Ixodes cookie* tick bites. This may lead to significantly increased numbers of cases of Powassan virus over time and over larger geographic regions.

Lessons from Animal Models of Lyme Disease

Dynamics of connective-tissue localization during chronic *Borrelia burgdorferi* infection.

Imai DM et al. Laboratory Investigation (2013) 93, 900-910

Background: The human immune system is responsible for controlling infection and preventing re-infection by bacterial pathogens such as *Borrelia burgdorferi*. Humans defend themselves against typical bacterial pathogens using a system called the adaptive immune system that makes immune cells and antibodies to fight infections. Atypical bacteria such as tuberculosis and syphilis are known to be able to evade the adaptive immune system and establish chronic infection. The mechanism by which *Bb* establishes chronic infection can be most easily explored using animal models where tissues samples can be easily obtained and analyzed.

Findings: This study using the mouse animal model of chronic Lyme disease provides insights into how *Bb* may persist in protected niches defined by collagen rich tissues in the skin, connective tissues of the joints, tendons, ligaments and the tissues surrounding nerves. Decorin is one of the molecules that *Bb* recognizes and binds to in the connective tissue. This study suggests that *Bb* is able to evade the immune antibodies by binding to decorin in protected collagen environments.

Cautions: Mechanisms of immune response and bacterial persistence in animal models may not be the same as human infection.

Implications: The mechanism of immune evasion in human Lyme disease is poorly understood. To the extent that the interaction of *Bb* with the mouse informs us about human immune responses there may be protective environments in which *Bb* hides from the human immune system. While difficult to do, studies in humans should attempt to obtain human tissue to examine for *Bb* persistence in collagen rich connective tissue.

Microbiology of *Borrelia burgdorferi*

A Manganese-rich Environment Supports Superoxide Dismutase Activity in a Lyme Disease Pathogen, *Borrelia burgdorferi*. Aguirre JD et al. J Biol Chem. 288. No 12: 8468-78

Background: The Lyme disease pathogen *B. burgdorferi* is a unique bacterial pathogen that has evolved to persist in its host. Humans tightly limit the availability of free iron as a defense against most bacterial infections. However, *Bb* is unique in its lack of need for iron in its metabolism. An important *Bb* enzyme called SodA superoxide dismutase (SOD) is essential for virulence and human infection and is adapted to using manganese as a co-factor.

Findings: SodA is essential for *Bb* virulence. *Bb* has the ability to accumulate the high levels of manganese needed to activate SodA. The unique properties of the *Bb* SodA may represent adaptation to expression in the manganese-rich and iron-poor animal environment in which *Bb* lives.

Cautions: These laboratory findings may not apply to the complex environment in which *Bb* lives in animal tissues.

Implications: The reliance of *Bb* SodA on manganese for metabolism and virulence may present an opportunity to discover new approaches for prevention and treatment of Lyme disease.