The Controversies, Challenges and Complexities of Lyme Disease: A Narrative Review.

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ABSTRACT - Purpose: Lyme disease has become an increasingly important global public health concern. **Method:** A narrative review was conducted and designed to present a broad perspective on Lyme disease, and describe its history and development in terms of clinical care and public health implications. A structured literature search was conducted based on the question; *what is currently known about Lyme disease?* **Results:** The narrative review is presented in chronological order in terms of a summary of the history of Lyme disease, the complexities of clinical diagnosis, the problematic interpretation of serologic testing, the conflicting guidelines for diagnosis, treatment and management of chronic Lyme, and benefits of antibiotic treatment. **Conclusion:** Despite growing global incidence of the Lyme disease, treatment has not attracted pharmaceutical investment, and the evidence base and international guidelines for treatment and management of chronic Lyme continue to be conflicting and controversial. The challenges of this immune mediated tick borne disease for public health policy and clinical practice are summarised, alongside directions for future research.

INTRODUCTION

Lyme disease has become an increasingly important global public health concern.[1,2,3] Lyme disease was originally identified in Lyme, Connecticut, and was based on an unusual cluster of children with juvenile rheumatoid arthritis.[4] Geographic distribution and incidence of Lyme disease is on the increase worldwide, and has become the most common vector-borne illness in Europe particularly Austria, Czech Republic, Germany, Slovenia, and Switzerland; and in China, Australia, Africa and North East United States (US).[2,5,6,7,8,9,10,11] Lyme disease or Lyme Borreliosis is caused by spirochaetes of the *B burgdorferi sensu lato o* species complex and is transmitted by infected *Ixodes scapularis* or *Ixodes ricinus* ticks.[5,6,7,10,11] In 2000, Rowe reported that Lyme disease in Europe is caused by any one of three tick borne spirochetes in the *B. burgdorferi sensu lato* complex—*B burgdorferi sensu stricto*, *B afzelii*, and *B garinii*, whereas in the US, only the first species is involved. A new Borrelia genospecies causing Lyme Borreliosis has since been identified in the US.[12] In 2016, it is estimated that between 20 and 25% of ticks in Europe are infected with *B burgdorferi sensu lato*, with risk of symptomatic infection after a tick bite estimated to be between 1 and 3%.[13] Co-infection with other pathogens (*Ehrlichia, Neoehrlichia, Rickettsia, Babesia* and *Theileria*) is also on the increase worldwide. There is no vaccine to prevent Lyme Borreliosis.[11] Prevention strategies centre on use of insect repellents, application of pesticides and removal of ticks, with no pharmacological prevention strategy available.[10]

METHODS

A narrative review was conducted and designed to present a broad perspective on Lyme disease, and describe its history and development in terms of clinical care and public health implications. A structured literature search was conducted based on the question; *what is currently known about Lyme disease?* Search terms include Lyme, Lyme Borreliosis, Chronic Lyme Disease, Borrelia burgdorferi, and tick borne disease. Studies were excluded if not in the English language and if they did not present detail on Lyme disease. There was no restriction on date range, and all types of articles, including opinion pieces were included. The narrative review is presented in the form of an *Editorial* and in chronological order in terms of the following key themes; a summary of the history of Lyme disease, the complexities of clinical diagnosis, the problematic interpretation of serologic testing, the conflicting guidelines for diagnosis, treatment and management of chronic Lyme, and benefits of antibiotic treatment.

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RESULTS

History of the Disease

Lyme Borreliosis is an immune mediated disease secondary to exposure to *Borrelia burgdorferi*.[4,5] It is a complex disease where both the specific disease causing organism and the host responses appear to affect the disease course.[14] Different strains of *Borrelia* are exist with clinical manifestations of Lyme disease (and co-infections) varying between the US and Europe, and characterised by a diverse range of acute and chronic manifestations.[15] It is similar to another spirochetal disease, namely syphilis, in that it can be divided into three key stages; *early; early disseminated* and *late disseminated* manifestations of the disease.[7] Infection progresses to disseminated disease in approximately 50% of untreated individuals.[16,17,18,19,20,21,22,23] CDC estimates that between 10 and 20% of patients who are appropriately treated for infection will remain symptomatic for a variable and unspecified length of time.[18] The public health impact of Lyme disease where estimated (in the Netherlands) carries a substantial burden of disease.[24]

The Complexities of Clinical Diagnosis

The clinical diagnosis of Lyme is based on clinical manifestations and appropriate serology.[4] Early manifestations include nonspecific signs and symptoms such as headache, fever and myalgias.[10] The disease typically commences with an erythematous rash known as *erythema migrans* (EM),[4,25] due to local skin infection which is observed in between 60–80% of infected people several days to weeks after the tick bite.[10,11] The EM rash expands by 2-3cm per day over several days with some parts clearing to result in a bulls eye image.[10] Diagnosis of Lyme borreliosis is based on patient history of potential exposure to ticks, infection risk with *B. burgdorferi sensu lato,* the EM rash and development of specific symptoms, exclusion of other causes and appropriate serological or other diagnostic tests indicating a positive a positive *Borrelia* serology.[6,7,26] Epidemiologic context is extremely important, with the probability of a tick bite (likelihood of contracting Lyme disease) highest in individuals who spend time outdoors (particularly in wooded, brushy, or grassy habitats) in a geographically endemic area, and at certain times of year. Hence, patient travel history is especially important in clinical practice, as individuals may be infected not locally, but as part of a visit abroad to a geographic areas endemic for Lyme or co infections.[18,27,28] Dissemination occurs soon after the tick bite, but signs and symptoms of late disease may not be evident for weeks, months or even years.[3,28,29,30,31] Early dissemination of this multi-systemic, multistage, inflammatory disease can involve the skin, muscles, joints or the central nervous and peripheral nervous systems.[32] The infecting pathogen can spread to organs and other tissues, and can severely affect the patients nervous system, joints, heart and skin.[4,5,11,26,32] Arthritis is the most common late state symptom in the US, but in Europe, radiculomyelitis, peripheral neuropathy, or chronic skin involvement (acrodermatitis chronica atrophicans) is more common.[14] Lyme carditis is a real diagnostic and therapeutic challenge for clinicians.[5] It is not uncommon for patients to initially present with late stage disease.[3] This complicates clinical diagnosis, with additional complicating factors making diagnosis problematic including the negation of tick bite, absence of EM, atypical clinical picture, onset of symptoms outside of the period of tick activity, and negative serological results in the initial stages of the disease.[5,10,33] More recently, the debate centres around the ICD system for Lyme Borrelisis, where the diverse range of manifestations, stages and complications of this disease are not stated, and are restricted to the acute form of Lyme.[2]

The Problematic Interpretation of Serologic Testing

Complications exist around the role of serologic testing in the clinical diagnosis and management of the patient.[3] Serologic tests, enzyme-linked immunosorbent assays (ELISAs), and Western blots are used by clinicians to diagnose untreated Lyme disease.[34,35] Most commercial laboratories will perform both IgG and IgM Western blots.[18,36,37] Interpretation of serology is however problematic and centres on assay heterogeneity, high background sero-prevalence in endemic areas, lack of clinical validation of assays in Europe, accuracy of antibody tests, and the presence of diverse strains of Borrelia in the US and Europe, all of which contribute to delays in diagnosis and patient treatment.[3,38,39,40,41,42,43] *B. burgdorferi* antibody testing should be performed only in patients presenting with clinical signs suggestive of infection.[1] Complexities lie in the early stage of disease where the antibody test may not indicate a positive result, rendering treatment ineffective. It is important that serologic features are interpreted correctly in order to avoid a false diagnosis of Lyme disease.[4,44] Serologic features are often misinterpreted, and false positives can occur if confirmatory laboratory testing is not

conducted.[4,33] Complexities additionally occur when clinicians use serology to rule in or out persistent Lyme disease,[3] with some disagreement on this approach with current evidence suggestive that none of the available clinical serologic tests can determine if a patient has ongoing infection. Positive serology in patients who have been treated for Lyme is not indicative of ongoing infection.[3,18] Finally, it is '*not all about Lyme',* and many clinicians fail to test for other co-infections with similar clinical manifestations as Lyme, both tick borne (*Babesia, Rickettsiae, Anaplasma, Bartonella, Q fever*) and non-tick borne (*Chlamydia pneumonia, Mycoplasma pneumonia*). Hence, there remains a clear difficulty in the lack of a '*gold standard'* as there is no antigen specific or PCR specific test commercially available worldwide for clinicians to use, and testing relies on imperfect indirect immunological measures to assist with diagnosis. Rapid detection using tick tests for *B burgdorferi sensu lato* infection are limited in terms of sensitivity and specificity and not recommended to guide treatment.[13]

Conflicting Guidelines for Diagnosis, Treatment and Management of Chronic Lyme

Despite growing global incidence of the Lyme disease, treatment has not attracted pharmaceutical investment, and the evidence base and international guidelines for treatment and management of chronic Lyme continue to be conflicting and controversial.[1,45,46] Treatment is generally with antibiotics such as doxycycline, amoxicillin or cefuroxime (2-4 weeks) and is generally more successful for early forms of the disease.[3,9,11,28] Early short-term prophylaxis with oral doxycycline is however contraindicated in children under 8 years and pregnancy.[10] Azithromycin is a potential antibiotic agent for prophylactic topical use.[47,48,49] Guidelines are conflicting. CDC[8] recommends according to the Infectious Disease Society of America (IDSA) guidelines for the treatment of Lyme disease. These guidelines recommend early prophylactic antibiotic treatment with doxycycline if patients have a recognized tick that has been present for over 36 hours judged from the degree of engorgement of the tick, with treatment started within 72 hours of the tick being removed, there is evidence of *B. burgdorferi* in over 20% of ticks in the area where the tick bite occurred and doxycycline is not contraindicated. The guidelines stress the importance of identifying the *Ixodes s*pecies of tick before treatment may begin. This however may not always be possible if the tick has been removed by the patient. Very few countries have the expertise to be able to make such identification, and clinicians may advocate that patients who have a tick-borne infection for periods shorter than 36 hours would also benefit from antibiotic treatment. IDSA[39] recommend antimicrobial treatment with oral doxycycline when erythema migrans develops. However, this approach is associated with systematic drug exposure for 10-21 days, with sub clinical infection not effectively treated and potentially allowing the disease to progress.[10] Failures can however occur with shorter course treatments for early Lyme infection. Hence, guidelines for the management of patients with Lyme disease developed by the International Lyme and Associated Diseases Society (ILADS) and the German Borreliosis Society[50] favour longer term, combination antibiotic therapies.

Controversy continues around whether infection persists and causes chronic symptoms, despite antimicrobial treatment.[9] The debate centres on whether clinical manifestations are active infection or post-infectious auto-immunity. Patients with ongoing persistent symptoms after the standard 2-4 week recommended antibiotic therapy have been denied further antibiotic treatment.[46] This is a result of the ongoing controversy around whether long term chronic infection with the Lyme spirochete, *B.burgdorferi,* and associated tickborne pathogens is exists.[9,46,51] Clinical challenges therefore exist in the treatment of disparate patient groups, which include patients with untreated late-stage infection (late neuroborreliosis), patients with subjective symptoms that persist after treatment (*'post-treatment Lyme disease syndrome': PTLDS*), and patients with unexplained subjective complaints which may or may not be accompanied by positive test results for *B. burgdorferi* infection in serum (here called *'Chronic Lyme disease: CLD*)[1,52] CLD is used to describe a range of atypical symptoms such as fatigue and chronic pain which occur due to lengthy *B.burgdoferi* infection.[53,54] CLD currently lacks an accepted clinical definition, and generally diagnosed patients have other illnesses.[1] PLDS describes patients who, after treatment for Lyme disease with an accepted treatment regimen, present within 6 months or many years later, with non-specific symptoms such as fatigue and widespread musculoskeletal pain. Complexities centre on the fact that CLD and PSLD share similar clinical symptoms to *Fibromyalgia* and *Chronic Fatigue Syndrome*, and with misdiagnosis of *Fibromyalgia* and *Chronic Fatigue Syndrome* occurring in patients with CLD/PSLD.[28,51,52,55] It is uncertain what pathophysiologic mechanisms (or

multiple mechanisms) are responsible for Lyme disease.[3] These include presence of other untreated infections; a post-infectious state; permanent or temporary tissue damage; secondary conditions triggered by the initial infection and persisting despite bacterial eradication; immune dysfunction due to auto-antibodies or unregulated inflammation, and/or persistent *B burgdorferi* infection. Supporting evidence for most of these mechanisms are limited.[28,45] There is support for all potential mechanisms, with exception of persistent infection,[18,28,56] with some maintaining that persistent infection is a demonstrated cause of persistent Lyme disease, with other mechanisms playing a role.[45,57]

Benefits of Antibiotic Treatment.

Controversies are evident around clinical management and the potential benefits of antibiotic treatment.[3] The challenges of Lyme disease centre on the lack of evidence to support use of antibiotics for longer than 4 weeks, or the persistence of spirochaetes in treated patients.[4,11] There have been a number of '*point and counterpoint'* editorials on the benefits (or not) of longer treatment for Lyme disease.[46,58,59] IDSA and CDC do not recommend prolonged treatment with antibiotics[18,28] and some studies advocate against prolonged treatment in these patients.[11,60,61] Others in contrast indicate that retreatment[45,62] and prolonged antibiotic therapy may be useful and justifiable in patients with persistent Lyme disease symptoms, and with coinfection with tick borne agents.[46] Frequent treatment relapses and failures with short term therapy are documented by other authors.[31,63,64,65] The safety of long term antibiotic use, for three to six months, or longer, has now been demonstrated and can provide a new possible avenue for treatment.[50,66,67] Longer courses of antibiotic treatment and re-treatment are reported to incur benefit for Lyme disease patients with persistent symptoms.[57,68,69,70] A limited number of NIH-funded trials have been conducted on the treatment of chronic Lyme disease,[71,72,73] with two of the three clinical trials demonstrating that re-treatment improved some patients' measures, such as fatigue and pain.[71,73] Others have shown improvement in cognitive function, in those with Lyme encephalopathy.[62] Antibiotic treatment is also effective in about 90% of patients with Lyme arthritis.[74] Hence, the challenge of having no '*gold standard'* to determine *'objective markers'* makes recommended clinical pathways debatable.

DISCUSSION

The author recognises that narrative reviews whilst useful for providing a broad historical overview of a public health topic, are a dynamic process and are therefore not reproducible, and may contain selection bias. That said, this *Editorial* intends to bring together key themes pertaining to Lyme disease, and has highlighted and drawn attention to the complexities of clinical diagnosis of Lyme disease, interpretation of definitions and treatment guidelines, and challenges for clinical practice and public health. Lyme disease represents a serious challenge for global and national health organizations.[1,2,3,45,75] It is a complex and debilitating illness with patients experiencing both acute and persistent manifestations, which impair quality of life, and yet are poorly understood.[45] Despite growing global incidence of the Lyme disease, treatment has not attracted pharmaceutical investment, and the evidence base and international guidelines for treatment and management of chronic Lyme continue to be conflicting and controversial.

Challenges for clinicians centre on the lack of sensitive laboratory techniques available to optimally diagnose, and the debate as to recommended management of the disease as to whether conditions can become chronic. Patients suffering from this disease are in an unenviable position, caught between clinicians from opposing peer reviewed clinical guidelines generated by IDSA and ILADS. Patients have established their own special groups to provide advocacy for their cause. Polarisation within the different Lyme related guidelines and debates that are circulating within different special interest groups continues[18,76,77,78,79,80,81,82,83] and contribute to a unique and critical public health phenomenon whereby patients and individuals suffer. In the context of public health policy, public awareness raising warrants a stronger approach,[2] including in terms of governmental travel guidance yielding accurate health warnings for travellers in the countries and regions under the wide global range of borreliosis.[45] It is vitally important to utilize an enhanced set of ICD codes to ensure quality of *borreliosis* surveillance to inform national prevalence data, burden of disease estimates, public health policy and the direction of patient and population awareness raising.[2] Enhanced epidemiological studies of the prevalence of infections in different locations, in different wildlife populations and in ticks themselves are warranted, alongside rigorous investigations into

the clinical conditions of individuals found to be positive.

Further it remains paramount to support investment of resources to better understand the disease pathway and its pathophysiologic mechanisms, identify variables associated with poor patient outcomes and to develop effective preventative and therapeutic regimens for known tick bites, EM rashes and persistent disease.[4,9,33,45,52,58,84,85] Developing enhanced and sensitive assays targeting the diverse ranges of Borrelia species is warranted so as to support speedy diagnosis and treatment across the globe. Lastly, of great concern is the misdiagnosis and untreated tick borne diseases often diagnosed as chronic inflammatory aged related degeneration (for example arthritis, dementia, stroke), and notwithstanding the increased complications with aging for those with Lyme disease. Particular efforts to better understand chronic Lyme are warranted, and within the sphere of supporting those whose lives and existence are severely compromised. Of note is low awareness in the few studies who investigated medical practitioner awareness of Lyme disease, highlighting the need for continued medical education to reduce misdiagnosis and inappropriate treatment.[2,75,86] The scientific uncertainty and the wide range of treatment modalities underscore the need for shared decision-making and enhanced support for those suffering from the disease.[3,87,88,89]

AUTHOR STATEMENTS

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