Preface

Lyme Disease: Knowing Good Evidence to Help Inform Practice

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Editor

Depending on the clinical situation and presence or absence of preconceived notions, evaluations for Lyme disease can range from efficient visits solved with a short course of antibiotic therapy to involved encounters that include a review of long-standing, nonspecific symptoms such as fatigue and pain that are less likely to represent an active infection. While the majority of patients with authentic Lyme disease improve with treatment, some have a slower resolution of symptoms and still others appear to have problems persisting beyond 6 months, which is called posttreatment Lyme disease syndrome (PTLDS). Those who have true *Borrelia burgdorferi* infection are relatively easily to determine; however, others may be well complicated by confusion regarding test result interpretation as well as competing ideas about Lyme disease from Internet sources or alternative practitioners who often use the term "chronic Lyme disease" or diagnose concomitant tick-borne coinfections. As Lyme disease is the most common vector-borne infection in North America, clinicians who diagnose and treat Lyme disease need to be aware of not only evidenced-based recommendations but also opposing ideas and theories that may be part of an office-based evaluation and discussion.

A PERSONAL PERSPECTIVE

As a young faculty member in the mid-1990s, I was asked to see patients in a newly established outpatient clinic in suburban Baltimore County, Maryland. Having just completed my infectious diseases fellowship, Lyme disease was a bit of a novelty

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diagnosis during my training at Johns Hopkins Hospital, located deep as it is in urban Baltimore City, a locale decidedly free of ticks. On occasion, a patient referred from the suburbs would be hospitalized with advanced heart block deemed due to *B burgdorferi* that an antibiotic appeared to solve rather quickly for expeditious discharge. Otherwise, my experience with this tick-borne pathogen was minimal. The 1995 publication of codified serologic testing to assist in the diagnosis of patients with Lyme disease was not something mentioned or discussed by my teachers during training.[1] My clearest recollection of a useful quote from that time was that Lyme disease "hadn't crossed the Potomac and doesn't occur in the mountains," a seemingly useful phrase that seemed to have geographically appropriate Civil War–based overtones backed up by early serologic studies.[2,3] When treatment for Lyme disease was discussed, most experts recommended 2 or 3 weeks of antibiotics such as doxycycline or amoxicillin with resulting success.[4,5] So, armed with this perspective, I found myself underprepared for what soon became the most common reason for outpatient infectious diseases consultation: to assist in the diagnosis and the treatment of Lyme disease. More often than not, these evaluations were often neither easy nor quick for me or many of my patients. These experiences soon prompted an in-depth education and fascination for this infection, which even in my first few years often seemed to be diagnosed more liberally in Maryland than suggested criteria.[6]

EPIDEMIOLOGY

From the initial 1976 clinical description by Steere and colleagues[7,8] of Lyme arthritis among a cohort of children afflicted with an apparently epidemic form of joint disease to the final isolation of the causative spirochete by Willy Burgdorfer and colleagues[9] in 1981 from ticks from Shelter Island, New York, the range of potential problems caused by this infection grew to include the characteristic erythema migrans rash as well as cardiac and neurologic problems. From this New England and Mid-Atlantic base, Lyme disease has expanded geographically over the past decades, but remains an infection for which key clinical questions depend on the epidemiology of whether a given patient may have had a tick bite by an *Ixodes scapularis* tick potentially carrying *B burgdorferi.* From my perspective, more than 20 years after seeing my first patients for Lyme disease consultation, Northern Virginia is now clearly endemic for Lyme disease (so the Potomac has been breached!), and patients routinely acquire the infection in hilly western Maryland (Feldman K, personal communication, 2015).[10] This slow but not glacial expansion bodes a challenge for those practicing medicine on the borders of known endemic regions. Those seeking up-to-date and comprehensive perspective on the epidemiology of Lyme disease would be well-served by Mead's article examining trends in the United States as well as the potential for acquisition of infection in other endemic regions such as Eurasia (See article by Mead, "Epidemiology of Lyme disease", in this issue). Perhaps just as important is knowing where Lyme disease is improbably acquired to avoid misdiagnosis or inappropriate antibiotic therapy.[11]

LYME DISEASE OR NOT?

An accurate diagnosis best informs treatment. This simple statement, if applied to Lyme disease, vexes many a patient and clinician alike. Much of this confusion arises from improper interpretation of serologic tests for Lyme disease, most notably, reliance on IgM immunoblots for symptoms of beyond 4 weeks' duration despite admonition otherwise due to high rates of inaccuracy, or application of such testing in nonendemic regions where acquisition of true infection is improbable and therefore

false positive findings are highly likely.[11–13] Objective and evidence-based diagnostics are widely available and their use and interpretation are well represented by the review of Marques (See article by Marques, "Laboratory Diagnosis of Lyme Disease Advances and Challenges", in this issue), which is highly important for diagnostic accuracy when less characteristic findings such as an erythema migrans rash are lacking.[14] Infection present for only a week or two often results in negative serologic tests; this is not unexpected given the time required for immunologic responses to be mounted, but is partly the reason Lyme disease serology has a reputation as an inaccurate test. On the other hand, it is not uncommon to encounter patients who have tests in hand "proving" they have Lyme disease from so-called Lyme specialty labs that offer assays that have not been well-characterized or have a questionable basis.[15,16] Savviness must extend beyond the customary to include good knowledge of potential pitfalls and a well-measured pause before taking diagnostic information for granted. Quite frequently, I am e-mailed or otherwise curbsided by colleagues in other specialties, such as general medicine, neurology, and rheumatology, asking whether a certain test for Lyme disease is a valid or truly secures the diagnosis.

Clinicians who may not consider Lyme disease frequently or who wish to review in-depth information on the spectrum of *B burgdorferi* infection would be well served by reading the excellent treatises (See article by Nadelman, "Erythema Migrans", in this issue), Halperin on neurologic consequences of infection (See article by Halperin, "Nervous System Lyme Disease", in this issue), Melia and colleagues on Lyme carditis (See article by Melia and colleagues, "Lyme Carditis", in this issue), Arvikar and Steere addressing Lyme arthritis (See article by Arvikar and Steere, "Diagnosis and Treatment of Lyme Arthritis", in this issue), and Lyme disease in children by Sood (See article by Sood, "Lyme disease in children", in this issue). Though many areas, such as treatment for an erythema migrans rash, appear well settled, others are not yet well studied in rigorous fashion, such as how to handle antibiotic-refractory Lyme arthritis. These expert clinicians offer valuable insights and approaches for many scenarios that may arise. These articles also help catalog the conditions that either are extraordinarily rare or have no clearly defined association with Lyme disease but are tenuously grasped by some based perhaps on chance coincidence, such as "congenital" Lyme disease, cardiomyopathy, hearing loss, optic neuritis, multiple sclerosis, Alzheimer disease, Parkinson disease, or amyotrophic lateral sclerosis.[17–22]

Knowledge regarding Lyme disease is only a part of what clinicians should know regarding illnesses that could represent other potential infections transmitted by the black-legged deer tick. Excellent reviews covering these aspects include human granulocytic anaplasmosis by Dumler and Bakken (See article by Dumler and Bakken, "Human Granulocytic Anaplasmosis", in this issue) and babesiosis by Krause and colleagues (See article by Krause and colleagues, "Babesiosis", in this issue). Several emerging infections borne by the deer tick that are less familiar but capable of posing serious disease include Powassan virus, *Ehrlichia muris*-like agent and *Borrelia miyamotoi*; these entities are well recounted by Wormser and Pritt (See article by Wormser and Pritt, "Update and Commentary on Four Emerging Tick-Borne Infections: Ehrlichia muris–like Agent, Borrelia miyamotoi, Deer Tick Virus, Heartland Virus, and Whether Ticks Play a Role in Transmission of Bartonella henselae", in this issue). These infections may cause flulike illness with fever as well as cytopenias that should raise the specter of tick-borne disease, and in the case of Powassan virus, acute neurologic disease. On the other hand, some patients are told that these coinfections are responsible for chronic symptoms, such as fatigue or pain, that had not responded to antibiotics targeting Lyme disease. A recent systematic review of the literature did not find convincing evidence that anaplasmosis,

babesiosis, or bartonellosis is present in such patients or that their nonspecific symptoms respond to antimicrobial therapy.[23]

Although coinfections are at times invoked for chronic conditions, Lyme disease is more frequently considered a convenient or default explanation when evident explanations are not in hand. One such patient who presented to a number of specialists at Johns Hopkins was a 62-year-old man from the Eastern shore of Maryland who developed decreased hearing, joint pains, numbness, fatigue, and low-grade fever. Doxycycline treatment prior to his evaluation did not yield durable benefit but concern existed by his referring provider and the patient for antibiotic-unresponsive Lyme disease; the patient was ultimately diagnosed with granulomatosis with polyangitis, an uncommon and difficult-to-diagnose disorder.[24] As Lyme disease remains a clinically diagnosed infection based on appropriate epidemiology plus either symptoms with history of erythema migrans rash or objective symptoms and serology, it is both underdiagnosed and overdiagnosed. Yet, a worrisome aspect began soon after the description of Lyme disease, as some physicians advocated for both a wider role for the infection as a cause of numerous problems and a long-term antibiotic therapy for those who had slow resolution of symptoms.[25,26] Physicians practicing evidence-based medicine began to see numerous patients who were labeled with Lyme disease but had no evidence of infection.[27,28] For patients who do seem to be troubled by long-term symptoms after treatment for Lyme disease, trials to date have not demonstrated benefit of additional antibiotic therapy.[29] This has evolved as one of the major aspects of what is often referred to as the debate or the controversy regarding Lyme disease. While I am empathetic to patients who are suffering, many patients have medically unexplained symptoms not due to Lyme disease.

Some find Lyme disease or "chronic Lyme disease" to be more plausible explanations for complex constellations of symptoms than syndromic diagnoses, such as chronic fatigue or fibromyalgia.[30] Many patients are confused by the apparently polar sets of diagnostic and therapeutic advice voiced by most established professional societies as compared with those articulated by advocates of chronic Lyme disease. For providers who are sorting out patients who might have PTLDS or who bring up concerns of "chronic Lyme disease," two helpful reviews help bring perspective and highlight educational points for patients (See article by Aucott, "Post-treatment Lyme Disease syndrome"; See article by Lantos "Chronic Lyme disease", in this issue). Regardless of the cause, patients who do suffer from long-term fatigue, musculoskeletal pains, and subjective neurocognitive disorders usually appreciate thoughtful evaluations and discussions of what may be their diagnoses; they often readily engage in dialogs regarding the limits of current medical science, and they welcome advice on interventions that may lead to functional improvements. Practically, however, this is rarely accomplished with one visit or even two.

Many questions remain about *B burgdorferi*, an organism that harbors a complex genome and provokes host immune responses that remain to be more fully characterized. I have learned considerably from the experts who have authored these articles, and who have clearly put heart and soul into providing the best information currently known about Lyme disease and potential coinfections in this issue of *Infectious Diseases Clinics of North America* (Auwaerter, ed, "Lyme disease" IDCA, Volume 29, Issue 2, June 2015). With some apology, I have taken more space directed toward what is not Lyme disease or coinfections, but it is the reality that at least for a specialist at a referral center, this is now more often the case in consultation than management of true *B burgdorferi* infection. I admire the dedication and persistence of all who are working to help advance the field and provide the better care for our patients.

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