

Lyme disease: Is it or is it not?

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This past summer, Lyme disease was the topic of a Focus section in the *Globe and Mail* (1). In this section, the reporter described her experience of having physicians unable and then unwilling to diagnose her symptoms of “skin on fire, dizziness and chest pains, twitching muscles, and trouble keeping balance” as Lyme disease following a tick bite three years previously on Prince Edward Island. She reported finding support for her diagnosis after obtaining a positive test from a California laboratory and after seeing approximately 20 physicians. In her article, she speaks to the controversy surrounding the diagnosis and treatment of Lyme disease, and the tension it creates between those who believe they have it and the physicians they see.

Controversy is not new to medicine, and the Lyme disease controversy is a case in point. In the United States (US), the lay press has given the term ‘Lyme camps’ to describe the two opposing views, held on the one hand by academic-based physicians who use limited-duration antibiotic therapy to treat Lyme disease, and on the other hand by community-based physicians and advocacy groups who believe in open-ended duration antimicrobials to treat Lyme disease (2). The Infectious Diseases Society of America was compelled to write to the US House of Representatives in August 2005, cautioning against passing legislation that might allow for the prolonged antibiotic treatment for Lyme disease, which is not supported by the best available evidence (personal communication).

Lyme disease was first recognized 30 years ago by Allen Steere and colleagues as an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities (3). His group of investigators, and another from New York State, concluded that a spirochete, *Borrelia burgdorferi*, carried by the *Ixodes dammini* tick was the etiological agent of Lyme disease after isolating this organism from skin, cerebrospinal fluid and blood of patients with the clinical syndrome and showing an immunological response (4,5). Credit is given to two women, one a concerned mother, for bringing this epidemic of arthritis to the attention of public health officials and physicians (6). Lyme disease is now the most common reportable vector-borne infection in the US. In 2003 and 2004, there were 20,738 and 18,523 cases, respectively, reported to the Centers for Disease Control and Prevention (7). Eighty per cent of reported cases were from nine northeast and midatlantic states. Lyme disease is also transmitted in Asia and Europe by ticks of the *Ixodes ricinus* complex (of which *Ixodes scapularis* [previously classified

as *I dammini*] is one member), sometimes with regional variations in clinical manifestations (8).

Lyme disease is not a national notifiable disease in Canada, making it very difficult to identify in any systematic way the number of cases and trends over time. It is reportable in some provinces. Certainly, the potential for *B burgdorferi* exposure exists in most Canadian provinces. Adult *I scapularis* ticks, also known as blacklegged deer ticks, have been detected in low numbers in British Columbia, Saskatchewan, southern Manitoba, Ontario, the Eastern Townships of Quebec, Nova Scotia, New Brunswick, Prince Edward Island and Newfoundland (9,10). Established populations of these blacklegged deer ticks are found only along the north shore of Lake Erie, particularly in Long Point, Point Pelee and Rondeau Provincial Park, in selected localities along the shores of Lake Ontario, and near Lunenburg, Nova Scotia (10,11). In other areas where infected blacklegged tick populations have not been established, it is presumed that the ticks are introduced into the area by migratory birds (9,10). It is estimated that 10% of these nonendemic ticks are infected with *B burgdorferi* (10). Most provincial department of health Web sites have information on the prevalence of infected deer tick populations in their area. The number of reported human cases of Lyme disease in Canada has been very small and is also available on several provincial health department Web sites. Most provinces have identified zero to five cases/year, with Ontario reporting 15 to 40 cases/year since 1991, 50% of which are likely acquired outside Ontario (11). There have been only three confirmed Nova Scotia-acquired cases to date, even with the established infected tick population near Lunenburg.

The risk of developing Lyme disease after a tick bite and its clinical manifestations have been well described in the context of randomized, controlled trials of vaccination and antimicrobial prophylaxis after tick bites, as well as in longitudinal observational studies of populations from endemic areas. Shapiro et al (12) found that 1.2% of children and adults in a Lyme-endemic area of Connecticut (15% of deer ticks infected with *B burgdorferi* as determined by polymerase chain reaction) developed Lyme disease after a tick bite. There were no asymptomatic seroconversions in this cohort. A slightly higher rate of infection (3.2%) was found in a cohort of patients bitten in a hyperendemic area of New York State (13). In this latter study, all transmissions were associated with bites from nymphal ticks (not adult or larval) and there were no transmissions in the 48 patients where the nymphal tick had been

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feeding for less than 72 h (13). Again, there were no asymptomatic seroconversions in the study population. In two vaccine studies conducted in endemic areas, attack rates for Lyme disease were 1.26% (14) and 1.99% (15) in the nonimmunized control subjects.

The most characteristic and earliest manifestation of Lyme disease is erythema migrans (EM), formerly known as erythema chronicum migrans. In one vaccine trial (16), 70% to 80% of study subjects with definite and possible Lyme disease had EM. Another study (17) has suggested that the incidence of EM with Lyme is 83%. However, EM may be both overdiagnosed and underdiagnosed (18), in part due to the potential for less classic manifestations (19). In the above-noted vaccine study cohort (16), 18% of patients had systemic symptoms without EM. None had upper respiratory or gastrointestinal tract symptoms. It is clear that a high index of suspicion for Lyme disease should be maintained when evaluating patients from endemic areas with systemic symptoms following a tick bite. Arthritis is the second most common manifestation and occurs in both stages 2 and 3, although it is most commonly associated with stage 3 (17,20). Persons under 20 years of age are more likely to have arthritis than those over 20 years of age and are less likely to have EM (10% versus 32%, respectively) preceding the arthritis, but these groups experience no difference in the occurrence of neurological or cardiac manifestations (17).

There are several different modalities for the laboratory diagnosis of Lyme disease, and these have recently been reviewed in *Clinical Microbiology Reviews* (21). Culture of *B burgdorferi* from clinical specimens is not used in routine clinical practice for several reasons, including logistics (lack of consistent, high-quality growth medium, slow growth and expense) and poor sensitivity (21). While polymerase chain reaction-based techniques have been used, they also suffer from low sensitivity in blood and cerebrospinal fluid and potential false-positive results due to accidental contamination of samples with a small quantity of target DNA (21).

Thus, the laboratory-based diagnosis of Lyme disease is primarily an immunological one, based on detection of antibodies against various *B burgdorferi* antigens. Since the etiological agent was first identified, a number of immunological tests have been developed and tested. For the most part, these diagnostic tests have been studied by using clinically defined Lyme disease as the gold standard, perhaps giving some clinicians and patients concerns about their performance characteristics and contributing to the debate about the diagnosis of Lyme disease. In addition, significant inter- and intralaboratory variations in the serodiagnosis of Lyme disease have been reported (22,23).

Serological tests for *Borrelia* include ELISA, enzyme-linked immunoassay (EIA), indirect immunofluorescence assay (IFA) and western blotting or immunoblotting (IB). A number of different commercial products are available, and band criteria for interpreting IB have been published (24). In one study (25) of 57 patients with culture-confirmed EM, sensitivity and specificity of IFA was 100%, whereas EIA was found to be 45% sensitive and 86% specific. By using reference sera from patients with a clinical diagnosis of Lyme disease, other investigators have found the sensitivity of EIA to range from 31% for EM lesions less than seven days in duration to 100% when EM was present longer than 14 days (26). IB was found to be positive in 86% of patients with EM, the sensitivity being dependent on the duration of EM and always higher than for

EIA (26). A very early study of ELISA and IFA for Lyme disease found sensitivities varying from 41% to 80% for early infection and from 87% to 96% for the later stages of infection, with specificity ranging from 65% to 100% (27). These findings have been supported by a second study of culture-confirmed EM where, at days 8 to 14 after baseline, 91% of patients had a positive ELISA and/or immunoglobulin (Ig) M IB result (28). One year later, 16% of patients still had a positive EIA result and 38% had a positive IB result (28). A review of Lyme diagnostics by Aguero-Rosenfeld et al (21) summarized the findings of a number of published studies examining the serodiagnosis of Lyme. In these studies, test sensitivity ranged from 33% to 49% for ELISA and 43% to 44% for IgM IB in acute phase EM to 100% for EIA and 96% to 100% for IgG IB in arthritis. Sensitivity was just slightly lower for neurological involvement at 79% for ELISA and 64% to 72% for IgG IB. Thus, it can be seen that IB may slightly outperform ELISA in the early stages of Lyme disease, but that the two are comparable for later stages. The main role for IB in the recommended two-step approach to serodiagnosis of Lyme disease is to improve specificity. Equally evident is that serology has poor utility in acute EM, which is a clinical diagnosis and does not require serological confirmation. Finally, antibody concentrations may remain positive for many months, even in treated patients. Despite the availability of 70 serological assays to aid in the diagnosis of Lyme disease and recommendations for the use and interpretation of these tests, the Centers for Disease Control and Prevention recently had to publish a caution regarding some commercial laboratories testing for Lyme disease with nonapproved tests or interpretive criteria (29).

A reasonable amount of literature exists describing the antimicrobial therapy of the various stages of Lyme disease, including several randomized, controlled trials. In an early study (30) that compared the outcome of patients treated with penicillin with a historical cohort of nontreated patients, a 10-day course of penicillin seemed to shorten the course of EM and reduce the risk of arthritis. In 1983, it was shown that tetracycline and penicillin were superior to erythromycin in hastening the resolution of symptoms in adults with Lyme disease, and the tetracycline data suggested a trend toward superiority to penicillin ($P=0.07$) in preventing late complications (31). In a small randomized, controlled trial conducted in 1989 (32), cefuroxime and doxycycline (each for 20 days) were equally effective in treating early Lyme disease. Lyme arthritis did not develop in any patient one month after treatment. A subsequent study (33) showed that doxycycline for 10 days is as effective as a longer course (20 days) or a 10-day course preceded by a single dose of intravenous ceftriaxone. Only one patient in that trial failed therapy and required treatment with intravenous ceftriaxone for meningitis. There were no differences in neurocognitive testing between the three treatment groups at 30 months (33). In patients with acute disseminated Lyme without meningitis, intravenous ceftriaxone for 14 days and a three-week course of oral doxycycline had similar clinical cure rates of 85% and 88%, respectively (34). Of interest, among patients whose infections were cured, 27% in the ceftriaxone group and 14% in the doxycycline group reported residual symptoms, most commonly arthralgia, at follow-up (34). To examine whether prolonged antibiotic therapy would be of benefit to symptomatic patients with a documented history of treated Lyme disease, a trial comparing 30 days of intravenous ceftriaxone followed by 60 days of oral doxycycline

versus placebo was begun in 1997 (35). This trial was terminated by the data and safety monitoring board after a planned interim analysis when it became evident that it was highly unlikely there would be a difference in the two treatment groups (35). In the 105 evaluable patients before the study ended, only 40% in the treated and 36% in the untreated group improved (35).

There are no large, randomized, controlled trials comparing different regimens in the treatment of Lyme arthritis and other manifestations of Lyme disease. On the basis of the available case series and small trials, the Infectious Diseases Society of America has published practice guidelines for the treatment of these (and early) manifestations of Lyme disease (36).

The persistence of symptoms in some patients treated for Lyme disease has already been noted. This contributes, in part, to the debate surrounding the entity that has been called 'chronic Lyme'. Nowakowski et al (37) followed 96 patients (59 of whom were followed for more than five years) after these patients had a diagnosis of, and were treated for, Lyme disease. Only 10% of patients were symptomatic at their last visit and, even then, symptoms tended to be intermittent and mild (37). In contrast, a retrospective cohort study by Shadick et al (38) in a Lyme-endemic area of Massachusetts found that 34% of persons with previous Lyme disease had long-term sequelae, such as arthralgias, fatigue and concentration difficulties. Delayed antibiotic therapy (average of 34.5 months) was a risk factor for sequelae, making it difficult to interpret these findings in the setting of prompt initiation of treatment. More recently, Shadick et al (39) demonstrated that, although patients with a history of treated Lyme disease had more joint pain, symptoms of memory impairment and poorer functional status than control patients who never had Lyme disease, there were no differences on physical examination or neurocognitive performance. These findings were corroborated in a randomized, controlled trial of treatment for post-treatment chronic Lyme (40), in which symptomatic patients had no objective evidence of cognitive impairment. Finally, a population-based study (41) in Connecticut found a similar frequency of Lyme symptoms (such as pain and fatigue or difficulty with daily activities) between patients with Lyme disease from 1984 to 1991 and age-matched controls without Lyme disease.

Despite these findings, many patients continue to receive prolonged antibiotic therapy for what is diagnosed as 'Lyme disease', most often chronic Lyme disease. As early as 1990, one investigator reported that only 37% of patients referred to him had active or prior Lyme disease to account for their symptoms, and that 91 courses of antibiotic therapy in these 100 patients were probably unwarranted (42). Steere et al (43) excluded Lyme disease in 452 of 788 patients referred to them for the evaluation of Lyme disease. Almost 50% of these non-Lyme patients had a positive serological test in another laboratory that was negative when tested in Dr Steere's laboratory. Sixty per cent of patients referred to the Yale University Lyme Disease Clinic in Connecticut had no evidence of current or previous Lyme disease and 75% reported previous antibiotic use (median 42 days) for this diagnosis (44). Six per cent of these patients experienced a major adverse drug event, including 2% each for antibiotic-associated colitis and neutropenia. Another group of patients (n=40) with previous Lyme disease were also heavily treated with antibiotics (median 75 days) without resolution of symptoms and a similar experience with

major adverse drug events (44). Patients in that study without active Lyme disease had a median of four serological tests done (range one to 16) before referral (44). A survey of Lyme testing behaviours in two Wisconsin reference laboratories found that 27% of tests were inappropriate, and that the patient rather than the clinician requested 26% of tests (45). Patient-requested tests were more likely to be inappropriate than physician-requested tests (OR 5.8, 95% CI 2.5 to 13.6). The potential for the recognized adverse events associated with long-term antibiotic therapy appears to be a risk patients seeking treatment for chronic Lyme are prepared to take. Many infectious diseases physicians are not as comfortable exposing patients to these risks in the absence of evidence for the benefit of long-term antimicrobial therapy for patients suffering symptoms after completing the standard course of therapy for Lyme disease. Concerns regarding the safety of long-term antibiotics may increase if recent research suggesting a link between prolonged antimicrobial therapy and cancer is substantiated (46).

Much has been learned about Lyme disease in only 30 short years. There is no doubt that more remains to be determined, including how best to manage patients with persistent symptoms after treatment for Lyme disease and whether diagnostic methods can be improved. Until then, physicians and patients are left to manage with the best evidence available. It is unfortunate that tension has arisen over the diagnosis and management of Lyme disease. In the end, we all want what is best for the patient.

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