

Lyme disease: clinical diagnosis and treatment

Hatchette TF^{1,2,3*}, Davis I^{1,2} and Johnston BL²

¹ Department of Pathology and Laboratory Medicine, Capital District Health Authority (CDHA), Halifax, Nova Scotia

² Department of Medicine, CDHA and Dalhousie University, Halifax, Nova Scotia

³ Department of Pathology, Dalhousie University, Halifax, Nova Scotia

* Corresponding author: todd.hatchette@cdha.nshealth.ca

Abstract

Background: Lyme disease is an emerging zoonotic infection in Canada. As the *Ixodes* tick expands its range, more Canadians will be exposed to *Borrelia burgdorferi*, the bacterium that causes Lyme disease.

Objective: To review the clinical diagnosis and treatment of Lyme disease for front-line clinicians.

Methods: A literature search using PubMed and restricted to articles published in English between 1977 and 2014.

Results: Individuals in Lyme-endemic areas are at greatest risk, but not all tick bites transmit Lyme disease. The diagnosis is predominantly clinical. Patients with Lyme disease may present with early disease that is characterized by a “bull’s eye rash”, fever and myalgias or with early disseminated disease that can manifest with arthralgias, cardiac conduction abnormalities or neurologic symptoms. Late Lyme disease in North America typically manifests with oligoarticular arthritis but can present with a subacute encephalopathy. Antibiotic treatment is effective against Lyme disease and works best when given early in the infection. Prophylaxis with doxycycline may be indicated in certain circumstances. While a minority of patients may have persistent symptoms, evidence does not demonstrate that prolonged courses of antibiotics improve outcome.

Conclusion: Clinicians need to be aware of the signs and symptoms of Lyme disease. Knowing the regions where *Borrelia* infection is endemic in North America is important for recognizing patients at risk and informing the need for treatment.

Introduction

Lyme disease is the most common vector-borne zoonosis in North America, where it is estimated that each year more than 300,000 individuals in the United States (US) are infected by *Borrelia burgdorferi*, the bacterium that causes Lyme disease(1). Data from Canada are sparse, as Lyme disease only became nationally reportable in 2009. The number of reported infections in Canada in 2012 was 315, which is likely an underestimate and includes cases that are the result of infections acquired during travel to other endemic regions, such as Europe (2-4).

The range of *Ixodes* ticks, the vector for *Borrelia*, has expanded greatly over the last 20 years, making Lyme disease an emerging infection in Canada. *Ixodes* ticks have been identified in British Columbia, southeastern Manitoba, southern and eastern Ontario, and specific areas in New Brunswick, Nova Scotia and Quebec (4,5). As the *Ixodes* tick expands its range, more Canadians will be exposed to *B. burgdorferi*, and clinicians will need the expertise to manage tick bites and diagnose and treat Lyme disease.

Awareness of the extent of local Lyme disease, early detection and treatment are important for managing this emerging infection. The objective of this article is to review the clinical diagnosis and treatment of *B. burgdorferi* infection for the front-line clinician.

Methods

A literature search was done using PubMed and restricted to articles published in English between 1977 and 2014. The following search terms were used: Lyme disease and treatment, Lyme disease and arthritis, Lyme disease and clinical presentation, Lyme disease ticks and risks, Lyme disease and pregnancy, neuroborreliosis, chronic Lyme OR post-Lyme syndrome AND treatment (clinical trials). Abstracts were reviewed for clinically relevant articles, and additional references were obtained from the articles identified in the initial search. Although there are different strains of *Borrelia* in North America and Europe, which are associated with overlapping but distinct clinical presentations, this review will focus on the clinical manifestations that are common to Canada. It does not describe the various aspects of diagnostic testing, which is reviewed in a companion paper (6).

Findings

Who is at risk of Lyme disease and why?

An individual must first be bitten by a tick that is infected with *B. burgdorferi* for infection to occur. While infected ticks can be sporadically deposited in different regions in Canada by migratory birds, the risk of getting Lyme disease is greatest in an area where the ticks are persistently present or endemic, and the risk depends on the proportion of ticks that are infected. Even in areas where the ticks have become endemic, the proportion infected by this spirochete varies and is evolving. Clinicians may want to check with their local public health departments to understand where the current Lyme endemic areas are within their jurisdiction. It is important to obtain a thorough travel history from the patient, as Lyme disease is endemic in other areas of North America and Europe, and travel-related Lyme disease accounts for a proportion of the documented cases in Canada. It is also important to relay this travel history or suspicion of European *Borrelia* infection to the diagnostic laboratory, as the confirmatory testing for North American and European *Borrelia* strains differs.

What is the risk of Lyme after a tick bite?

While studies are limited in numbers and size, data from the US and Europe suggest that the risk of acquiring Lyme disease, even after a bite from an infected tick, is small – in the range of < 1% to 6% (7). In studies that have examined the efficacy of antibiotic prophylaxis in persons presenting with a tick bite in Lyme-endemic areas (where the prevalence of *B. burgdorferi* in ticks ranged from 15% to 50%), the rate of infection among those who received placebo ranged from 1.1% to 3.4% (8–11). These rates are consistent with a prospective study of patients bitten by ticks in a Lyme-endemic area of New York State, where infection developed in 3.7% of those bitten by a tick (12).

The risk of infection following a tick bite is related to how long the tick has been attached and is explained by the *Borrelia* life cycle in the tick. The spirochete first has to migrate from the tick's gut to its salivary glands before it can be injected into the human through the bite. In order to do this, the bacterium must undergo antigenic change to its outer coat that favours human infection (13–16). This process takes about 36 hours (14). If the tick is removed during this time frame, infection is almost always prevented. In an antibiotic prophylaxis trial in the US, no study participants receiving placebo or prophylaxis were infected if the tick fed for less than 72 hours (11). This is further supported by data from another prospective study in an endemic region, in which participants were at greatest risk of infection if the tick had been attached for more than 72 hours (12).

Who should receive prophylaxis after a tick bite?

There are a number of factors that require consideration when deciding whether to offer prophylaxis after a tick bite (**Table 1**). All of the prophylaxis trials have been conducted in regions that would be considered hyperendemic for Lyme disease, where the burden of infection in ticks is > 20% and where the antibiotics were administered within 72 hours of removing the tick (8–11). An early meta-analysis of antibiotics for prophylaxis of Lyme disease reported a pooled infection rate in those who received placebo of 1.4%, compared with 0% for those receiving an antibiotic (17). Each of the included trials was small and failed to show any significant effect of prophylaxis, as the incidence of infection in those taking placebo was low (8–10). A subsequent randomized placebo controlled trial showed that a single dose of doxycycline could reduce the rate of Lyme disease (11).

Table 1. Criteria and recommended prophylaxis after a tick bite (19)

Criteria for prophylaxis*	1. The attached tick can be reliably identified as an <i>I. scapularis</i> (deer/blacklegged) tick that is estimated to have been attached for > 36 h on the basis of the degree of engorgement or by certainty about the time of tick acquisition.	
	2. Prophylaxis can be started within 72 h of tick removal.	
	3. The local rate of <i>B. burgdorferi</i> infection in ticks is > 20% (check with local public health).	
	4. Doxycycline is not contraindicated.	
Recommended prophylaxis	Adults and children > 8 years of age	Single 200 mg dose of doxycycline given orally (4.4 mg/kg for patients < 45 kg)
	Children < 8 years of age and pregnancy	Not recommended

* Consider antibiotic prophylaxis after a tick bite when the individual meets all of the criteria.

An updated systematic review and meta-analysis suggested that, to prevent one case of Lyme disease, prophylaxis of 49 cases would be needed (18). Patients in whom infection developed were successfully treated without any long-term sequelae. Given that there were relatively few infections in each of the studies and that these were successfully treated, the use of antimicrobial prophylaxis must be considered in the context of potential side effects, which were reported but were not severe.

How do patients with Lyme disease present and how are they treated?

Although patients with *B burgdorferi* infection can be asymptomatic, most cases of Lyme disease present as one of three stages, which may occur sequentially if an earlier stage was untreated: early localized disease (usually < 30 days from exposure), early disseminated disease (< 3 months after exposure) and late disseminated disease (> 3 months after exposure) (**Table 2**).

Table 2. Clinical manifestations of Lyme disease (19,24,39)

Stage	System	Manifestation	
Early localized disease (< 30 days)*	Skin	Erythema migrans (note: must be > 5 cm in diameter, painless and slowly expanding)	
	Systemic	Fever Arthralgias Headache	
Early disseminated disease (< 3 months)*	Skin	Multiple erythema migrans	
	Systemic	Fever Arthralgias Headache Lymphadenopathy	
		Heart	Atrioventricular block Tachyarrhythmias Myopericarditis Myocardial dysfunction
		CNS	Aseptic meningitis Cranial neuropathy (especially facial nerve palsy) Motor or sensory radiculopathy

Stage	System	Manifestation
	Ocular	Conjunctivitis (rare)
Late disseminated disease (> 3 months)*	MSK	Oligoarticular arthritis
	CNS	Encephalopathy Axonal polyradiculoneuropathy Chronic encephalomyelitis
	Ocular	Retinitis (rare)

* Note: While there may be exceptions, these time frames provide clinicians with a general guide on when the different manifestations tend to occur.

CNS = central nervous system.

MSK = musculoskeletal.

The treatment of Lyme disease depends on the stage and organ system involved and is summarized in a clinical practice guideline that has been developed by the Infectious Diseases Society of America (IDSA) (Table 3) (19). The clinical presentation and some of the literature that supports those treatment recommendations are summarized in the sections that follow.

Table 3. Infectious Disease Society of America guidelines for the treatment of Lyme disease (19)*

Treatment of adults and children older than 8 years with Lyme disease	Erythema migrans or early disseminated disease, including Bell's palsy, but without other CNS involvement	<ul style="list-style-type: none"> • Doxycycline 100 mg po bid x 14–21 days (contraindicated in pregnancy) • Amoxicillin 500 mg po tid x 14–21 days • Cefuroxime 500 mg po bid x 14–21 days
	Early Lyme with CNS involvement	<ul style="list-style-type: none"> • Ceftriaxone 2 g IV once daily x 14–28 days • Pen G 4 x10⁶ units IV q 4 h x 14–28 days • Doxycycline 100–200 mg po bid x 28 days (alternative if others not possible)
	Early Lyme with carditis	<ul style="list-style-type: none"> • Same treatment as early Lyme with CNS involvement, but use IV initially with high grade heart block or if admission to hospital is necessary.
	Late Lyme without CNS involvement**	<ul style="list-style-type: none"> • Doxycycline 100 mg po bid x 28 days • Amoxicillin 500 mg po tid x 28 days • Cefuroxime 500 mg po bid x 28 days
	Late Lyme with CNS involvement (late neuroborreliosis)	<ul style="list-style-type: none"> • Ceftriaxone 2 g IV once daily x 14–28 days • Pen G 4 x10⁶ units IV q 4 h x 14–28 days
Treatment of children 8 years or younger with Lyme disease	Early localized disease	<ul style="list-style-type: none"> • Amoxicillin 30 mg/kg per day, orally, divided into three doses (max 1.5 g/day) for 14–21 days • For children allergic to penicillin, cefuroxime 30 mg/kg per day, orally, in two divided doses (maximum 1 g/day) for 14–21 days
	Early disseminated and late disease: <i>multiple erythema migrans</i>	<ul style="list-style-type: none"> • Oral treatment as the above for 21 days
	Early disseminated and late disease:	<ul style="list-style-type: none"> • Oral treatment as the above for 21 days

	<i>isolated facial palsy and first episodes of arthritis</i>	
	Early disseminated and late disease: <i>persistent/recurrent arthritis, carditis and meningitis/encephalitis</i>	<ul style="list-style-type: none"> • Ceftriaxone or penicillin IV at pediatric dosing

* These recommendations are off-label, evidence-based best practices.

** Recurrent or persistent joint swelling – repeat 4 week course of oral antibiotic as above. Use of IV ceftriaxone should be reserved for relapse or persistent joint swelling without improvement with oral treatment.

CNS = central nervous system.

Asymptomatic infection

Approximately 1.6%–7% of infected individuals may have asymptomatic infection (7, 20). The prognosis for patients with asymptomatic infection is generally good. Within a large vaccine study conducted in 10 US states where Lyme is endemic, asymptomatic infections were documented in 6% (15/269) of study participants. While the majority of study participants received treatment when the seroconversion had been documented, only 1 of 8 who did not receive treatment went on to show arthritis over the 12 months after seroconversion (20). Although the follow-up period was relatively short, these data support the notion that asymptomatic infection does not require treatment, and disease will ultimately declare itself if infection persists.

Early localized disease (< 30 days)

Early disease usually presents as an acute illness characterized by fever, headache and myalgia with the presence of a single, localized skin lesion known as erythema migrans (EM). This characteristic skin eruption is present in approximately 80% of patients with early disease and will resolve without antibiotic treatment over a median of 28 days (21, 22). While most patients will present with erythema migrans within seven days of the initial tick bite, the incubation period can vary between 3 and 30 days (23). The skin lesion is characteristically an annular erythematous lesion > 5 cm in diameter that slowly increases in size and is usually painless and non-pruritic. The lesion sometimes develops central clearing, but it can be more homogeneously erythematous (19, 23, 24). It is important to note that many people can have a reaction to the tick saliva and show a localized reaction resembling erythema migrans. However, unlike erythema migrans this reaction often develops within the first three days of the bite, is 5 cm or less in diameter and does not expand.

Erythema migrans can be subtle or even go unnoticed, particularly if the bite was in an area that is difficult for the patient to see, such as behind the knee. Diagnostic testing is insensitive at this stage and not recommended in a patient who has links to an endemic area (6).

Treatment: Several clinical trials conducted in the US (23, 25–28) and Europe (29–31) has informed the antimicrobial treatment of early Lyme disease. In these trials, individuals with a clinical diagnosis of erythema migrans were randomly assigned to one of several treatment options. The agents used included amoxicillin, penicillin, ceftriaxone, a macrolide (erythromycin or azithromycin) and a tetracycline or doxycycline in somewhat varying doses and for varying lengths of times. Azithromycin therapy was given for 5 or 10 days, beta-lactams were given for 10–30 days, and tetracycline/doxycycline was given for 10, 14 or 20–21 days. Follow-up frequently lasted for several months after completion of therapy, and patients were monitored for complete and partial resolution of symptoms, treatment failure and late manifestations of illness that were considered either minor or major.

The studies found similar efficacy for amoxicillin, azithromycin, cefuroxime and doxycycline independent of the dose and duration of therapy. The one trial that included erythromycin showed it to be less effective than penicillin and tetracycline. A large retrospective cohort study of 607 patients confirmed these findings, 99% of patients with early local or disseminated Lyme remaining treatment-failure free at two years whether treated for ≤ 10 days, 11–15 days or > 15 days (32). One study that looked specifically at early disseminated Lyme disease compared ceftriaxone 2 g daily for 2 weeks with doxycycline 100 mg twice daily for 3 weeks (33). Clinical cure was similar for the two (85% for ceftriaxone and 88% for the doxycycline), with 14% (doxycycline) and 27%

(ceftriaxone) of patients having residual symptoms, usually mild arthralgias and fatigue, at nine months after completing treatment.

Prognosis: Both clinical trials (23, 25–31) and observational studies (32,34–36) provide information about the prognosis for treated early Lyme disease. With the currently recommended therapies, greater than 80% of patients will have complete resolution of symptoms at long-term follow-up. While it is not unusual for individuals to have symptoms such as fatigue and arthralgias after treatment for Lyme, most studies reported either no or few (< 5%) late manifestations of disseminated Lyme.

To determine whether patients who had early Lyme disease are more likely to have persistent symptoms after their acute infection, investigators in Slovenia compared a cohort of patients treated for erythema migrans with a control group of individuals who did not have Lyme disease (36). They found that the frequency of new or increased symptoms in patients with this condition did not exceed the frequency of such symptoms in the control group. At 12 months, only 2.2% of Lyme disease patients reported new or increased symptoms, and in none of the patients were the symptoms disabling. These findings are similar to those of a study done in the US involving patients with and without Lyme disease from 1984 to 1991 (37). The frequency of new symptoms and increased difficulties with daily activities were similar in the two groups, those with Lyme disease and age-matched controls without Lyme disease.

In summary, the evidence from these studies suggests that although patients with Lyme may have symptoms that persist or appear after treatment is complete, the frequency of those symptoms is comparable with what one would see in individuals who do not have Lyme disease.

Early disseminated Lyme disease (< 3 months)

Early disease may be followed by disseminated disease, with the development of multiple secondary annular lesions and multisystem and intermittent cardiac, neurological, ocular or articular manifestations. The development of multiple secondary annular lesions and systemic symptoms, including fever, arthralgias, headache and lymphadenopathy, usually occurs within several weeks of the localized erythema migrans (38). In one early study, half of the patients presenting with this condition went on to show multiple erythema migrans lesions (38).

The other manifestations of early disseminated infection, such as Lyme carditis and neurologic infection (known as neuroborreliosis), tend to occur weeks to months after initial infection (38). Patients with Lyme carditis can present with conduction abnormalities, tachyarrhythmias, myopericarditis or myocardial dysfunction (39). The most common presentation is atrioventricular block ranging from first to third degree heart block, often requiring temporary pacing. Carditis usual occurs within two months of the presenting erythema migrans, but a history of the condition is not always present.

Treatment is effective, and carditis is rarely fatal (40). While earlier data showed that carditis developed in up to 10% of patients with untreated Lyme (39), recent data suggest that rates are much lower; this may be due to improved recognition of *Borrelia* infection and effective treatment (19). US data from 1996 to 2006 suggest that only 0.8% of patients reported to have Lyme disease have conduction abnormalities (41). Physicians should think of Lyme as a cause of unexplained conduction abnormalities in patients who have recently been to a Lyme-endemic area. However, in the absence of a history of erythema migrans, the presentation is too non-specific to warrant empiric treatment without serological confirmation (19).

Neuroborreliosis has a clinical spectrum that can include meningitis, facial paralysis, motor or sensory radiculopathy, and cognitive symptoms. In North America, neuroborreliosis commonly presents with cranial nerve involvement (especially Bell's palsy), with or without aseptic meningitis. Symptoms can appear anywhere from two to eight weeks after erythema migrans (42). Lyme disease can be responsible for Bell's palsy in 10%–50% of children and adults in Lyme-endemic areas and can be bilateral in up to 23% of patients (43–47). Clinicians should suspect Lyme disease as the cause of facial palsy when it occurs in Lyme-endemic areas during the tick season, is associated with headache and other non-cranial nerve neurologic findings, including papilledema, or is bilateral (44, 47–50).

In regions where Lyme is endemic, it can be challenging to differentiate early neuroborreliosis from other causes of central nervous system infection. The cerebrospinal fluid is usually abnormal, with a white cell count that is

elevated to levels similar to those of patients presenting with viral meningitis (48, 51). However, compared with other causes of aseptic meningitis, patients with Lyme meningitis are less likely to have fever and more likely to have a higher preponderance of mononuclear cells (total percentage of monocytes and lymphocytes) in the cerebrospinal fluid, a longer duration of headache, and cranial nerve involvement (48,52,53).

The rule of sevens: A clinical prediction rule has been developed to help stratify the likelihood of Lyme-related meningitis in children. Children are unlikely to have Lyme-related meningitis if they have all of the following: headache for fewer than seven days, less than 70% mononuclear cells in their cerebrospinal fluid and absence of a seventh nerve palsy. This “rule of 7s” has 96% sensitivity and 95% specificity for distinguishing aseptic meningitis from Lyme neuroborreliosis. On the basis of the rule of 7s, patients who lack these features can be managed conservatively while Lyme serological results are pending (53, 54).

Treatment: A study done in the US in the early 1990s of patients with disseminated Lyme disease (without meningitis) compared ceftriaxone 2 g daily for 14 days with doxycycline 100 mg twice daily for 21 days (33). The cure rate was similar for the two regimens (88% for ceftriaxone and 85% for doxycycline), 27% of ceftriaxone-treated patients and 14% of doxycycline-treated patients having residual symptoms at the end of treatment.

In a large series of 101 adults with Lyme-related Bell’s palsy, the palsy resolved completely in more than 86% at a median time of 26 days (range 1–270 days) despite the fact that only 36% had received antibiotic treatment. Fifteen percent had mild residual weakness, and only one person had a severe deficit. Patients with residual dysfunction were more likely to have bilateral disease (43).

The prognosis in children is equally good. In a cohort study, 94% of children treated with antibiotics were asymptomatic four weeks after treatment. All but one patient had resolution of symptoms by six months, and no children had evidence of chronic disease two years later (34). In 43 children who presented with Bell’s palsy attributable to Lyme disease, most felt that they were cured, and there was no difference in the daily activities of infected children compared with those of a non-infected group (55). These studies in patients with Lyme neuroborreliosis highlight the importance of early recognition and treatment in order to improve response to treatment. At the same time, it was demonstrated that a prolonged course of amoxicillin given orally after a three week course of intravenous ceftriaxone did not alter outcome as compared with placebo (56).

Late Lyme disease (> 3 months)

If left untreated, Lyme disease can evolve into late disease, which presents with persistent arthritis and/or persistent neuroborreliosis. The different strains of *Borrelia* in North America and Europe are associated with overlapping but distinct clinical presentations. In Europe, late Lyme disease presents with dermatologic syndromes that are rare in North America, including acrodermatitis chronica atrophicans and lymphocytoma cutis (24). In North America, arthritis is a much more common manifestation of late Lyme disease, whereas in Europe neuroborrelia is more commonly seen and presents as a chronic encephalitis or painful radiculopathy called Bannwarth’s syndrome in up to 86% of cases (57).

If European Lyme disease is suspected on the basis of the clinical presentation and the patient’s travel history, the laboratory should be notified to ensure that the appropriate serological test can be used, as the confirmation tests for North American and European *Borrelia* are different. A more detailed comparison of the differences between North American and European Lyme disease has been provided by Hengge and colleagues (24).

Late Lyme arthritis

In North America, up to 60% of untreated Lyme disease cases show monoarticular or oligoarticular arthritis, usually involving the knees, with other joints such as the ankle, elbow and wrist less commonly affected (58–60). In one study, all patients with late Lyme arthritis had symptoms appear within two years of infection. In 14 of 16 patients with untreated Lyme-related facial nerve palsies arthritis ultimately developed (61). Remembering a tick bite has not been a helpful feature in diagnosing Lyme arthritis, as up to 84% of cases did not recall exposure to a tick (32, 62).

Lyme disease serology is very sensitive and specific for the diagnosis of Lyme arthritis, and a negative test essentially rules out infection (6). However, the results of Lyme disease testing can take time, and because the presentation can mimic septic arthritis, which requires immediate treatment, it is important to try and differentiate the two.

Three studies have attempted to develop a clinical prediction model to distinguish Lyme arthritis from septic arthritis in Lyme-endemic areas. Although there is an overlap between the two entities, Lyme arthritis tends to involve the knees preferentially, is less frequently accompanied by fever and local signs of inflammation, and in general has lower inflammatory markers (62–64). One study found refusal to weight bear as the strongest predictor septic arthritis compared with Lyme disease (63). Another study in children found that an erythrocyte sedimentation rate of < 40 mm/hour and a peripheral white blood cell count < 10×10^3 cells/mm³ could effectively rule out septic arthritis (64). While the synovial fluid is inflammatory with elevated leukocyte counts, there is overlap with septic arthritis, and the cell count can range from $1,700 \times 10^3$ cells/ μ L to $> 100,000 \times 10^3$ cells/ μ L, predominantly polymorphonuclear cells (58, 60, 63). In one review, children with Lyme disease had higher inflammatory markers than adults (60).

Up to 10% of patients will have evidence of synovitis six months after treatment for Lyme arthritis, termed antibiotic refractory Lyme arthritis (65). Currently, the only recommendation for the use of the polymerase chain reaction (PCR) to detect *Borrelia* DNA in the diagnosis of Lyme disease has been in patients with persistent synovial swelling, to determine whether retreatment is necessary (19). However, the significance of a positive test result after primary treatment is unclear. There are data to suggest that any *Borrelia* detected are not viable, calling into question whether there really is persistent infection in these patients (66).

Late Lyme arthritis treatment: There are few studies that have examined the treatment of late Lyme arthritis. Two studies (67,68) comparing penicillin or ceftriaxone with placebo in late Lyme arthritis in adults found benefit with antibiotic therapy, but the cure rate was still < 50%, although better with ceftriaxone than penicillin. A European randomized trial comparing penicillin and ceftriaxone, both intravenously for 10 days, in patients 13 years of age and older demonstrated a symptom remission rate of 87.9% for ceftriaxone and 61.3 % for penicillin. Finally, a study involving children and adults with late Lyme in the US in the mid-2000s (69) found that 28 days (70% cure) of ceftriaxone had no advantage over 14 days (76% cure) in terms of clinical cure and was associated with more treatment discontinuations due to adverse events. In some series up to 25% of children and 50% of adults required a second course of antibiotics because of refractory arthritis symptoms. Those who went on to show refractory arthritis were successfully treated with nonsteroidal anti-inflammatories, steroid injections or disease-modifying drugs. None developed long-term sequelae (59, 60).

Late neuroborreliosis

The most common manifestation of neuroborreliosis in North America is subacute encephalopathy with subtle cognitive changes, whereas a chronic encephalomyelitis characterized by spastic paraparesis and cognitive impairment is more common in Europe (24, 70). In one case series of 37 American patients, neuroborreliosis manifested approximately two years after erythema migrans as subacute encephalopathy; axonal polyradiculoneuropathy with objective sensory and electromyography abnormalities; or leukoencephalitis; or a combination of the three (42). It is important to note that the patients had objective findings and serological evidence of infection.

Late neuroborreliosis treatment: All of the original studies examining treatment of neuroborreliosis that were identified in our search were undertaken in Europe (56, 71–77). While the clinical manifestations of Lyme disease are somewhat different in Europe and North America, presumably the treatment principles are similar. These different studies compared a variety of different drugs, treatment doses and treatment durations. Generally, however, the comparators were intravenous ceftriaxone/cefotaxime, intravenous penicillin or oral doxycycline (200 mg–400 mg daily) for anywhere between 10 days and 3 weeks. Patients had a mix of early and late neurological disease, and follow-up was often for several months after treatment had stopped. The treatment success was comparable for the different treatment arms, but the dose of doxycycline was higher in some of these studies than that used for early Lyme disease. Treatment success was generally higher than 80% but as low as 33% in one group of patients with late Lyme neuroborreliosis who received ceftriaxone for two weeks.

What is the prognosis after delayed treatment?

There are relatively few data examining the effects of delayed treatment. Two retrospective studies showed that patients who had a longer duration of symptoms before treatment were more likely to have persistent subjective musculoskeletal and cognitive symptoms. However, there were no objective physical findings or neurocognitive

testing abnormalities compared with uninfected controls (78, 79). Similar findings were reported in patients involved in studies of early Lyme disease, in which it was found that those who did not receive treatment on initial presentation with facial palsies were more likely to have body pain, physical limitations and a lower physical composite score on the SF36 (36 item Short-Form General Health Survey) compared with controls who received antibiotics at the time of presentation. They were also more likely to have mild neurocognitive symptoms, but their overall “mental composite” score on the SF-36 standardized form was not different from that of the control group (61).

Can patients with Lyme disease have persistent symptoms after treatment?

It is clear that a proportion of patients with confirmed evidence of previous Lyme disease continue to have symptoms after standard antimicrobial treatment. The terms “chronic Lyme disease” and “post-Lyme disease syndrome” have been applied by some clinicians to patients with symptoms persisting more than six months after treatment with the recommended agents. Persistent symptoms include fatigue, generalized musculoskeletal pain and cognitive impairment without objective findings or microbiological evidence of active infection.

Given that some patients have persistent symptoms after treatment of their Lyme disease, the question has been raised of whether there is benefit to prolonged antimicrobial therapy. Four randomized placebo controlled trials, all conducted in the US, have addressed this issue. The larger of the studies (80) included two separate studies (i.e. seropositive and seronegative studies) of patients clinically diagnosed with acute Lyme disease. Both studies enrolled patients who had previously been treated with a recommended antibiotic regimen and reported ongoing symptoms. The subjects were placed into the seropositive or seronegative study according to their serological status at the time of enrollment. There were 129 patients enrolled in the two studies, and participants were randomly assigned to receive either ceftriaxone 2 g daily for 30 days followed by doxycycline for 60 days, or placebo. Outcome measures included cognition, memory, pain and activities of daily living.

There were no differences between the treatment vs placebo groups in outcomes in either the seronegative or seropositive studies, and they were terminated early after an interim analysis by the Data and Safety Monitoring Board, on the basis that the studies would not be able to identify a difference between treatment vs placebo. A sub-study using data from this trial also found no differences between the treatment and control groups in mood and cognitive-related quality of life measures (81).

Krupp and colleagues compared 2 g daily of ceftriaxone for 28 days with placebo in 55 patients whose Lyme disease had been previously treated with a standard regimen (82). While the ceftriaxone group showed improvement in fatigue, there was no difference in cognition on formal testing. Three patients had intravenous line infections and one had anaphylaxis in reaction to ceftriaxone. Finally, 37 adults were randomly assigned to receive 10 weeks of ceftriaxone or placebo after completing treatment for Lyme disease (83). The patients who received ceftriaxone had non-sustained, mild improvements in cognition and a 26.1% adverse event rate versus 7.1% in the placebo group.

On the basis of these findings, the Infectious Diseases Society of America guideline does not recommend additional antimicrobial or prolonged treatment for patients who have completed a standard course of therapy for their Lyme disease (19). Any benefit that might be derived is small and not sustained, and has been associated with an excess risk of adverse events that may be life-threatening.

How should Lyme disease in pregnancy be managed?

While there have been reports of Lyme disease in pregnant women and sporadic case reports of transplacental transmission of *B burgdorferi*, there is not a clear link between fetal infections and adverse outcomes (84, 85). Clinical, serological and epidemiological studies of *Borrelia* infection in pregnancy have failed to demonstrate an association between infection and adverse outcomes (84–86). Because doxycycline is contraindicated in pregnancy, treatment and prophylactic options are different than in the non-pregnant adult.

Some data suggest that a 10 day course of ampicillin may be an effective prophylactic strategy, although the risk of a rash developing in reaction to the beta lactam is greater than the risk of Lyme disease, and therefore the Infectious Diseases Society of America (IDSA) guideline does not recommend prophylaxis in the setting of

pregnancy (18,19,86). If an *Ixodes* tick bites a pregnant woman, she should be monitored for 30 days for signs and symptoms of Lyme disease and treated with amoxicillin or cefuroxime if it develops (19).

Can individuals be re-infected with *Borrelia burgdorferi*?

Relapses are recurrent symptoms that are the result of failure to cure the original infection, whereas re-infection is the recurrence of symptoms as a result of a new exposure to an infected tick, leading to a new infection. Although erythema migrans lesions can relapse if not treated with antibiotics (23), their recurrence after successful treatment is more likely to be re-infection than relapse (87).

Re-infection can occur in as many as 2%–21% of patients living in endemic areas who have had Lyme disease (78, 88–90). On examination, re-infection typically presents with an erythema migrans lesion at a different site than the original lesion more than 1–2.5 years after the original infection and not within 11 months of the first infection (87, 89, 91). In one series, 79% of patients with re-infection presented with erythema migrans at a different site than the previous infection, and 21% presented with a febrile illness with myalgias. Re-infection after late Lyme disease characterized by arthritis or neuroborreliosis is very rare (90, 91).

Laboratory diagnosis of re-infection becomes a challenge, given that serology, including IgM, can remain positive for many years (92). Diagnosis is reliant on the clinical presentation of a new erythema migrans lesion at a different site. Recent data suggest that patients treated for re-infection have excellent outcomes. Patients with re-infection reported less fatigue than both the non-infected control group and patients with their first infection, suggesting that repeated infections present a lower risk of persistent symptoms (91).

Conclusions

Lyme disease is an emerging infection in Canada, and it is important that clinicians be aware of its epidemiology, clinical presentations and management. While sporadic cases of Lyme disease are possible from infected ticks that are imported on migrating birds, individuals living in or traveling to Lyme-endemic regions will be at greatest risk of infection. A thorough travel history is essential in a person presenting with symptoms suggestive of Lyme disease, particularly if symptoms compatible with one of the neurologic syndromes that are more common in Europe are present. It is important to inform the laboratory of a positive travel history, as the serologic testing for North American and European *Borrelia* strains is different.

Given the constantly expanding tick population it can be challenging to clearly define regions constituting the highest risk for Lyme disease, and it is important to remain abreast of local Lyme epidemiology through local public health.

Conflict of interest

The authors have no conflicts of interest to declare.

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