Lyme Disease

A Canadian perspective

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SUMMARY

Lyme disease is an expanding community health issue in the United States. This has led to greater public awareness in Canada, although the disease remains rare here. We review the biology of ticks and show how feeding patterns are relevant to disease transmission. Diagnosing Lyme disease is sometimes problematic, but treatment can be effective, particularly in the early stages. Preventive measures are aimed at avoiding tick contact and early tick removal.

RÉSUMÉ

Aux États-Unis, la maladie de Lyme devient un problème de santé communautaire croissant. Les Canadiens sont de plus en plus sensibilisés à ce problème, malgré sa rareté de ce côté-ci de la frontière. Les auteurs présentent une synthèse de la biologie des tiques et nous montrent comment leur mode d'alimentation favorise la transmission de la maladie. Le diagnostic de la maladie de Lyme est parfois problématique mais son traitement est efficace, surtout pendant les premiers stades d'évolution. Les mesures préventives visent à éviter le contact avec les tiques et à procéder rapidement à leur exérèse.

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LYME DISEASE IS STILL RARE IN Canada. the explosive spread of the disease in the United States over the past 10 years has not yet resulted in a similar explosion here. However, the ecological substrate to support ticks exists in Canada as well. Furthermore, a recent analysis of Lyme disease in New York state shows that the disease has been spreading progressively toward the Canadian border.[1]

For the Canadian practitioner, the importance of Lyme disease lies not only in its appearance but in suspecting that it may appear. Because it has gained national renown in the United States, Canadians are now familiar with the disease and its variable presentation. Difficulties in diagnosis and treatment are also well publicized. This combination often leads to a situation where a patient is convinced he or she has a disease and a practitioner is unprepared to decide otherwise. Yet the disease usually follows well established patterns, and diagnosis and treatment are often not difficult once one learns to recognize typical presentations.

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The following case history illustrates two common errors in diagnosis: not recognizing a typical presentation and not having a complete history.

Case history

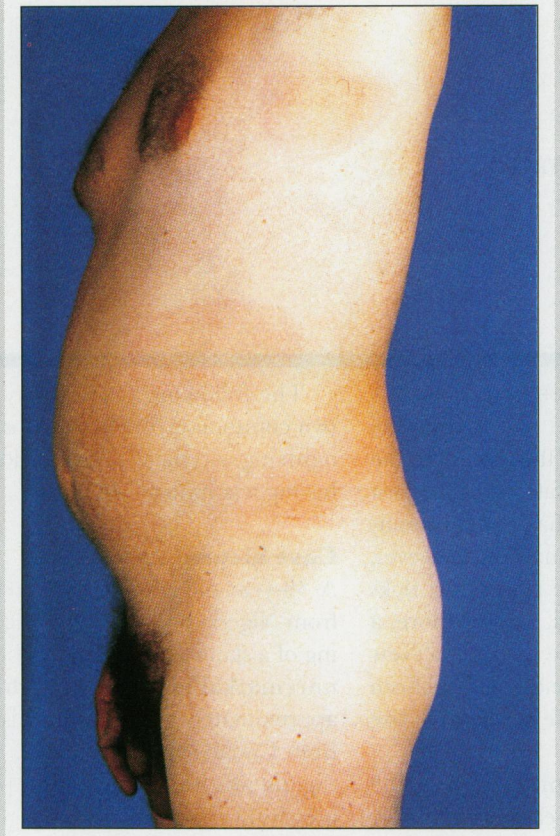
A 38-year-old mining engineer returned from Nigeria on November 10, complaining of a skin rash. His medical history was unremarkable. His rash, which began approximately 1 week after his departure from Canada on October 21, began as a slightly pruritic erythematous plaque progressively expanding in the right groin. A week or two later, multiple similar expanding lesions appeared on his trunk, legs, and arms. The lesions were largely asymptomatic, and the patient felt well other than a slight headache. There was no fever, myalgia, or arthralgia. The examination was unremarkable, except for the multiple erythematous plaques, some of which were clearing from the centre (*Figure 1*).

A consulting dermatologist correctly diagnosed Lyme disease (erythema chronicum migrans). His diagnosis was supported by results of skin biopsy and a positive serologic test (1:512 by immunofluorescent assay). The rash cleared rapidly after the administration of tetracycline, and the patient has remained well.

The key to diagnosis was recognizing the characteristic skin lesion. However, the

patient's history was incomplete. He had visited his sister in Pennsylvania immediately before his trip to Africa and had walked through a wooded area known to harbour the Lyme disease agent.

Figure 1. **Multiple erythematous plaques on the trunk, legs, and arms**



Physicians must be aware that travel to specific locations in the United States and Canada may be diagnostically important.

Causative agent

In the early 1970s an epidemic of "juvenile arthritis" occurred in children and young adults living in Lyme, Conn, and surrounding villages. The cases were referred to an investigating team at Yale University who suspected an infectious origin.[2] Cases were often preceded by an erythema migrans skin rash, which was originally described in Europe by Afzelius in 1909 and which had been associated with a previous tick bite. The disease was originally named Lyme arthritis because of its geographic origin and its predilection for joints. The geographic distribution of the disease coincided with the distribution of a newly recognized tick named *Ixodes dammini.*

Although a spirochetal etiology for erythema migrans had been suggested as early as 1948,[3] isolation attempts were unsuccessful until 1982 when Burgdorfer et al reported a new spirochete from *I dammini* ticks collected on Shelter Island, New York.[4] Serological studies and culture of the organism established this spirochete as the causative agent in Lyme disease.[5] The spirochete, named *Borrelia burgdorferi*, can be recovered with relative ease from the midgut of the *Ixodes* tick by culturing on Barbour-Stoenner-Kelly medium. However, the organism has been particularly difficult to grow from human sources.

Ticks

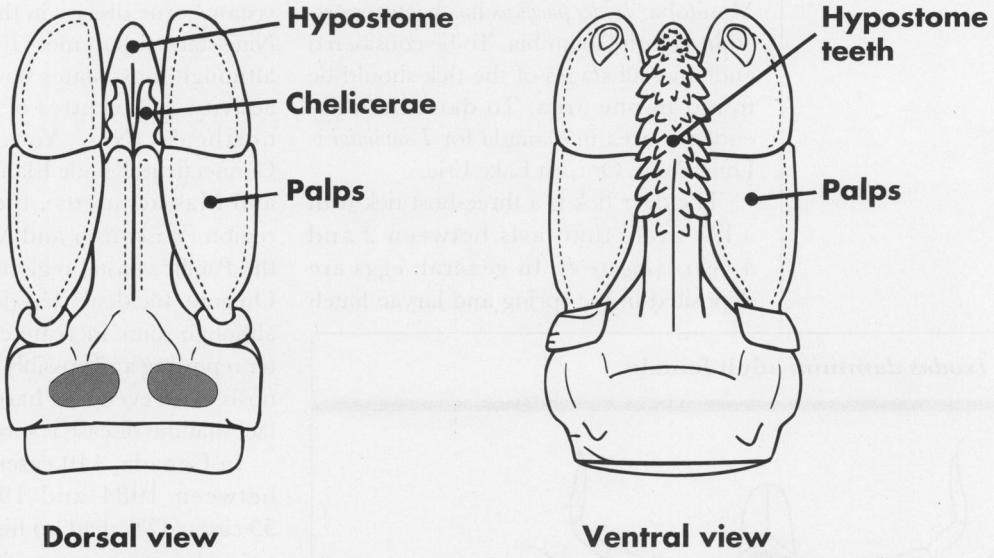
Interest in Lyme disease has revived medical interest in ticks and their biology. Ticks are arachnids belonging to the subclass Acarus (which also includes mites). All stages of development are obligate blood feeders: larvae have three pairs of legs; nymphs and adults four.

Most ticks can be classified into two families: *Ixodidae* (hard ticks) and *Argasidae* (soft ticks). The former have shiny, chitinous bodies and include most of the medically important species. The latter have soft, dull bodies.

Ticks are second only to mosquitoes in their importance as vectors of disease to humans and animals. Several factors make ticks good disease carriers: they must feed on vertebrate blood; many species have a range of hosts; their feeding patterns are conducive to pathogen transmission; and pathogens can be passed across stages (transstadial transmission) and to offspring (transovarial transmission). In addition, they have high reproductive potential and substantial longevity. Ticks can transmit viruses, bacteria, protozoa, and fungi.[6] To prevent tick-borne diseases, we must understand the carrier's biology and feeding process, the latter being the main route through which pathogens are transferred from one host to another.

Biology. *Ixodidae* ticks feed slowly, and each stage feeds only once. They look

Figure 2. **Tick mouthparts**



Reprinted with permission from the Minister of Supply and Services Canada, 1992.[7]

actively for hosts. Mating usually occurs on the host; females feed until repletion and males die after mating. Females drop off the host to lay their eggs.

The life cycle of hard ticks includes four stages: egg, larva, nymph, and adult. Life cycles are categorized by the number of hosts on which the tick feeds. One-host cycles involve a single host (eg, *Dermacentor albopictus*: all stages feed on moose). Two-host ticks are uncommon in the United States and Canada: immature stages feed on one host; adults on a different species. Three-host ticks are common. Larvae and nymphs prefer small hosts, while adults prefer larger ones.

Tick species found in Canada include some important disease carriers: *Ixodes cookei* (Powassan encephalitis), *I dammini* and *I pacificus* (Lyme disease), *Dermacentor andersoni* (Rocky Mountain spotted fever, tularemia), *Ornithodoros hermsi* (relapsing fever), *Rhipicephalus sanguineus* (tularemia), and *Haemaphysalis leporispalustris* (tularemia).[7]

Feeding. Each tick stage actively seeks a host. The tick climbs a grass, reed, or bush and senses the passage of a potential host. It must make direct contact because it cannot fly or jump. Once it finds a suitable host, it attaches by cutting the host's skin with a pair of specialized mouth appendages called chelicerae (*Figure 2*). The sharp teeth cut the flesh to permit entry of another highly specialized mouth structure, the hypostome (a ventrally curved structure covered with rows of teeth). The hypostome attaches the tick firmly to its host: in some species this attachment is aided by the secretion of a cement substance. It is very difficult to dislodge a tick once it is attached.

After attaching, the tick starts ingesting blood, which contains many ions and water that the tick does not need. About 24 hours after attachment, the tick begins regurgitating excess ions and water and returning them to the host.[8] *Ixodes dammini* probably transmits the Lyme disease spirochete to the host during this process because there is evidence that *B burgdorferi* is abundant in the tick gut.[9] Therefore, if a tick is detached from its host before regurgitation starts, the possibility of transmission is reduced.

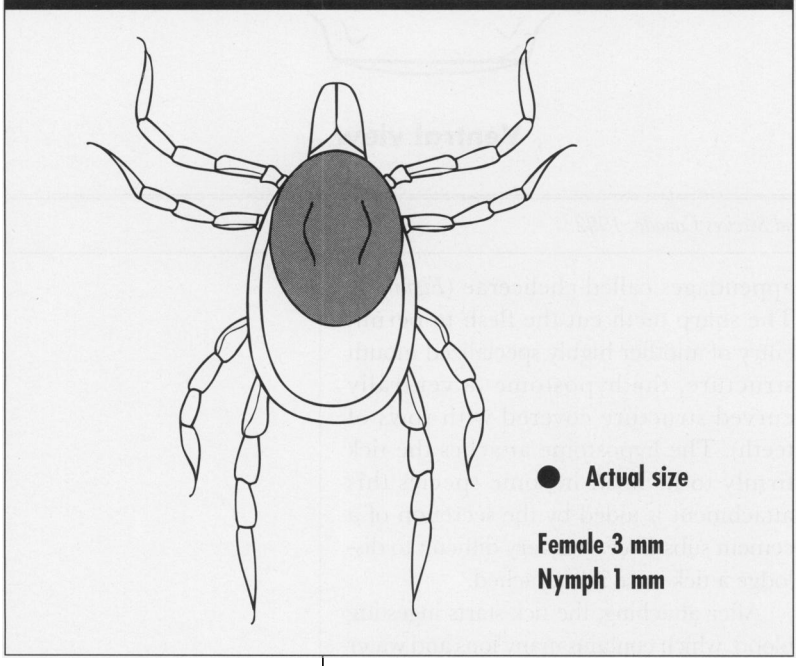
Ixodes dammini (deer tick). In the United States, this species is reported in the northeastern and midwestern states, and recently in Virginia, Indiana, New Hampshire, and Vermont. The fact that the vector is found does not necessarily mean that the Lyme disease pathogen is present.

In Canada, specimens of *I dammini* (*Figure 3*) have been found in Prince

Edward Island, Nova Scotia, New Brunswick, Quebec, Ontario, and Manitoba. *Ixodes pacificus* has been reported in British Columbia. To be considered endemic, all stages of the tick should be found in one area. To date, the only endemic area in Canada for *I dammini* is Long Point, Ont, on Lake Erie.

The deer tick is a three-host tick with a life cycle that lasts between 2 and 4 years (*Figure 4*). In general, eggs are deposited in the spring and larvae hatch about a month later. During the summer, the larvae feed once. In the fall, with the onset of cold weather, they enter a resting period. The following spring the larvae molt into nymphs, which feed during the summer. Both immature stages feed on a variety of hosts; in the northeastern United States, they commonly feed on the white-footed mouse. At the end of the summer, nymphs molt into adults, which actively seek hosts during the fall. Adults can feed on a variety of large mammals, but they usually choose the white-tailed deer. Adults mate on the host; males die a few days later and females, after engorging, fall off and overwinter, laying their eggs in the spring.[10] *Ixodes dammini* has been found on at least 27 bird and 29 mammal species.[11] The stage considered responsible for most human infections is the nymph.[12]

Figure 3. ***Ixodes dammini*** **adult female**



Geographic distribution

Lyme disease is now the most common vector-borne disease in the United States. Nine states report more than 90% of cases although most states have some disease activity. The centres of disease are the northeast (New York, New Jersey, Connecticut, Rhode Island, Pennsylvania, and Massachusetts), the north central region (Wisconsin and Minnesota), and the Pacific coastal region (California and Oregon). Incidence has doubled annually, although some increase could reflect better reporting and possibly inaccurate diagnosis. However, it is hard to dispute the fact that the disease is spreading.

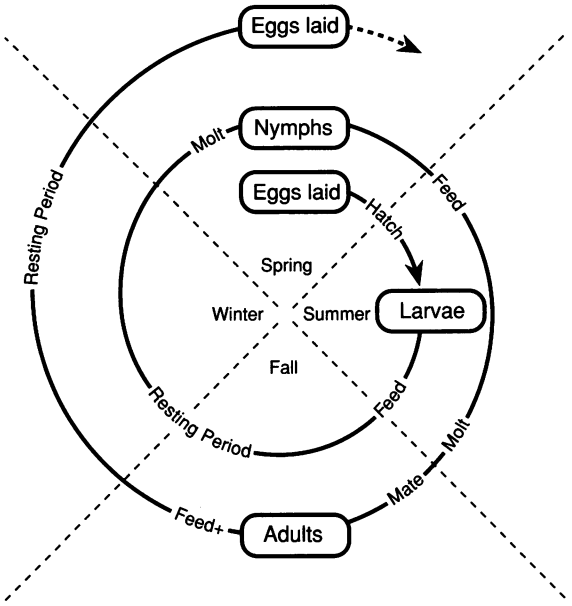
In Canada, 140 cases were reported between 1984 and 1990. Of these, 59 cases (42%) had no history of travel to an endemic area outside the reporting province. Ontario reported 58 cases; Manitoba 17; British Columbia 11; New Brunswick five; Quebec five; Saskatchewan one; and Newfoundland one.[13] In Ontario, about one third of endemic cases originated from the southwestern region between Hamilton and Windsor, although the highest per capita incidence may be in the northwest, near the Manitoba border (personal communication from Dr C. LeBer, Ontario Ministry of Health). Ontario now requires that Lyme disease be reported.

Clinical presentation

Lyme disease has certain similarities to another spirochetal infection: syphilis. Both spirochetes tend to present with a skin lesion, to then develop a secondary or disseminated stage, and finally to find sanctuary in the central nervous system and other organs and develop into clinical disease months or years after the initial infection. The temptation to label Lyme disease as progressing through a primary, secondary and tertiary stage has recently been eschewed because presentation is so variable. We will discuss the disease in three stages, emphasizing that stages may overlap and that one or more stage may not ever be apparent.

Early Lyme disease. The primary lesion is an erythematous expanding plaque known as erythema (chronicum) migrans. The lesion often begins as a small

Figure 4. ***Ixodes dammini's* 2-year cycle**



Adapted from Habicht et al.[10]

papule or macule at the site of the tick bite. The expanding borders are clearly delineated and slightly raised and lesions often clear centrally although others remain uniform. Eight to 14 days after it appears, the lesion averages 12 cm by 17 cm; at 15 to 28 days, 18 cm by 27 cm.[14] The lesion itself is usually asymptomatic, although mild pruritus is not uncommon. During this early stage, about half of patients experience constitutional symptoms including fever (55%), fatigue (48%), myalgia (47%), headache (38%), and lymphadenopathy (23%).[14] Skin lesions occur most frequently in the axilla, groin, and thigh areas.[15] The palms, soles, and mucous membranes are spared.

The primary lesion occurs an average of 7 days after the tick bite (range: 3 to 32 days).[15] The bite is commonly not noticed by the patient and is characteristically painless. About 60% to 83% of Lyme disease patients present initially with erythema migrans,[16] yet only about 31% recall the tick bite.[15] About 80% of cases occur in June or July, in keeping with the feeding pattern of the vector.

Early disseminated disease. In some patients, the spirochete disseminates, leading to a variable clinical picture that includes constitutional symptoms, secondary skin lesions, and localized organ involvement. Secondary lesions of erythema migrans appear over the body surface distant from the initial tick bite but again sparing the palms, soles, and mucous membranes. Systems and organs most commonly involved are the neurologic and musculoskeletal systems, the heart, and the eye.

Common neurologic syndromes are aseptic meningitis, painful radiculoneuritis, and cranial neuropathy. A lymphocytic meningitis appearing in the summer should alert one to the possibility of Lyme disease. Cerebrospinal fluid glucose is not depressed, but protein levels are elevated.[17] Radiculoneuritis presents with radicular pain (often thoracic), paresthesia, and asymmetric sensory and motor disturbances. Bell's palsy, sometimes bilateral, occurs in up to 10% of patients with disseminated disease. Bell's palsy is virtually indistinguishable from the idiopathic form and does not necessarily portend progression to more serious involvement of the central nervous system.

Cardiac involvement occurs in 4% to 8% of patients during this stage.[2] The manifestations are most commonly fluctuating degrees of arteriovenous block, but electrocardiographic evidence of myopericarditis and radionuclide

demonstration of ventricular dysfunction are reported. Frank heart failure is uncommon, and patients do not need permanent pacemakers, as the heart block is inevitably transitory.[18]

At this stage, musculoskeletal manifestations are mainly migratory painful attacks in the joints, tendons, bursae, or muscles.[19] Objective findings are initially absent; episodes last hours to days. About half of patients in the initial series (before current treatment regimens) developed a frank arthritis, characteristically intermittent, monoarticular or oligoarticular, and asymmetric. The knee is the most common joint affected, and if untreated, almost all patients will eventually have knee involvement. The knee is characteristically warm and swollen but not severely painful. Other joints commonly affected (in descending order of frequency) are shoulders, ankles, elbows, temporomandibular joints, wrists, and hips, followed by smaller joints of the hands and feet. The sacroiliac joints are spared.

Chronic disease. In a few cases the disease progresses to a chronic stage months to years after the initial infection. The most commonly affected systems are the joints and the central nervous system. Chronic arthritis usually affects only one to three large joints; the knee is the most common. Erosive, destructive disease may occur. The arthritis may remit spontaneously.

Recently, attention has been given to a chronic mild encephalopathy characterized by personality changes, such as somnolence, memory loss, speech disturbance, and depression.[20] This may be accompanied by persistent radicular pain, paresthesia, fatigue, or other symptoms.

Diagnosis

Diagnosis is usually established by a combination of clinical findings, history of possible exposure, and serology. Serologic testing is not yet standardized. Enzyme-linked immunosorbent assay (ELISA) testing is superior to immunoflourescent assay.[21] The Laboratory Centre for Disease Control in Ottawa will test specimens with ELISA and confirm with Western blot.

Seronegativity is usual in the early stage of the disease where clinical recognition is vital. Virtually all patients with late disease are seropositive except when they have already received antibiotic therapy. False-positive results occur in syphilis, other *Borrelia* infections, infectious mononucleosis, periodontal disease, rheumatoid arthritis, and systemic lupus erythematosus. Seropositivity must be interpreted in the clinical context.

The Canadian Consensus Conference on Lyme Disease has published a revised case definition for national surveillance.[13] The definition differs from its US counterpart in a greater dependence on history of exposure in an endemic area. The clinician must make treatment decisions on an individual basis.

Treatment

A few randomized clinical trials have studied different drugs and duration of administration. Several treatment recommendations have been published.[13,22,23]

In general, oral regimens are satisfactory for mild disease. Ceftriaxone appears to be the most potent parenteral agent and doxycycline the preferred oral agent. No good alternative has yet been found for penicillin-allergic children or pregnant women. Duration of treatment should be determined by clinical response.

Most patients treated early have a prompt response with no recurrence.[24] Patients with neurologic involvement respond less reliably, and only 55% of patients with established arthritis have a complete response.[25] Early treatment can prevent later misery. Fatigue may occur after treatment but will generally resolve spontaneously and does not require therapy.

Prevention

Prospects for a human vaccine for Lyme disease are still years away. Therefore, the best way to control human infections is to prevent tick bites. In endemic tick and Lyme disease areas, we recommend the following preventive measures.

- Walk on trails, not in the bushes where ticks are waiting for a host. Avoid areas where tick warning signs are posted.
- Wear light-coloured clothes so you can see crawling ticks. Wear long pants

tucked into socks, long-sleeved shirts, and closed shoes (avoid sandals).

- Use a tick repellent that contains diethyltoluamide, or DEET (read the label carefully before applying), on yourself and your pets.
- When you return from the woods, check yourself, children, and pets for ticks. If you find a tick, keep it in a tightly closed vial for identification. If the tick is attached, grab it as close to the skin as possible with a pair of fine tweezers or protected nails and pull firmly but gently. It is important that the mouthparts come out completely to prevent an infection and to identify the tick species properly. Alcohol, water, and soap can be used on the tick bite. The tick, with date and site of collection, can be sent to the provincial Ministry of Health for identification. It is important to note that not all tick species are vectors of Lyme disease and not all deer ticks are infected with the Lyme disease spirochete. ■

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References

1. White DJ, Chang H-G, Benach JL, Bosler EM, Meldrum SC, Means RG, et al. The geographic spread and temporal increase of the Lyme disease epidemic. *JAMA* 1991;266:1230-6.
2. Steere AC, Malawista SE, Hardin JL, Bosler EM, Meldrum SC, Means RG, Ruddy S, Askenase PW, Audiman WA. Erythema chronicum migrans and Lyme arthritis. The enlarging clinical spectrum. *Ann Intern Med* 1977;86:685-98.
3. Lennhoff C. Spirochaetes in etiologically obscure diseases. *Acta Derm Venereol (Stockh)* 1948;28:295-324.
4. Burgdorfer W, Barbour AG, Hayes JF, Benach JL, Gruywald TE, Davis JP. Lyme disease – a tick-borne spirochetosis? *Science* 1982; 216:1317-9.
5. Steere AC, Grodzicki MS, Kornblatt AN, Craft JE, Barbour AG, Burgdorfer W, et al. The spirochetal etiology of Lyme disease. *N Engl J Med* 1983;308:733-40.
6. Harwood RF, James MT. *Entomology in human and animal health.* 7th ed. New York: MacMillan, 1979.
7. Gregson JD. *The* Ixodidae *of Canada.* Ottawa: Agriculture Canada, 1956.
8. Piesman J, Mather TN, Sinsky RJ, Spielman A. Duration of tick attachment and *Borrelia burgdorferi* transmission. *J Clin Microbiol* 1987;25:557-8.
9. Burgdorfer W, Hayes SF, Corwin D. Pathophysiology of the Lyme disease spirochete, *Borrelia burgdorferi* in ixodid ticks. *Rev Infect Dis* 1989; 11(Suppl 6):S1442-50.
10. Habicht GS, Beck G, Benach JL. Lyme disease. *Sci Am* 1987;257(1):78-83.
11. Anderson JF, Magnarelli LA. Avian and mammalian hosts for spirochete-infected ticks and insects in a Lyme disease focus in Connecticut. *Yale J Biol Med* 1984;57:627-41.
12. Ginsberg HS. *Evology and management of ticks and Lyme disease at Fire Island National Seashore and selected eastern national parks.* Washington, DC: US Department of the Interior, National Park Service, 1990.
13. Consensus report. Consensus Conference on Lyme Disease. *Can J Infect Dis* 1991;2:49-54.
14. Berger BW. Dermatologic manifestations of Lyme disease. *Rev Infect Dis* 1989;11(Suppl 6): 1475-81.
15. Steere AC, Bartenhagen NH, Craft JE, Hutchinson GJ, Neman JH, Rahn DW, et al. The early clinical manifestations of Lyme disease. *Ann Intern Med* 1983;99:76-82.
16. Malane MS, Grant-Kels JM, Feder HM, Luger SW. Diagnosis of Lyme disease based on dermatologic manifestations. *Ann Intern Med* 1991; 114:490-8.
17. Reik L, Burgdorfer W, Donaldson JO. Neurologic abnormalities in Lyme disease without erythema chronicum migrans. *Am J Med* 1986; 81:73-8.
18. Steere AC, Batsford WP, Weinberg M, Alexander J, Berger HJ, Wolfson S, et al. Lyme carditis: cardiac abnormalities of Lyme disease. *Ann Intern Med* 1980;93(Pt 1):8-16.
19. Steere AC, Schoen RT, Taylor E. The clinical evolution of Lyme arthritis. *Ann Intern Med* 1987; 107:725-31.
20. Logigian EL, Kaplan RF, Steere AC. Chronic neurologic manifestations of Lyme disease. *N Engl J Med* 1990;323:1438-44.
21. Artsob H, Garvie M. Quality control assessment of Canadian laboratories testing for Lyme disease. *Can J Infect Dis* 1991;2:41-5.
22. Rahn DW, Malawista SE. Lyme disease: recommendations for diagnosis and treatment. *Ann Intern Med* 1991;114:472-81.
23. Medical letter. Treatment of Lyme disease. *Med Lett Drugs Ther* 1989;31:57-9.
24. Dattwyler RJ, Volkman DJ, Conaty SM, Platkin SP, Luft BJ. Amoxycillin plus probenecid versus doxycycline for treatment of erythema migrans borreliosis. *Lancet* 1990;336:1404-6.
25. Steere AC, Green J, Schoen RT, Tailor E, Hutchinson GJ, Rahn DW, et al. Successful parenteral penicillin therapy of established Lyme arthritis. *N Engl J Med* 1985;312:869-74.

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