

The Emergence of Lyme Disease in Canada: Epidemiology, Prevention, Diagnosis and Treatment

Michel P. Deilgat, CD, MD, MPA, CCPE

Centre for Food-borne, Environmental and Zoonotic Infectious Diseases, Public Health Agency of Canada, Ottawa, ON

Kathleen Kerr, MD, Dip Env Health

Environmental Health Clinic, Women's College Hospital, Toronto, ON



PROTECTING CANADIANS FROM ILLNESS



Public Health
Agency of Canada

Agence de la santé
publique du Canada

Canada

Disclosure of Commercial Support

- This program has received no financial support.
- This program has received no in-kind support.

Mitigating Potential Bias

- We will mitigate any potential bias by discussing appropriately all treatment and diagnostic options in our talk today

Tick story

“Quite a frightening little story of how tick infestations can cause panic even the tick removal part! I have advised him not to worry and to see his MD when he returns as the risk is still quite low and he is much calmer now but I can definitely envision the conversation related to how to remove the tick on his back with people who don’t understand his requests!”

Correspondance from a patient who came back from Columbia June 2014



EPIDEMIOLOGY OF LYME DISEASE

Ticks that transmit Lyme: what they look like



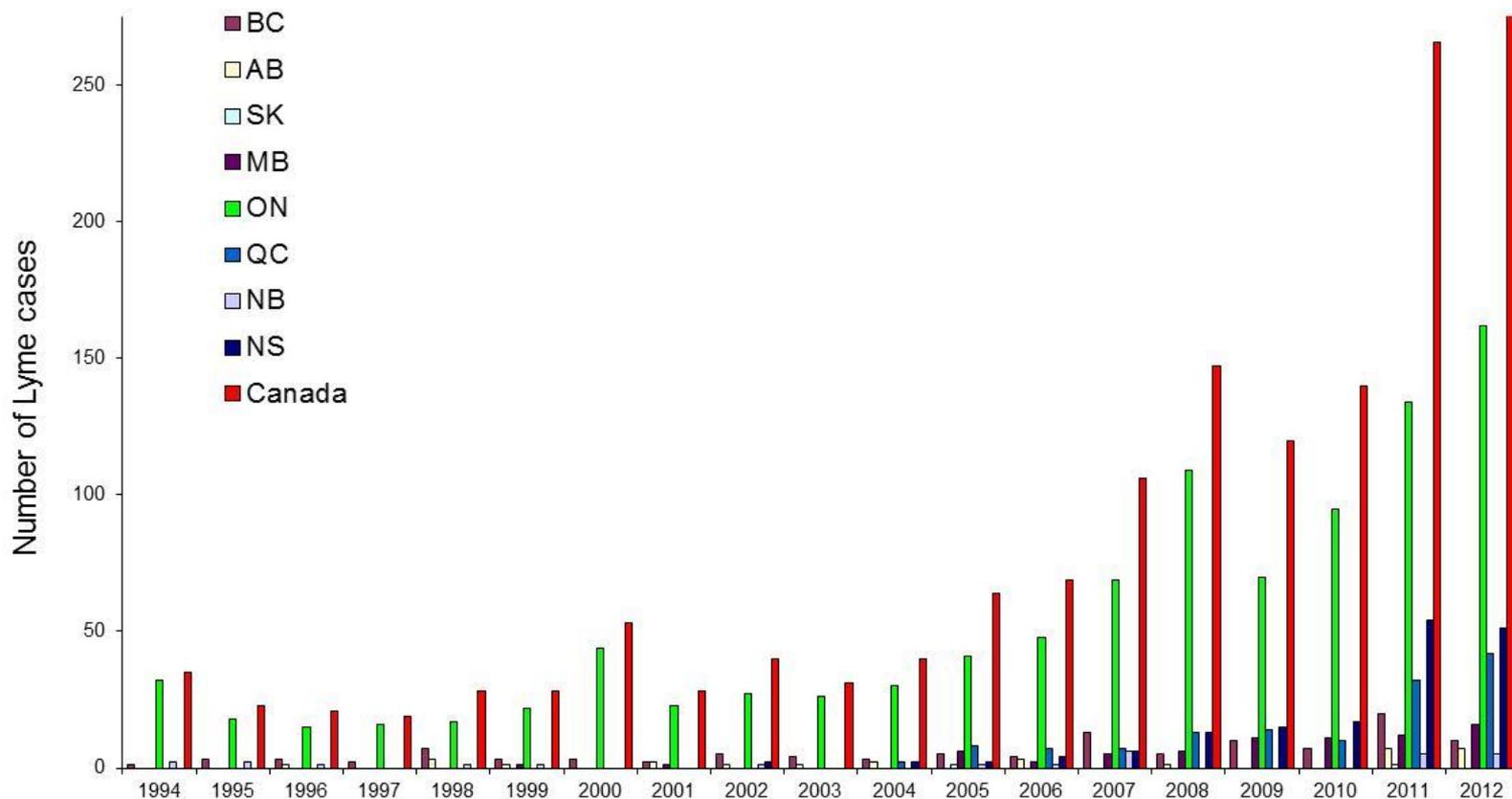
Notifiable Disease in Canada (since 2009)

The Agency currently has data for Lyme disease cases reported between 2009-2013*

* Numbers may change slightly as provincial or territorial public health organisations can from time to time retroactively identify cases and update their statistics.

Year	No. of Cases reported
2009	128
2010	132
2011	258
2012	315
2013	682
2014	?

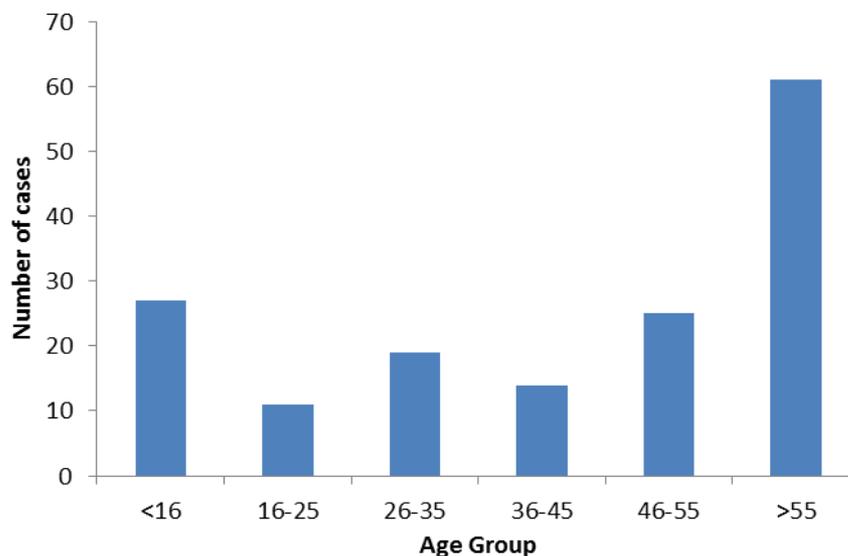
Lyme disease incidence in Canada



Note that Lyme disease became nationally notifiable in December 2009. Data from 2009 and earlier are based on voluntary submission of information from Provinces and Territories in which Lyme disease was notifiable. Data for 2011 are not yet finalised as we await data from some Provinces and Territories.

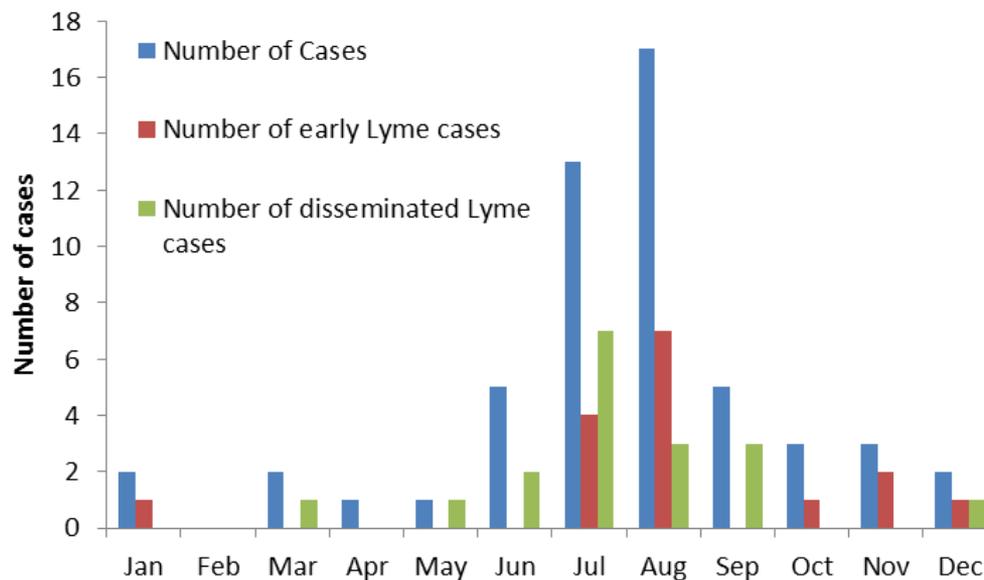
Risk of Lyme: WHO

- People who live, work and/or play in or near “Lyme endemic areas”
- Children under 16 and adults over 55
- Higher incidence in males in some studies



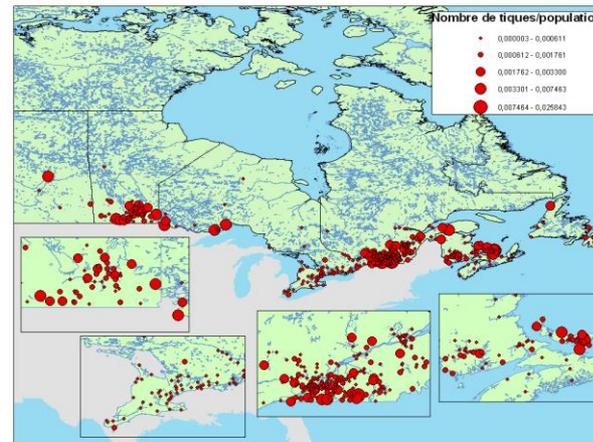
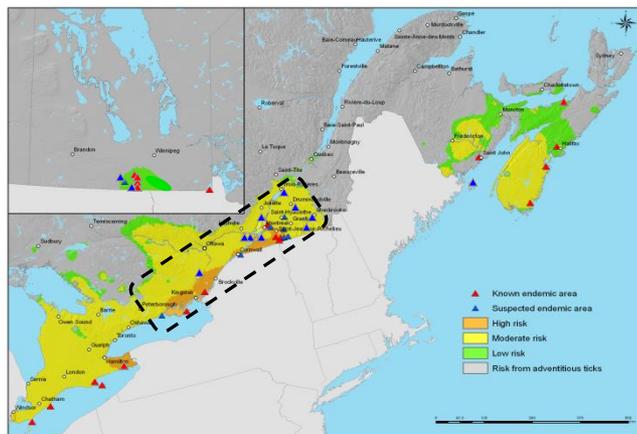
Risk of Lyme: **WHEN**

- Mostly occurs in spring and summer when ticks (and people) are active



Risk of Lyme: **WHERE**

- Occurs where the tick populations are established and are transmitting *B. burgdorferi* (“Lyme endemic areas”)
- Low, but not non-existent, risk of Lyme outside endemic areas due to ticks spread by migratory birds



Ogden et al., J. Med. Entomol. 2006;

Low level but more widespread risk due to ticks spread by migratory birds



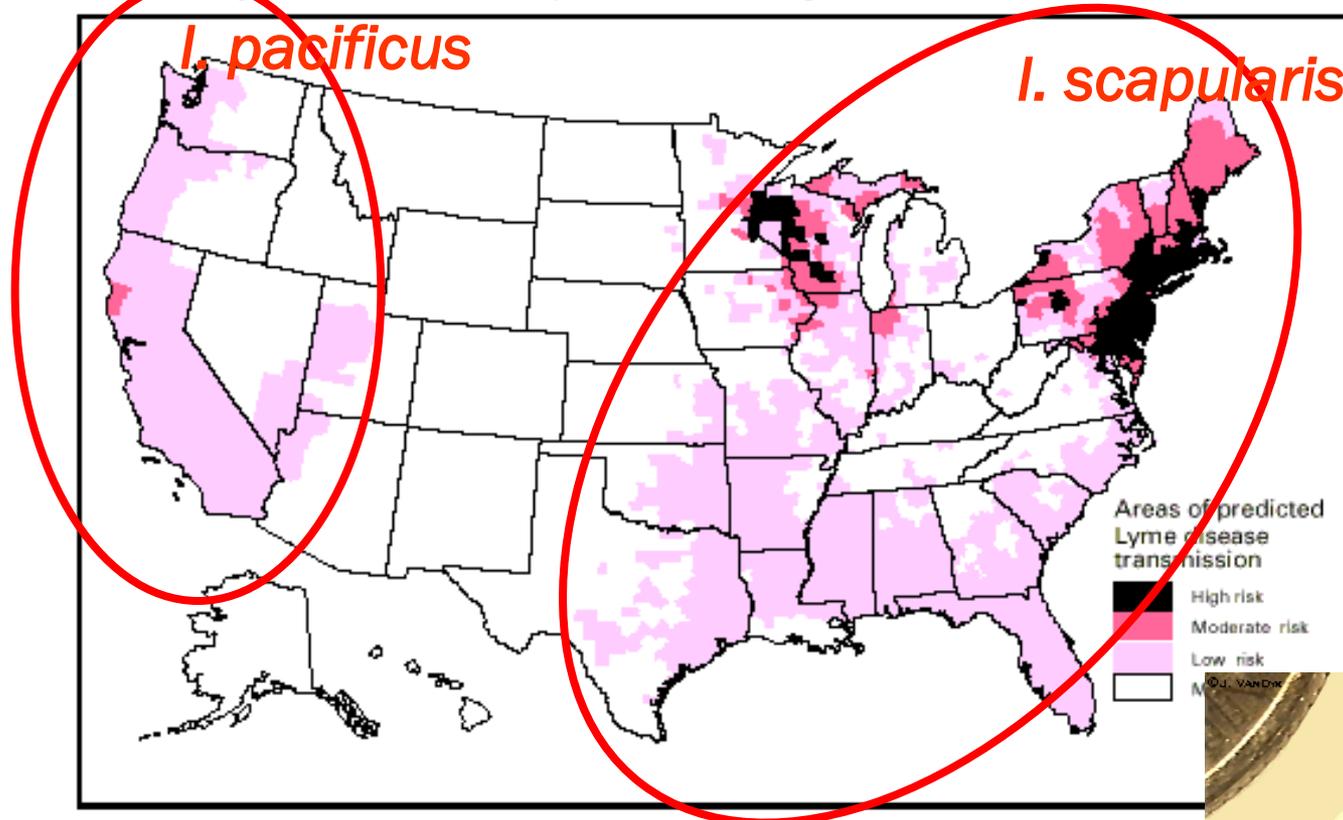
Photo by Bill Hilton Jr
(www.hiltonpond.org)



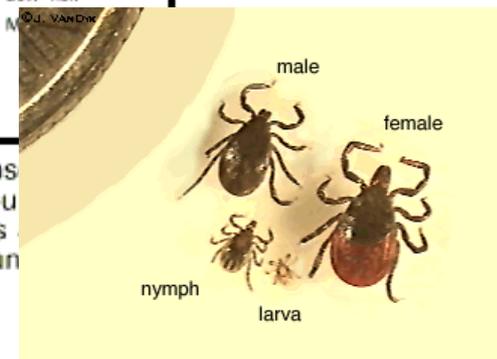
Ogden et al., Appl. Environ. Microbiol 2008

Canada Lyme disease issue is an expansion of USA LD epidemic

National Lyme disease risk map with four categories of risk



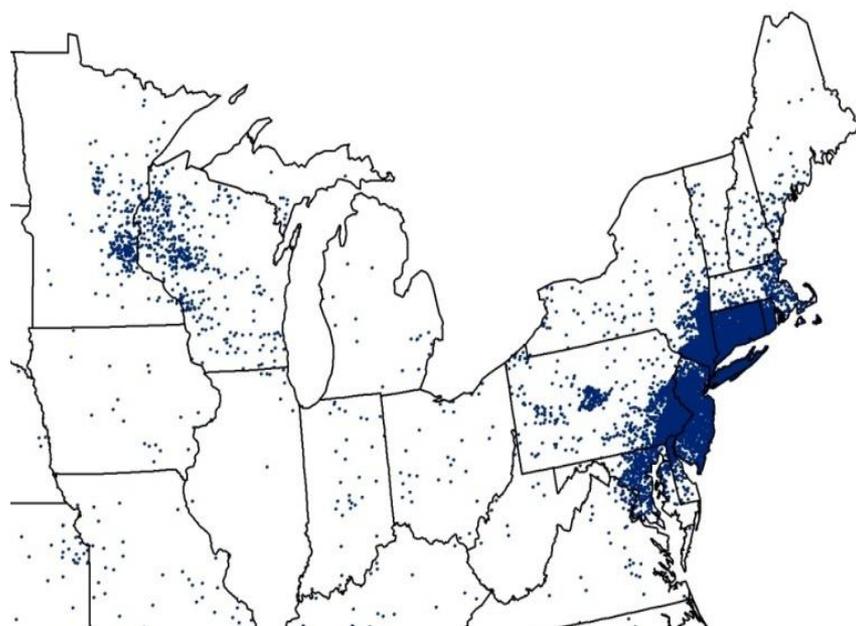
Note: This map demonstrates an approximate distribution of predicted Lyme diseases United States. The true relative risk in any given county compared with other counties may differ from that shown here and might change from year to year. Risk categories are defined in the accompanying text. Information on risk distribution within states and counties can be obtained from state and local public health authorities.



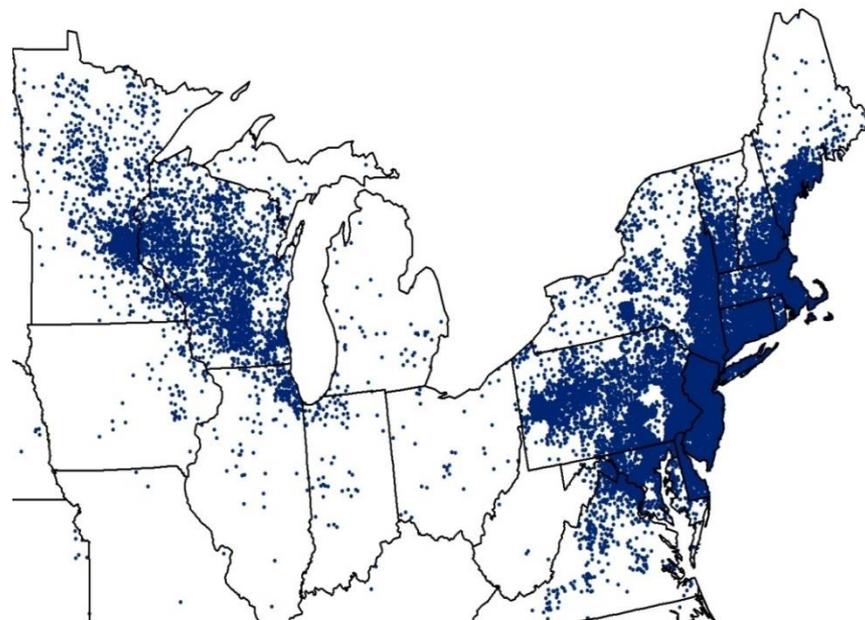
The Spread Northwards

Emergence of LD in Canada is due to a U.S. expansion of tick habitats and range. Over 30,000 cases/year (maps courtesy of CDC)

Number of cases reported to U.S. CDC are likely one-tenth of actual cases – there are potentially over 300,000 actual cases in the U.S.



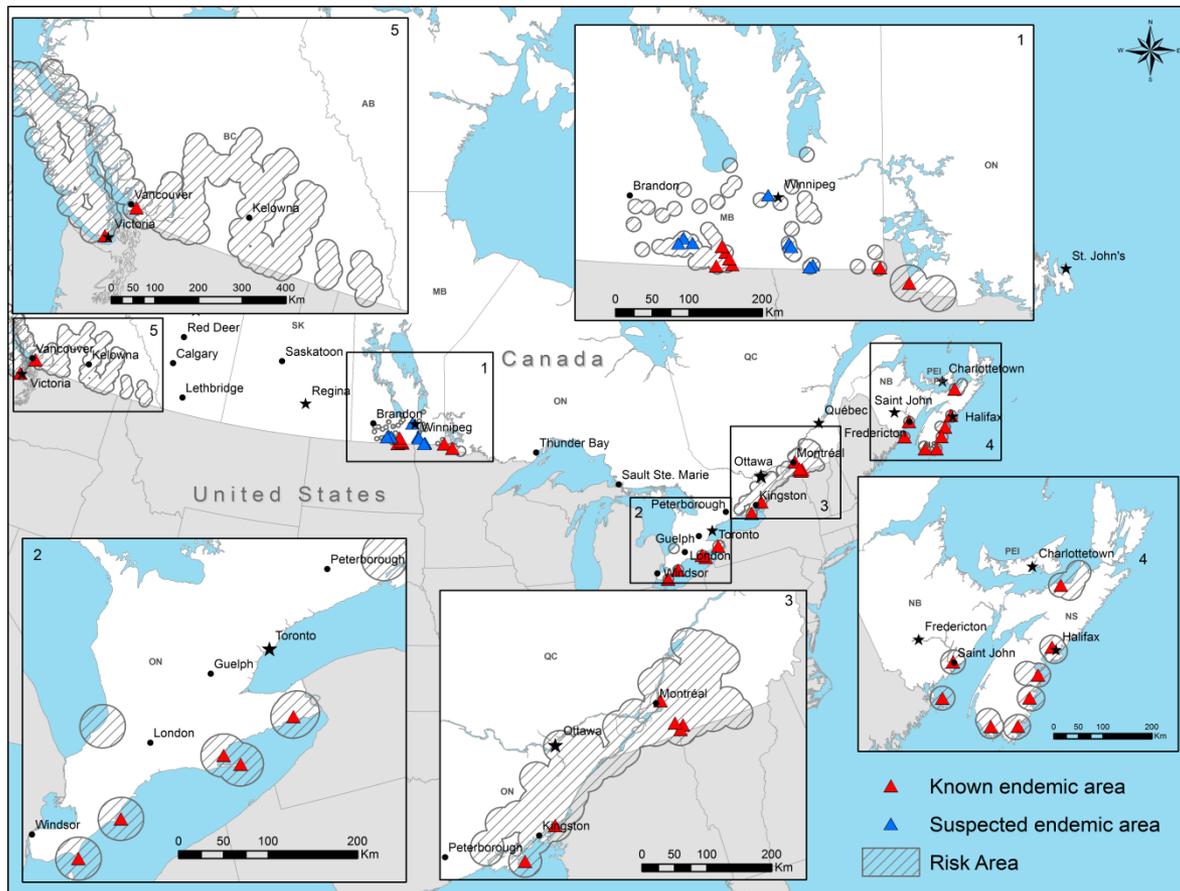
1996



2011

Risk Areas in Canada

Endemic and Suspected Endemic Areas



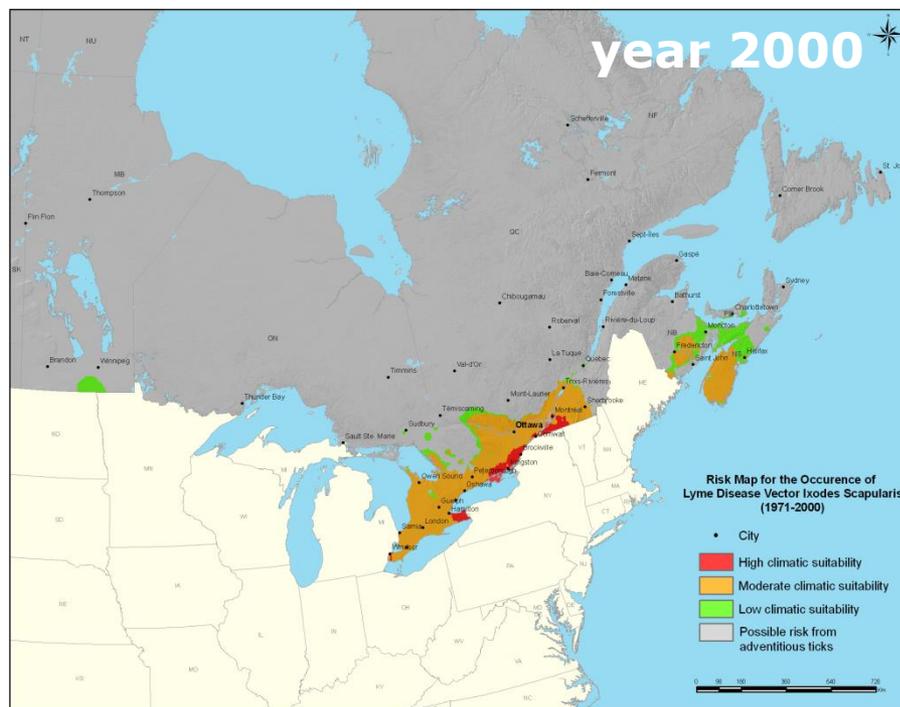
Surveillance Case Definitions – **CONFIRMED CASES**

- Clinical evidence of illness with laboratory confirmation by isolation of *Borrelia burgdorferi* from an appropriate clinical specimen, or by detection of *B. burgdorferi* deoxyribonucleic acid (DNA) by Polymerase Chain Reaction (PCR); or
- Clinical evidence of illness with a history of residence in, or visit to, an edemic area and with laboratory evidence of infection by approved serological methods and test interpretations

Surveillance Case Definitions – **PROBABLE CASES**

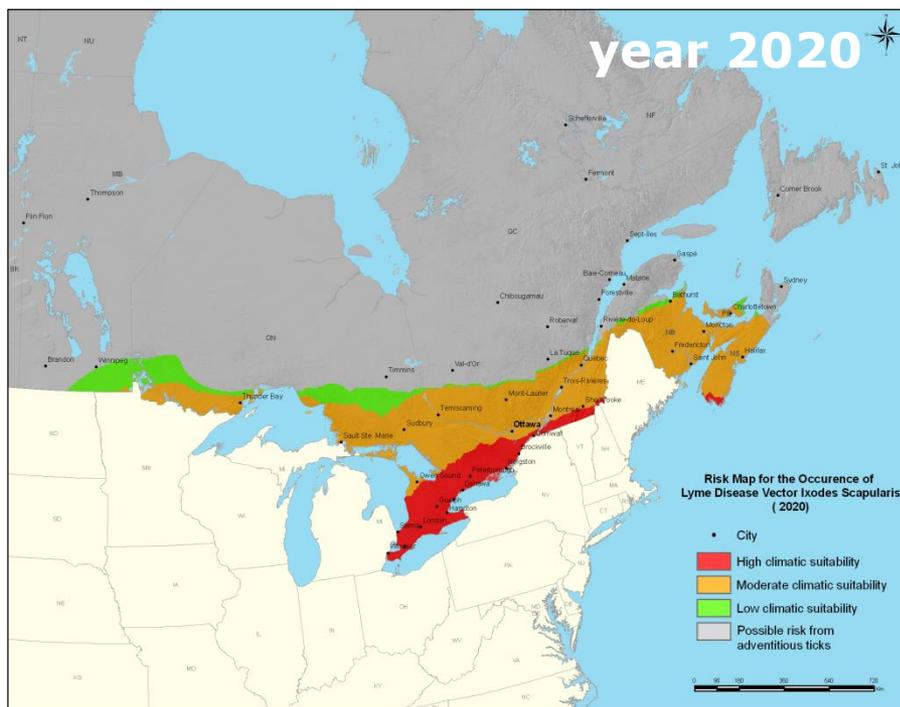
- Clinical evidence of illness without a history of residence in, or visit to, an endemic area and with laboratory evidence of infection (i.e., positive or equivocal ELISA and positive IgM and / IgG western blots; or
- Clinician-observed EM without laboratory evidence but with history of residence in, or visit to, an endemic area.

What the future may hold



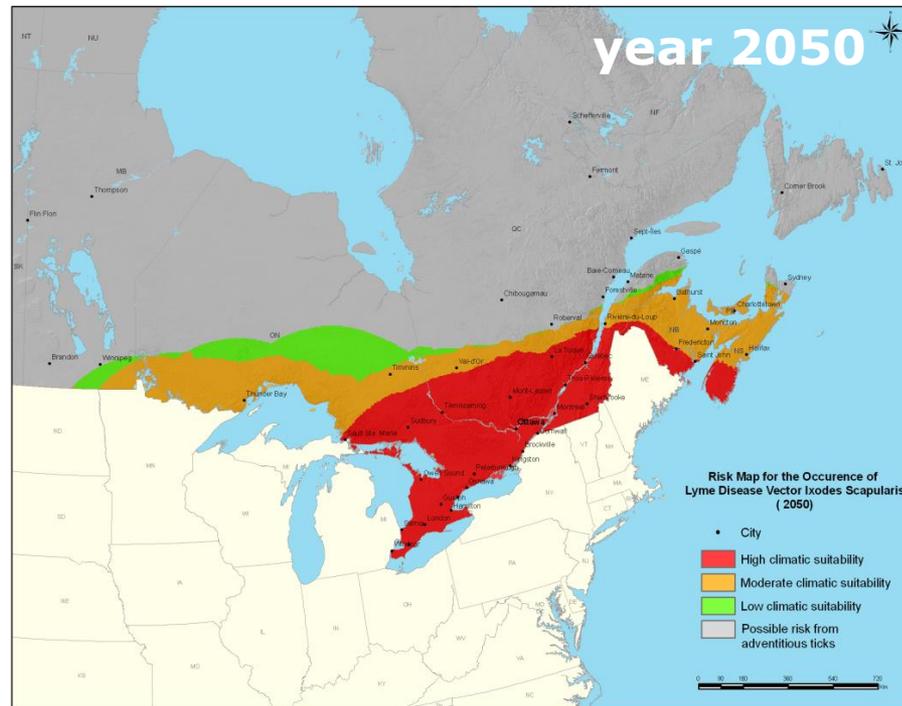
Ogden et al., Int J Health Geogr 2012

What the future may hold



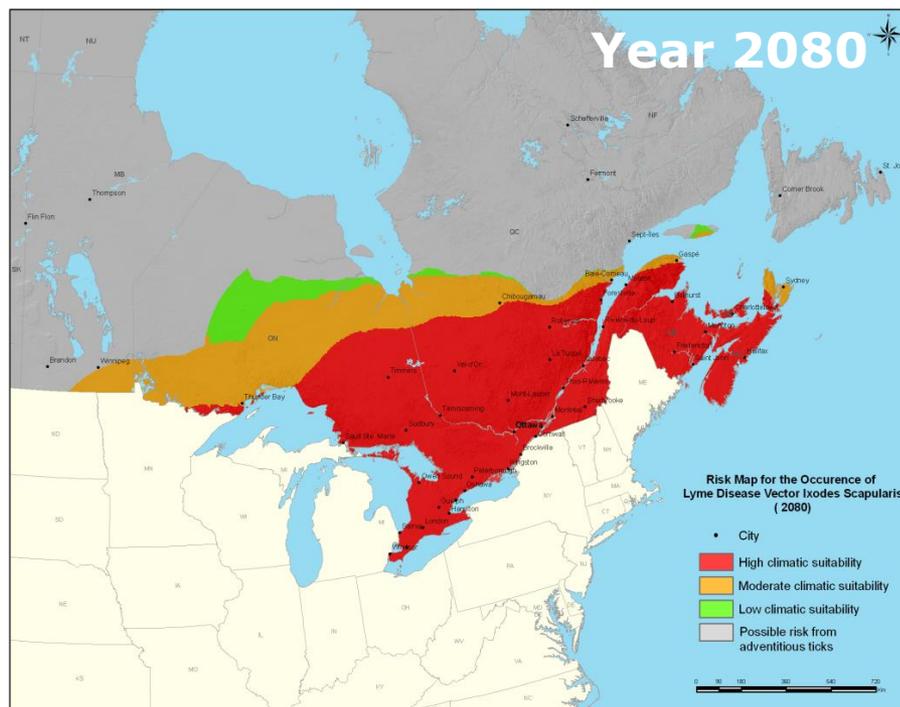
Ogden et al., Int J Health Geogr 2012

What the future may hold



Ogden et al., Int J Health Geogr 2012

What the future may hold

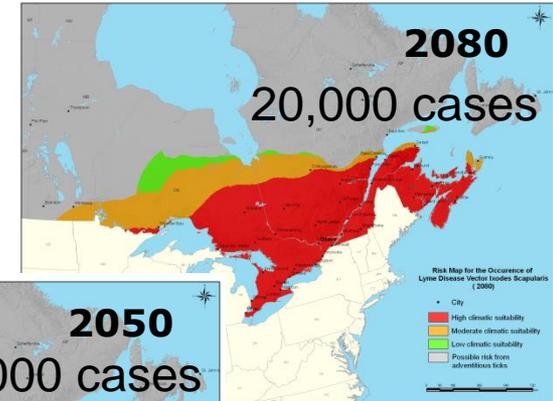
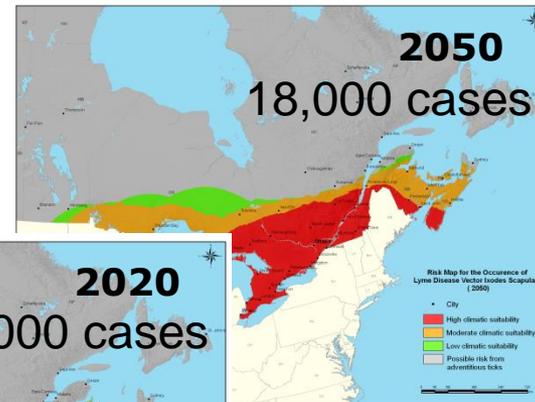
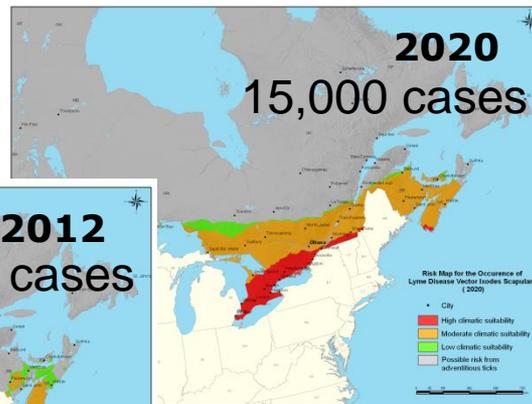
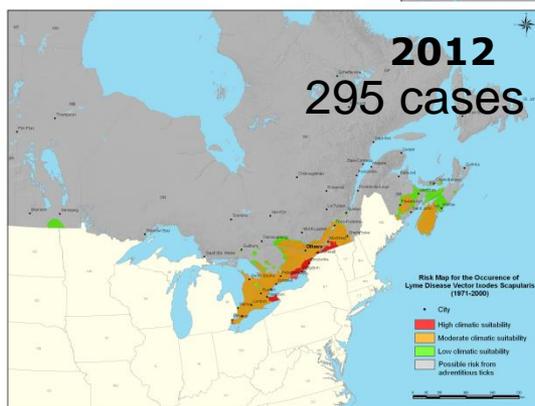


High risk
Moderate risk

Low risk
Risk of bird-borne ticks

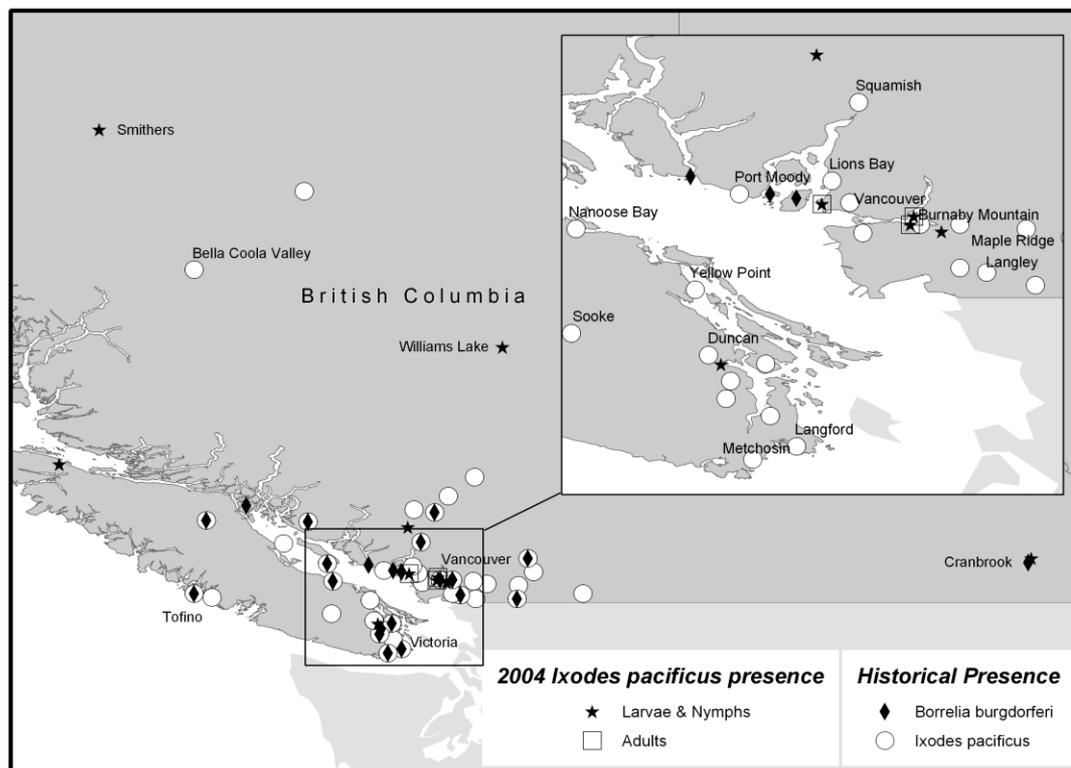
Ogden et al., Int J Health Geogr 2012

Exposure risk increasing rapidly, particularly in Eastern Canada



Early spread is hitting Canada's most densely populated areas first

In British Columbia



Widespread but low-level risk in south-western BC

Surveillance of Lyme disease in Canada: 2 Complementary Methods

- **PASSIVE surveillance** involves the voluntary submission of ticks found on human and domestic animals, by veterinarians and health care professionals (Ogden et al., 2006; 2010). This method can raise the suspicion of areas where ticks are establishing.
- **ACTIVE field surveillance** involves collection of ticks and/or wild animal hosts by standardised methods to determine whether populations of vector ticks and endemic cycles of *Borrelia burgdorferi* transmission have become established. These methods are used to identify where tick populations are becoming established (Lyme disease risk areas), and when multiple visits to the same site are possible, to confirm the occurrence of a Lyme disease endemic area (Health Canada, 1991)

A Vaccine for Lyme Disease

Then

- LYMErix: 1998 – 2002
- Discontinued due to contentious and unproven reports of side-effects and projections of low demand

Now

- Baxter – in Phase I/II trials of new vaccine using recombinant OspA as antigen (published in *The Lancet*); Anticipated public access: 2023
- Vaccine development using OspC protein as an antigen – veterinary market?
- Environment too litigious to encourage future development?



The Future

- The global demand will continue to grow as cases increase
- PHAC is monitoring any activities relating to licensing a vaccine by the US/ Europe...

Stay tuned...

- PHAC → Infectious Diseases → Lyme Disease → Health Professionals

What do health professionals need to know about Lyme disease?

<http://www.phac-aspc.gc.ca/id-mi/lyme/professionals-professionnels-eng.php>

Canada Communicable Disease Report (CCDR) ISSN 1481-8531 (On-line)

<http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/index-eng.php>

March 06, 2014 – Volume 40-5 (Lyme disease: Surveillance – New Public Health Intervention – Action Plan on Lyme Disease)

May 29, 2014 – Volume 40-11 (Clinical aspects of Lyme disease)

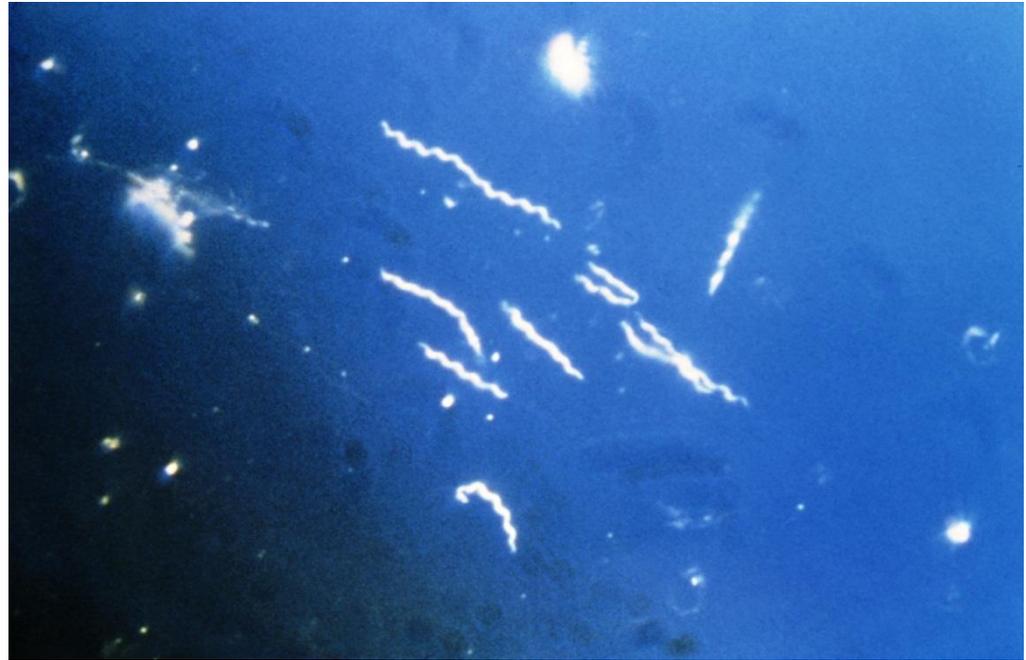
PBLP (Foundation for Medical Practice Education) – Lyme Disease (2015)

CLINICAL MANIFESTATIONS

Approach to the patient with Lyme disease

Lyme disease is a treatable multisystem illness caused by infection with the tick-borne spirochete *Borrelia burgdorferi*

The disease starts after an infected tick expels its salivary gland and abdominal contents into the skin of a human.



Pathophysiology

- *Borrelia burgdorferi* enters bloodstream at the time of tick feeding (after 24-36 hours of contact)
- Bloodstream phase → move out into skin, synovial membranes, heart and nervous system
- How the spirochete damages tissue is unclear, extent of tissue injury affected by aggressiveness of host inflammation, immunological reactions, and genetic attributes of the spirochaete.
- **Hypothesis:** direct injury / production of antispirochetal antibodies that cross-react with tissue antigens
- HLA-DR4 increased risks for such chronic illness
- Persistence of symptoms after treatment → exaggerated/sustained immune response?

Natural History of the Disease

- 20% of patients with **erythema migrans** will experience spontaneous resolution and no progression of disease
- 80% of patients (without treatment) disseminated disease
- **Oligoarthritis** common (60% - 80%) – resolve within 1-3 years, even without treatment
- Chronic neurologic / persistent joint symptoms – 5% - 10%
- Susceptibility to late chronic disease may be genetically determined

Clinical Presentations-untreated

Early Lyme Localized

- Erythema migrans
- Flu like symptoms

Early Lyme Disseminated

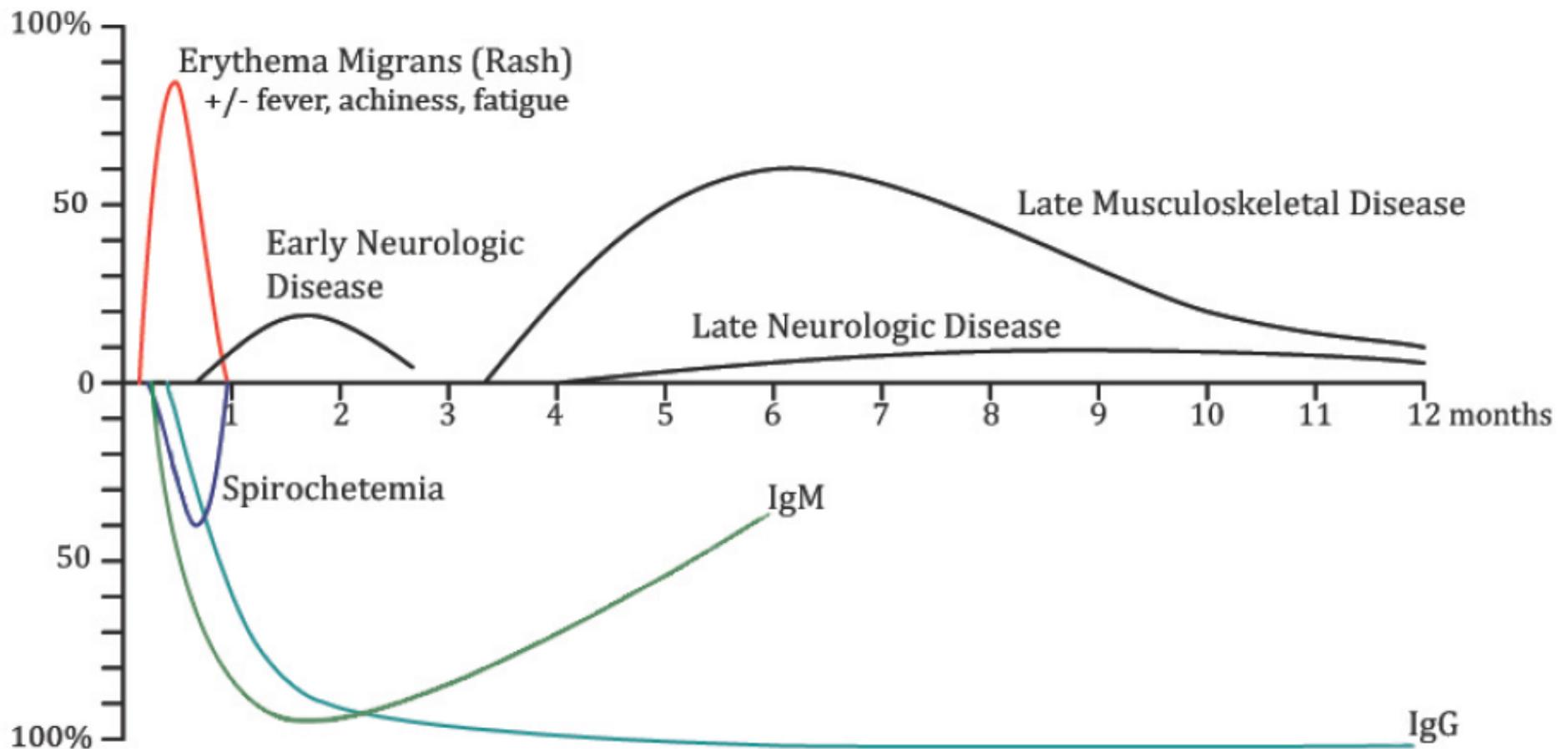
- Dermatologic-multiple EM
- Neurologic
- Cardiac
- Musculoskeletal(arthritis, tendonitis, bursitis)

Late Lyme disease, (Chronic Infection)

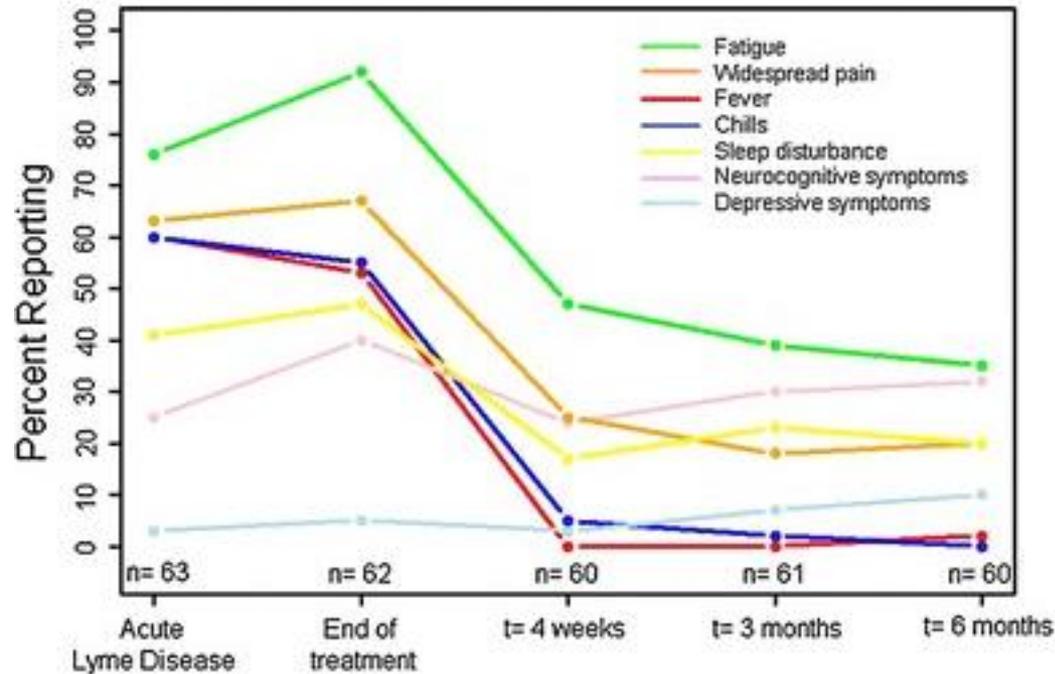
- Arthritis
- Neurologic

Untreated Lyme Disease is a Systemic Infection with both Early and Late Manifestations

Without Early Antibiotic Treatment late objective findings of Lyme disease occur in over half the patients



Symptoms change treated patients



N=63

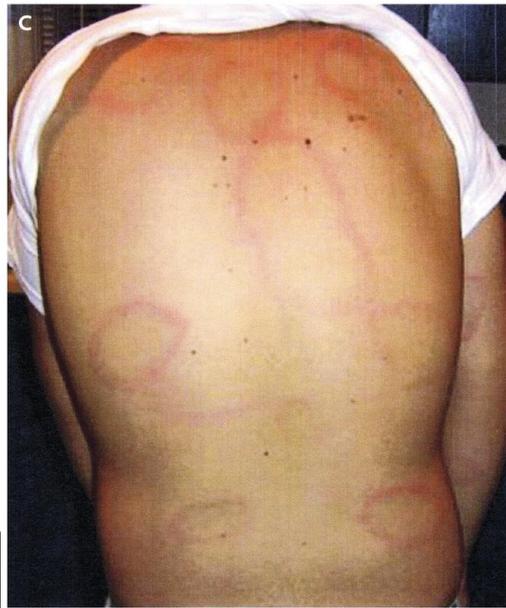
Self-reported symptoms of the cohort with acute Lyme disease over time

Aucott et al, Qual Life Res. 2013

Early localized Lyme disease < 30 days

- **1st clinical manifestation** - ~80% of infected persons – **expanding macular erythematous rash** (*erythema migrans*) – rash starts to fade by 3-4 weeks
- Not pruritic, not painful
- 15 cm approx. Min 5 cm
- Flu-like symptoms ('summer flu') without respiratory or GI sx.
- Regional lymphadenopathy may be present with the rash
- 20% of patients have flu-like symptoms without a rash or no acute–stage symptoms at all





 The NEW ENGLAND
JOURNAL of MEDICINE

Shapiro ED. N Engl J Med
2014;370:1724-1731

Early Lyme Immune Response

- About ½ of patients demonstrated lymphopenia (and increased liver enzyme levels).
- Several T cell chemokines were coordinately upregulated while chemokines that drive other immune cell types were not.

Soloski et al Serum Inflammatory Mediators as Markers of Human Lyme Disease Activity.
PLoS ONE 2014, (Johns Hopkins group)

CaseJune 2012 68 yr old female

“This photo was taken six hours before a tick was removed in the ED in Brockville. The doctor could not get it out. He broke it up into pieces and then froze the area and dug out the pieces.”

Patient uncertain how long it was there, under her arm. She had been gardening, her home is in a wooded, endemic area.



Differential diagnosis? Erythema Migrans or Cellulitis?

- 1 week later this patient was treated in emerg with Keflex for cellulitis
- (6 months later she was hospitalized with viral meningitis.)
- Never diagnosed with Lyme disease.



CASE: EM vs Cellulitis

- “Erythema migrans lesions usually occur in locations that would be unusual for community-acquired cellulitis, such as the axilla, popliteal fossa, back, abdomen, and groin; this distribution can be helpful for diagnosis.”

Wormser GP. N Engl J Med. 2006. Clinical practice. Early Lyme disease.

Table 2. Differential Diagnosis of Erythema Migrans.

Condition	Characteristics
Single erythema migrans lesion	Erythematous macule or papule at site of tick bite (although the tick is often not seen); enlarges relatively rapidly to 5–30 cm or more in diameter; typically flat and annular; usually uniformly erythematous or with heightened central erythema; may have central clearing; without treatment, persists for average of 3–4 wk*
Nummular eczema	Lesion usually smaller and less erythematous than erythema migrans lesion; does not enlarge rapidly; pruritic; well demarcated; skin may be thickened or weepy
Tinea (ringworm)	Rash with raised margins and scale on the edges; central clearing is typical; pruritic
Granuloma annulare	Small (2–5 cm in diameter), circular rash with erythematous papules and clear center; develops over weeks; often on dorsum of extremities
Cellulitis	Area of inflammation often at site of trauma to skin; warm; enlarges rapidly; rarely circular; may be tender and associated with fever
Insect bite	Often raised papule with central punctum; pruritic; usually smaller than erythema migrans lesion; rarely continues to enlarge
Spider bite	Necrotic lesion with central eschar; often very painful
Hypersensitivity to tick bite	Small lesion, does not expand as erythema migrans does; present at time tick bite is recognized or soon after; uniformly erythematous; often pruritic
Multiple erythema migrans lesions	Multiple ringlike lesions; typically do not enlarge rapidly; a larger, primary lesion may be present; often associated with systemic symptoms
Erythema multiforme	Multiple lesions, often quite small; mucosa, palms, and soles may be involved; cause may be apparent (e.g., drug or infection)
Urticaria	Pruritic, raised lesions; may appear and disappear rapidly

* A similar lesion is found in southern tick-associated rash illness (STARI), which occurs primarily in southeastern and south central states. STARI does not have extracutaneous manifestations. The cause of STARI is unclear; no diagnostic test is available.⁸



The NEW ENGLAND
JOURNAL of MEDICINE

Shapiro ED. N Engl J Med 2014;370:1724-1731

Early disseminated Lyme disease

< 3 months

- Hematogenous dissemination follows within several days to a few weeks in ~ 50% -80% of untreated patients
- **Generalized malaise & debilitating fatigue, headaches, neck stiffness,**
- **migratory arthralgias and musculoskeletal pain**
- **Dermatological:** new annular skin lesions smaller and less migratory – malar rash – diffuse erythema – urticaria have been noted
- **Cardiac involvement** noted in 5%-10% of patients – **Transient heart block** (asymptomatic first-degree atrioventricular block to complete heart block with fainting) – lasts 3-6 weeks – most severe forms of heart block~1 week

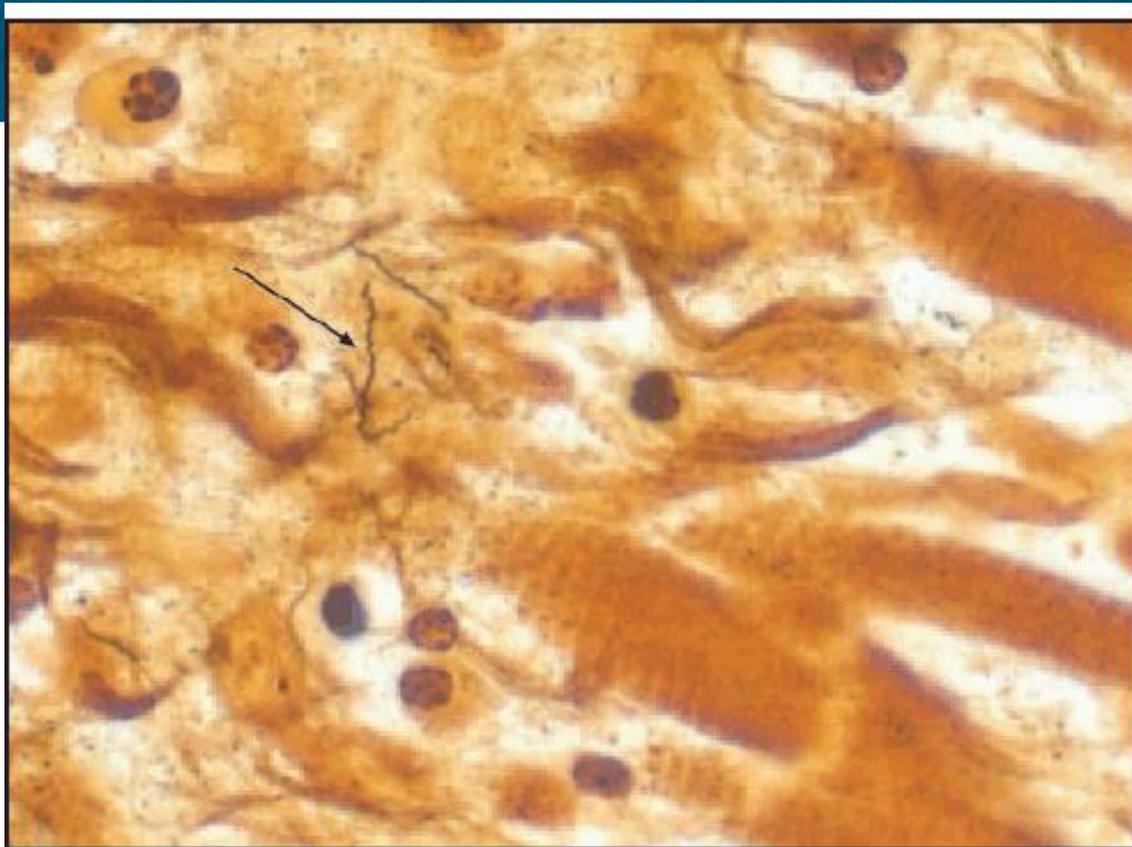
Lyme carditis

- Usually occurs with joint or nervous system manifestations, although the heart may be the only site of clinically apparent disease.
- 4% to 10% of untreated Lyme disease patients, uncommon with early tx.
- Most cases occur between June and December, as long as 7 months after initial illness. Lyme carditis is much less common in Europe.
- The Lyme bacterium can infect all parts of the heart, including the conduction system around the atrioventricular node, the outer or inner membranes of the heart, the cardiac muscle, and more rarely, cardiac blood vessels or heart valves.

Lyme carditis

- The predominant cardiac manifestation is partial heart block. Heart block usually is mild, with complete resolution within 6 weeks after onset.
- The most common symptoms are light-headedness, fainting, shortness of breath, palpitations, and/or chest pain.
- Heart block occasionally is complete and permanent, requiring insertion of a pacemaker.
- Death has been reported in a few cases.

Krause, Circulation. 2013



CDC Morbidity and Mortality Weekly Report (MMWR)
December 13, 2013 / 62(49);993-996

Warthin-Starry stain of cardiac tissue at 158X magnification demonstrating *Borrelia burgdorferi* spirochetes (arrow) in one of three patients whose death was associated with Lyme carditis — United States, 2013

Early disseminated Lyme disease < 3 months

Neurological

- weeks to months after initial infection (15%-20% of untreated patients)
- meningitis
- Uni/bilateral Bell's palsy – most common cranial nerve deficit
- Mild encephalopathy (mood change, somnolence, and memory disturbances)
- Peripheral neuropathy



CASE: 68 year old female viral vs Lyme meningitis

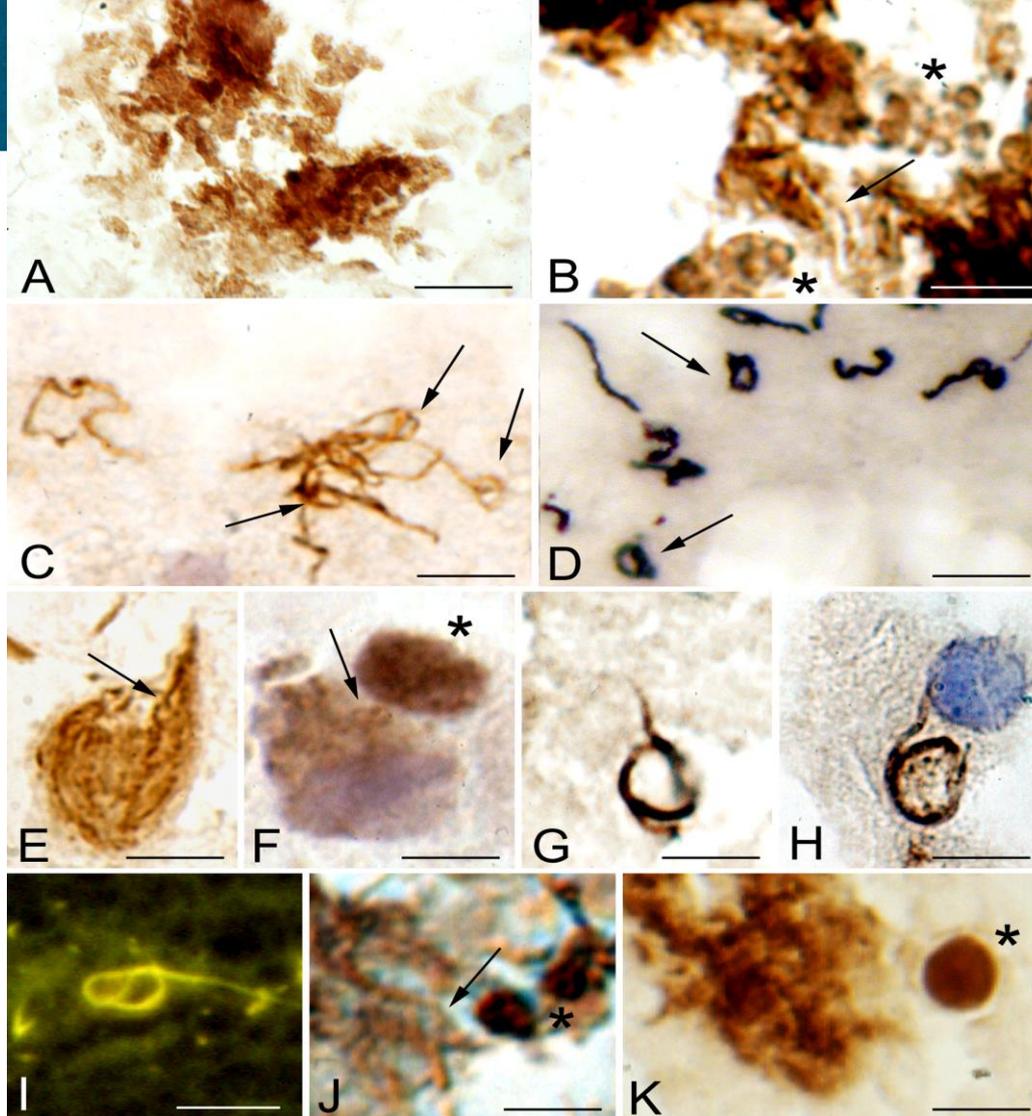
- January 2013, 6 months after the tick bite, back to Brockville emerg, diagnosed with meningitis, given IV ampicillin and Ceftriaxone for three days (test for bacterial meningitis took longer to come back because of the holiday)
- CSF showed lymphocytosis WBC 196 (0-5) and increased protein 1.48 (<0.45), Culture negative for bacteria.
- It was determined to be viral meningitis.....
- No Lyme testing done.

Cerebrospinal fluid findings in adults with acute Lyme neuroborreliosis

CSF finding in patients with acute lyme neuroborreliosis (LNB), viral meningitis (VM) and neurolyues (NL)

Parameter	LNB (<i>n</i> = 118) age (50 ± 17.1)	VM (<i>n</i> = 19) age (38.3 ± 17.3)	NL (<i>n</i> = 3) age (46.2 ± 13.8)
CSF leukocytes [μl^{-1}]	170.5 (57.0; 369) 196	97.0 (21.0; 210.0)	65 (7.0; 100.7)
CSF protein [mg/l]	1,232 (697; 1,926) 1.48	628 (493.0; 969)*	614 (328.0; 800.0)
QAlbumin $\times 10^3$	17.2 (9.7; 28.4)	9.1 (7.2; 14.7)*	7.6 (4.0; 11.7)
CSF lactate [mmol/l]	2.0 (1.6; 2.6)	2.1 (1.9; 2.3)	1.5 (1.3; 1.6)

Djukic at al, J Neurol. Apr 2012



Miklossy *et al.* *Journal of Neuroinflammation* 2008

- Extra- and intracellular atypical and cystic forms of spirochetes in the cerebral cortex of a patient with pathologically and serologically confirmed chronic Lyme neuroborreliosis where *Borrelia burgdorferi sensu stricto* was cultivated from the brain.

Lyme Meningitis may occur in the seronegative window

- diagnosis of LM is based CSF pleocytosis
 - associated with the occurrence of EM
 - and/or positive serologic tests.
- However, serology may be **negative** or indeterminate **early in infection when dissemination to the nervous system occurs.**
- Also, delays in performing or reporting these tests may lead to delays that can hinder diagnosis and treatment.
- More specific techniques for confirming LM include
 - » tests for intrathecal production of specific antibody and
 - » demonstration of *Borrelia burgdorferi* DNA by PCR, which is not rapid and is not very sensitive.

Eppes et al, *Pediatrics*, 1999

Meningitis

- Characterized by headaches that fluctuate in intensity from mild to severe with or without associated nausea, vomiting, light sensitivity, neck stiffness, or pain on eye motion.
- Spinal tap will usually show elevated white blood cells and elevated protein.

Encephalitis

- Sleepiness, mood swings and irritability, atypical spontaneous tearfulness or personality change, cognitive problems (typically with word finding problems, memory loss, slowed mental speed), balance problems, and sensory hyperarousal (e.g., vision, hearing).
- EEG at this stage may show mild slowing. Brain MRI may be normal or show white matter hyperintensities suggestive of inflammation.

http://www.columbia-lyme.org/patients/ld_lyme_symptoms.html

Cranial Neuropathies

- Seen in as few as 10% of patients with neurologic Lyme disease in the US, more common in Europe. CN VII Palsy is most common.
- Occur within days to weeks of the initial infection by a tick.
- Abnormalities in facial sensation may be inflammation of the trigeminal cranial nerve (CN V).
- If central vision appears cloudy or if there is pain on eye movements, these could be signs of an optic neuritis...blindness may occur if not detected and treated early.
- If CN III, IV, or VI are affected, the patient may present with double vision.
- With involvement of CN VIII, patients may experience ringing in the ears (tinnitus), loss of hearing, vertigo, or ataxia.

http://www.columbia-lyme.org/patients/ld_lyme_symptoms.html

Radiculoneuropathy

- symmetric or asymmetric sensory abnormalities, such as numbness or tingling.
- radicular pain sharp stabbing or burning or shooting pains that radiate down a dermatomal distribution,
- may also be elements of motor weakness.
- exclude other causes of distal paresthesias, such as diabetic and toxic-metabolic neuropathies, or other causes of radicular pain, such as structural compression.

http://www.columbia-lyme.org/patients/ld_lyme_symptoms.html

Encephalopathy

- cognitive problems early or months or years after the initial infection.
- short-term memory, verbal fluency such as in name or word retrieval, and slower speed of thinking, “brain fog”.
- difficulty in following normal speed of conversations, children may find homework assignments difficult

Neuropsychiatric symptoms

- irritability, easy tearfulness, anxiety, and depression.
- Rarely, patients with undetected Lyme disease may present with obsessive compulsive disorder, paranoia, auditory/visual hallucinations, or full blown mania.
- need for many hours of sleep, including daytime naps.
- Sensory hyperarousal occurs in about 50% of patients with later stage neurologic Lyme disease, most often affecting hearing and/or vision. These patients may resort to wearing earplugs, sound protectors, and/or sunglasses indoors.

http://www.columbia-lyme.org/patients/ld_lyme_symptoms.html



STATE OF CONNECTICUT
STATE DEPARTMENT OF HEALTH
79 ELM STREET • HARTFORD, CONNECTICUT 06115



OFFICE OF THE COMMISSIONER

August 3, 1976

Circular Letter #12-32
To: Directors of Health

In November 1975, several cases of arthritis in Lyme children were reported to the Connecticut State Department of Health. Dr. David Snyderman, Acting Director of the Preventable Diseases Division of the Department of Health discussed these cases with Dr. Allen Steere and Dr. Stephen Malawesta, Section of Rheumatology, Department of Internal Medicine, Yale University School of Medicine. Between them they planned a joint Health Department/Yale survey to detect additional cases in the Lyme area and to describe the disease in detail. Findings to date from this epidemiologic survey, clinical evaluation of patients,

Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities.

- “51 residents of three contiguous Connecticut communities -- 39 children and 12 adults -- who developed an illness characterized by recurrent attacks of asymmetric swelling and pain in a few large joints, especially the knee.....13 patients (25%) noted an erythematous papule that developed into an expanding, red, annular lesion, as much as 50 cm in diameter.”

Steere AC, et al (1977) Arthritis Rheum.

“The clinical evolution of Lyme arthritis.”

- Untreated patients: From 1 day to 8 weeks after disease onset, 10 of the patients (18%) began to have **brief episodes of joint, periarticular, or musculoskeletal pain** for as long as 6 years, but they never developed objective joint abnormalities.
- From 4 days to 2 years after disease onset, 28 (51%) had one episode or began to have intermittent attacks of **frank arthritis**, primarily in large joints; a few had polyarticular.
- The remaining 6 patients (11%) developed chronic synovitis later in the illness; of these, 2 (4%) had erosions, and 1 (2%), permanent joint disability.
- The spectrum of Lyme arthritis ranges from subjective joint pain, to intermittent attacks of arthritis, to chronic erosive disease.

Steere et al, Ann Intern Med. 1987

Table 1. Common musculoskeletal manifestations of Lyme disease in North America

	Early localized infection	Acute disseminated infection	Late-stage infection^a
Time to onset after tick bite	Days to 1 month	Weeks to a few months	Months
Systemic symptoms	None, or variable degrees of fever, headache	Fatigue, headache, malaise; occasionally fever	None, or fatigue, malaise; occasionally fever
Musculoskeletal signs/symptoms	None, or myalgia/arthritis	Migratory musculoskeletal pain in joints, bursa, tendons, muscles, lasting hours or days in a given location	Oligoarticular arthritis, usually involving the knee, lasting weeks to months, with recurrence; other joints include shoulder, ankle, elbow, hip, wrist; temporomandibular joint pain, bursitis, and tendinitis may be present; children may present with an acute arthritis resembling septic arthritis, but usually are able to bear weight on the affected joint; inflammation that persists in a single joint for >12 months is an unusual presentation of Lyme arthritis

^a Rare late musculoskeletal manifestations relevant to the rheumatologist are clinically apparent myositis, including orbital myositis, and dactylitis; carpal tunnel syndrome has been described but would be unusual in the absence of a polyneuropathy or associated wrist arthritis.

Early to late disseminated Lyme disease ~6 months

Musculoskeletal

- Onset is variable (~ 6 months)
- Pain and swelling noted in one or a few large joints (knee – most common)
- Joint effusion - ↑ neutrophils
- No more than 3 joints are usually involved – after attack joint to normal
- S&S last for several days to a few weeks, it may cause chronic, antibiotic-refractory arthritis.
- Frank arthritis in up to 60% of untreated patients

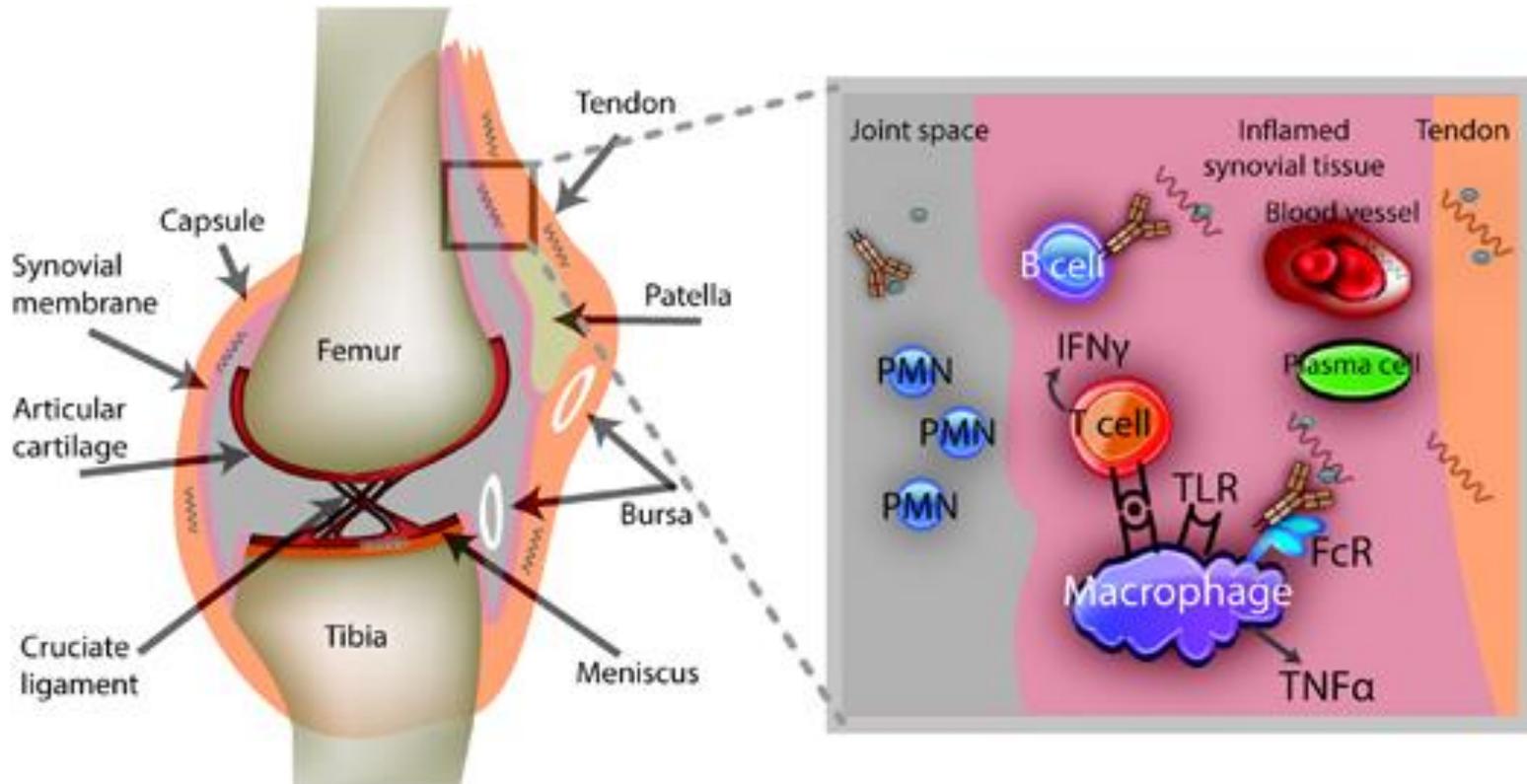


Enmeshed spirochetal debrislikely the triggering factor.

- “*B. burgdorferi* is known to adhere to type 1 collagen, decorin and other components of the connective tissue extracellular matrix
- ... preferentially spreads through the blood stream to structures in close proximity to the joint space such as the synovial membrane, joint capsule, tendons and/or tendon sheaths, ligaments, cartilage or menisci,
- where some bacterial cells may become **enmeshed** in a host-derived fibrinous or collagenous **matrix.**”

Wormser et al. The amber theory of Lyme arthritis: initial description and clinical implications Clin Rheum 2012

Review: Unraveling Lyme Disease



Bockenstedt and Wormser. Arthritis & Rheumatology. 2014

Late Lyme Disease- Chronic Infection

After a latent period of several months to 1 year after the original untreated infection – symptoms of chronic infection begin to appear

Bouts of arthritis

- transient forms of arthritis supplanted by a more persistent type that lasts months instead of weeks
- often knee – oligoarticular
- joint erosion – uncommon but reported rarely leads to permanent loss of function.

Skin changes- Europe

- a chronic atrophic form of *acrodermatitis* (unique to LD)

Symptoms

- Tiredness

Late Lyme Disease- Chronic Infection

Objective Neurologic impairment

- In up to 5 percent of untreated patients, *B. burgdorferi* may cause chronic **neuroborreliosis**, sometimes after long periods of latent infection.
- principal neurologic manifestation of Lyme disease representing polyneuropathy and encephalopathy (Distal paresthesias, radicular pain, and memory loss) Often – occur concurrently
- Rare: leukoencephalopathy with spastic paraparesis may develop
- 2/3 of patients: ↑ protein in CSF
- 50% Lyme antibodies in CSF
- Most – electrophysiological studies abnormal, axonal degeneration
- typically shows diffuse involvement of both proximal and distal nerve segments. (Steere 2001)

Confusing names

- **Late Lyme disease:** Previously *untreated*, chronic symptoms, sometimes referred to as **Chronic Lyme**, but these patients have *objective* signs and *positive* serology.
- Chronic Lyme disease: can refer to previously treated patients diagnosed with Lyme with persisting symptoms.
- Post-Lyme disease syndrome,
- Post-treatment chronic Lyme disease
- **Post treatment Lyme disease syndrome**

- Names used by different medical organizations at different times that generally refer to the same group of patients.

“Chronic Lyme disease”

- “Chronic Lyme disease” is often used to explain persistent pain, fatigue, and neurocognitive **symptoms** in patients without any evidence of previous acute Lyme disease.
- Once this diagnosis is given, prolonged treatment with multiple antimicrobial agents may follow.
- This review examines the scientific evidence for chronic *borrelia* infection and explains the approach to clinical evaluation and management in patients with a diagnosis of chronic Lyme disease.

Feder et al. A critical appraisal of "chronic Lyme disease". NEJM 2007

The Four Predominant Categories of Disease Associated with Chronic Lyme Disease

Category 1

Symptoms of unknown cause, with no evidence of *Borrelia burgdorferi* infection

Category 2

A well-defined illness unrelated to *B. burgdorferi* infection

Category 3

Symptoms of unknown cause, with antibodies against *B. burgdorferi* but no history of objective clinical findings that are consistent with Lyme disease

Category 4

Post-Lyme disease syndrome

Category 5

Late Lyme disease

Category 3 – “Chronic Lyme disease”

- “..do **not** have a history of **objective** clinical findings that are consistent with Lyme disease, but their **serum samples contain antibodies** against *B. burgdorferi*, as determined by means of standardized assays ...ordered to investigate chronic, subjective symptoms of unknown cause.
- Patientshave at most only equivocal evidence of *B. burgdorferi* infection, (since the predictive value of positive serologic results in this setting is low.)
- Although some clinicians would offer patients with category 3 disease an empirical trial of 2 to 4 weeks of an oral antibiotic, such patients should be told that the diagnosis is uncertain and that a benefit from treatment is unlikely.”

Feder H et al. N Engl J Med 2007

Probable Late Lyme disease

- Patients with ongoing symptoms and a positive IgG serology would meet CDC surveillance criteria for 'probable' Lyme disease.
- We suggest that in patients from Lyme endemic regions, the possible diagnosis of probable late Lyme disease is reasonable to consider in the setting of an unexplained illness and a history highly suggestive of Lyme disease exposure. These patients may benefit from testing for IgG antibodies to confirm exposure to *B. burgdorferi* and to suggest the possibility of late untreated infection.

Aucott J et al. Probable late Lyme disease: a variant manifestation of untreated *Borrelia burgdorferi* Infection. BMC Infect Dis 2012,

Probable Late Lyme disease

- The finding of a positive serology by itself is not diagnostic of active, untreated infection in probable late Lyme disease, as it is also present in the convalescent phase of resolved Lyme disease in the estimated 40% of individuals who are never treated during the acute phase and never develop late manifestations of Lyme disease.
- However in the context of otherwise unexplained symptoms it is a reasonable hypothesis that the patients' symptoms are a result of previously untreated infection with *B. burgdorferi*

Aucott J et al. Probable late Lyme disease: a variant manifestation of untreated *Borrelia burgdorferi* Infection. BMC Infect Dis 2012,

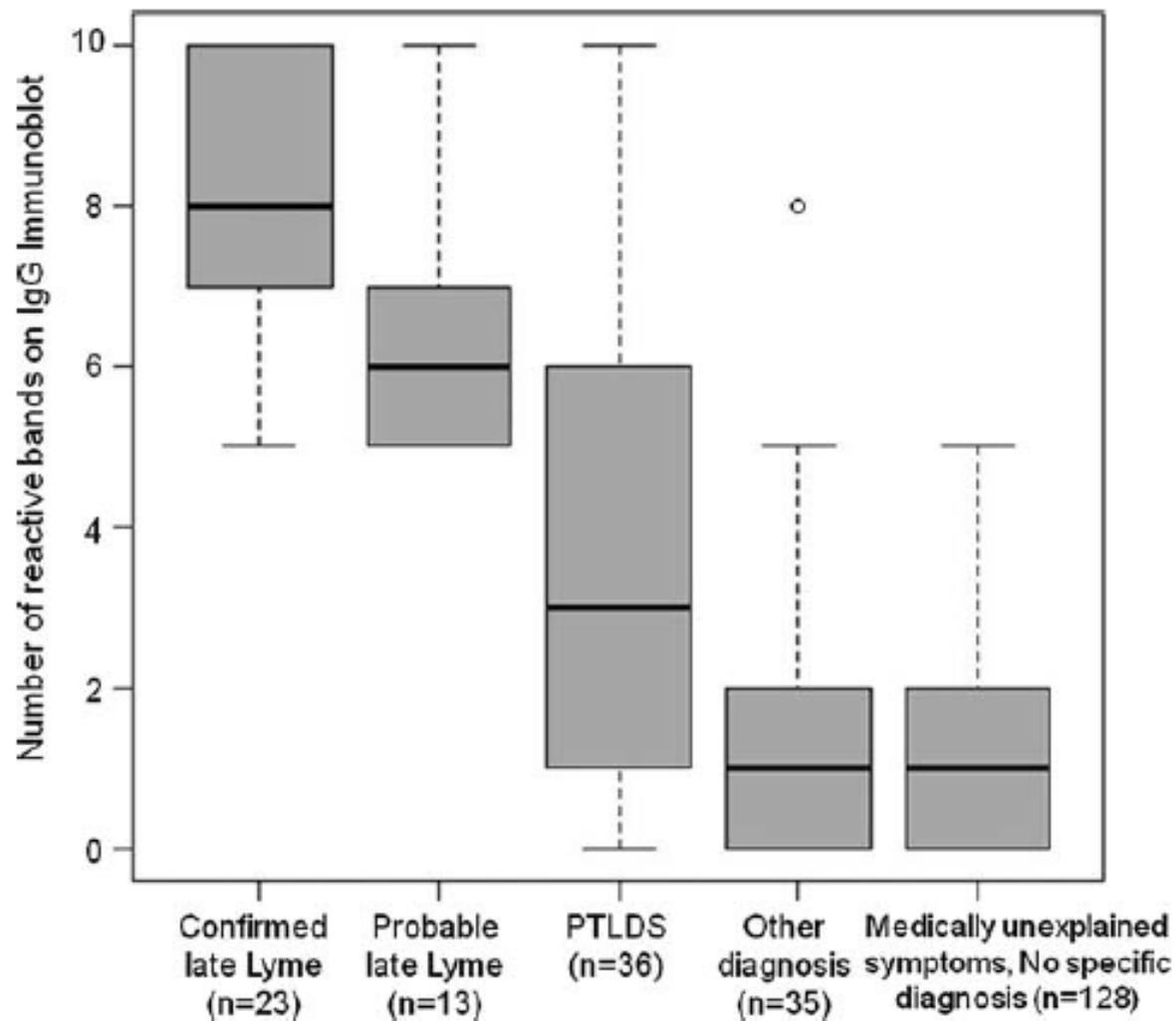


Figure 4 Box plots of the number of reactive IgG bands on commercially available serologic tests for antibodies to *Borrelia burgdorferi* by disease group (n = 235).

Category 4 Post Treatment Lyme Disease Syndrome

Centers for Disease Control and Prevention clinical definition

- Prior positive serologic analysis confirmed by IgG Western blotting,
- Received at least one course of recommended antibiotic therapy
- Had persistent or intermittent symptoms for at least 6 months after appropriate antibiotic therapy for Lyme disease.
- Common symptoms included widespread musculoskeletal pain and fatigue, memory and/or concentration impairment, and radicular pain, paresthesias, or dysesthesias.
- The onset of symptoms was coincident with or within 6 months of initial *B. burgdorferi* infection, symptoms were severe enough to interfere with daily life activities, and other causes were excluded.

Table 3. Evidence against Active Infection in Patients with Subjective Symptoms Persisting for More Than 6 Months after Antibiotic Treatment for Lyme Disease.

Signs and symptoms

Absence of concomitant objective clinical signs of either disease or inflammation and no progression to objective signs or development of inflammation^{29,32}

Similar symptoms common in persons who have never had Lyme disease^{24,25,30,31,48}

Laboratory tests

Persistence of symptoms independently of persistent seropositivity^{20,29,32,47}

Absence of either positive cultures or positive polymerase-chain-reaction results from clinical specimens^{32,40}

Treatment

No substantive response to antibiotic therapy in controlled treatment trials³²⁻³⁴

No documented resistance of *Borrelia burgdorferi* to recommended antibiotics²

Absence of recognized risks for failure of antibiotic therapy; these include host immunodeficiency or an infection in which there is local ischemia, a foreign body (biofilm), a sequestrum, or an abscess²

Other evidence

Certain studies in animals²

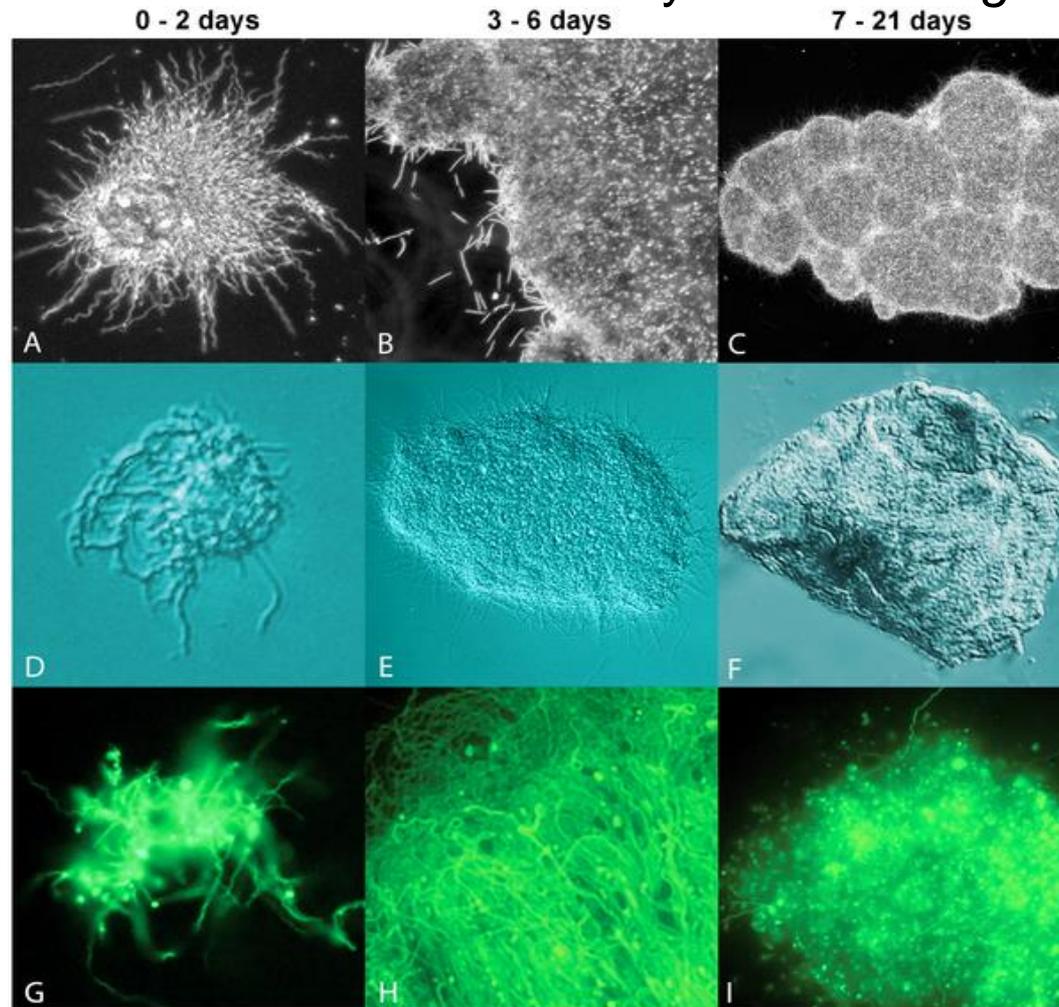
Lack of precedent for the use of long-term antibiotic treatment in other spirochetal infections^{23,49}



The NEW ENGLAND
JOURNAL of MEDICINE

Feder H et al. N Engl J Med
2007;357:1422-1430

“Characterization of Biofilm Formation by *Borrelia burgdorferi* In Vitro”



Sapi E, Bastian SL, Mpoly CM, Scott S, et al. (2012). PLoS ONE

Potential Coinfections.

Infectious Agent†	Characteristics
<i>Babesia microti</i> ¹	An intraerythrocytic parasite that can cause fever and anemia; usually cleared spontaneously by immunocompetent persons; may cause life-threatening illness in persons who are elderly or immunocompromised
<i>Anaplasma phagocytophilum</i> ¹	An intracellular bacterium that may cause severe acute illness, with fever, leukopenia, and thrombocytopenia
Deer tick virus ¹⁷ (a type of Powassan virus)	Can cause a serious, sometimes fatal encephalitis
<i>Borrelia miyamotoi</i> ¹⁸	Member of the relapsing-fever group of borrelia‡
Ehrlichia species Wisconsin	Intracellular bacterium‡

* Coinfections should be considered when patients with Lyme disease have severe or prolonged manifestations of infection or have anemia, leukopenia, thrombocytopenia, or unusually high or persistent fever.

† Like infection with *B. burgdorferi*, infections with these organisms are transmitted by ixodes ticks.

‡ There are few reports of humans infected with either *B. miyamotoi* or ehrlichia species Wisconsin, so the frequency and full spectrum of their manifestations remain to be determined.

Shapiro ED. *N Engl J Med* 2014;370:1724-1731

Treatment of Lyme disease (1)

* Infectious Disease Society of America guidelines

Treatment of adults and children older than 8 years with LD

Erythema migrans or early disseminated disease, including Bell's palsy, but without other CNS involvement

- . Doxycycline 100 mg po q 12h x 14-21 days
- . Amoxicillin 500 mg po q 8h x 14-21 days
- . Cefuroxime 500 mg po q 12h x 14-21 days

Early Lyme with CNS involvement

- . Ceftriaxone 2 g IV id x 14-21 days
- . Pen G 4 x 10⁶ units IV q 4 h x 14-28 days
- . Doxycycline 100-200 mg po q 12h x 28 days (alternative if others not possible)

Early Lyme with carditis

- . Same treatment as early Lyme with CNS involvement, but use IV initially with high grade heart block or if admission to hospital is necessary

Treatment of Lyme disease (2)

* Infectious Disease Society of America guidelines

Treatment of adults and children older than 8 years with LD

Late Lyme **without** CNS involvement

- . Doxycycline 100 mg po q 12h x 28 days
- . Amoxicillin 500 mg po q 8h x 28 days
- . Cefuroxime 500 mg po q 12h x 28 days

Late Lyme **with** CNS involvement (late neuroborreliosis)

- . 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 Lyme disease (3)

* Infectious Disease Society of America guidelines

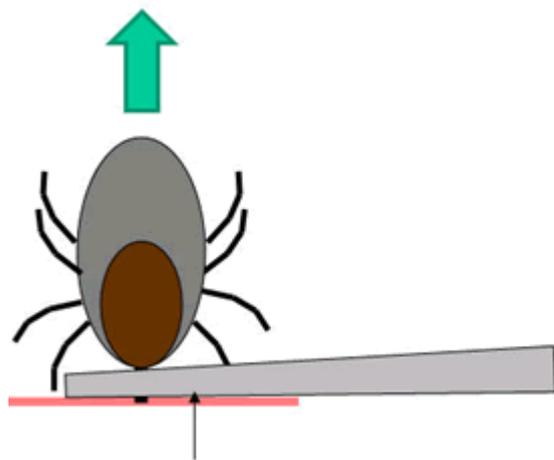
Treatment of children 8 years or younger with Lyme disease	Early localized disease	. Amoxicillin 30 mg/kg per day, orally, divided into three doses (max 1.5g/day) for 14-21 days
	Early disseminated and late disease: multiple erythema migrans	. Oral treatment as the above for 21 days
	Early disseminated and late disease isolated facial palsy and first episodes of arthritis	. Oral treatment as the above for 21 days
	Early disseminated and late disease: persistent/recurrent arthritis, carditis and meningitis/encephalitis	. Ceftriaxone or penicillin IV at paediatric dosing

Recommendations – Prevention and Prophylaxis

1. Teach patients the basics of avoiding tick habitats, dressing properly, using repellants safely, and removing ticks effectively
2. Prescribe prophylactic therapy (doxycycline, single 200 mg dose) for asymptomatic patients who experience a tick bite in a hyperendemic area, especially if the tick was attached for more than **36 hours** and was engorged at the time of removal and the patient presents within **72 hours** of discovering the tick
3. Omit prophylactic antibiotic therapy when a tick bite occurs in a nonhyperendemic area, especially if the tick was attached for less than **36 hours** and was not engorged when removed. Follow expectantly

Guidelines for removal and submission of ticks for identification and possible screening for disease-causing agents

<http://www.phac-aspc.gc.ca/id-mi/guide-dir-ti-eng.php>



FRONT VIEW:

The tweezers should be held at a right angle to the tick's body. Gently, but firmly, pull the tick up and away from the host's skin.

TAKE HOME MESSAGES

1. Recognize early and treat it
2. Recognize disseminated LD and... treat it
3. Prevention needs more emphasis with your patients (emerging and endemic areas!!!)

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To reach us:

Dr. Michel P. Deilgat, CD, MD, MPA(c), CCPE
Medical Advisor / Médecin conseil
Centre for Food-borne, Environmental and
Zoonotic Infectious Diseases (CFEZID)
Centre des maladies infectieuses d'origine
alimentaire, environnementale et zoonotique
(CMIAEZ)
Public Health Agency of Canada / Agence de la
santé publique du Canada
130 Colonnade Road, Room 174A
Ottawa, Ontario, K1A 0K9
Telephone: 613-608-5195 Fax: 613-946-5070
E-mail: michel.deilgat@phac-aspc.gc.ca

Dr. Kathleen Kerr MD, Dip Env Health
Staff Physician and Medical Research Liaison,
Environmental Health Clinic, Women's College
Hospital
Lecturer, Department of Family & Community
Medicine
Faculty of Medicine
University of Toronto
Telephone: 416-351-3764
E-mail: kathleen.kerr@wchospital.ca

"We need to be thinking differently about all aspects of our biology in order to understand how and why this illness is occurring. From the external influences of environmental toxins right through to the subtle shifts in our internal hormonal milieu, all are potentially relevant." -- Gull Herzberg

Questions?

