Lyme Disease and Tick Talk

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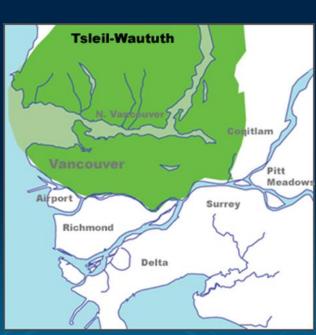
UBC and VGH

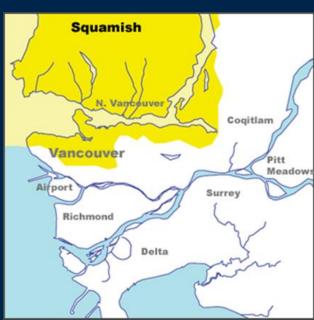
**Department of Pathology and Laboratory

Medicine, UBC and BCCDC

We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.







Territorial Acknowledgement
I acknowledge with gratitude and respect
that I live, work, and play in the unceded
traditional territories of the Lil'wat Nation





MM Disclosure

- 1.Research Funding from BCCDC Foundation for tick Surveillance Research
- 2. Obtained honorarium for giving a presentation to Bayer Inc.'s continuing education for Veterinarians in BC
- 3. Obtained honorarium for giving a presentation to Canadian Lyme Disease Research Network (CLyDRN)



WRB Disclosure : None

Learning Objectives

- 1. Be cognizant of the major presentations of Lyme Disease at different stages
- 2. Be aware of the epidemiology of Lyme Disease, particularly in British Columbia
- 3. Understand the clinical and laboratory diagnosis of Lyme Disease, and the pitfalls of each
- 4. Appreciate that Lyme Disease is readily managed using recommended diagnostic methodology and treatment regimens
- 5. Be exceedingly wary of alternative non-evidence based "recommendations"
- 6. Recognize the complexity and importance of appropriately aiding those who think they have chronic Lyme Disease, an entity that if it exists does not benefit from antimicrobial therapy

Outline

- Definitions WRB
- Lyme Disease Overview WRB
- > Tick MM
- > Epidemiology MM
- Diagnosis laboratory MM
- Diagnosis clinical WRB
- Management according to traditional medicine WRB
- Alternately diagnosed Lyme Disease travesty WRB
- Prevention WRB
- Vaccines MM

Lyme Disease - Overview

- Most commonly reported vector borne illness in North America
- > Causative agent: Borrelia burgdoferi , B. afzelli, B.garinii
- > Mode of Transmission: Tick bite, *Ixodes ricinus* complex
 - Ixodes scapularis, Ixodes pacificus (black legged tick)
- ➤ Incubation period: 3-30 days
- Clinical Features:
 - Early localized disease
 - Early disseminated disease
 - Late Lyme disease
- Definite Lyme Disease is usually cured with currently recommended regimens

Categories Labelled "Lyme Disease"

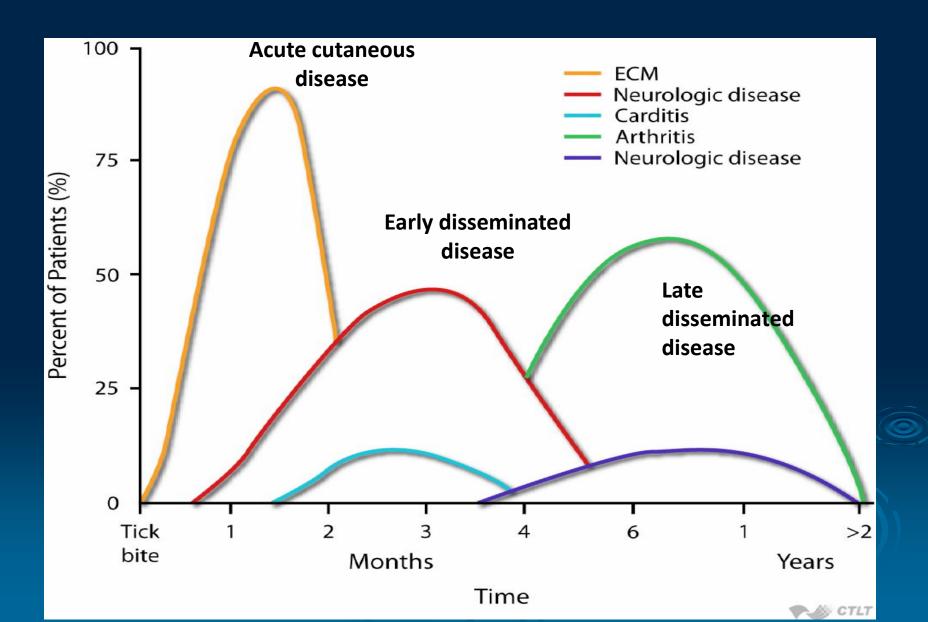
- 1. people who have Lyme disease where disease is diagnosed on appropriate clinical grounds in early disease, or by reference laboratory testing in disseminated Lyme disease, in accordance with National Laboratory Guidelines (e.g. CDC, UK PHS, ECDC, NML).
- 2. people who are given a label such as **post treatment Lyme disease**, where they had clear evidence of Lyme disease as in #1, but have incomplete resolution of symptoms after standard antimicrobial therapy
- 3. people who have alternately diagnosed Lyme disease where they are diagnosed on clinical grounds, supported only by alternative laboratory tests, the validity of which is questioned by major reference laboratories
- 4. people who are diagnosed based purely on clinical grounds, and if testing is done, test seronegative at a time beyond the initial stage of Lyme disease (gut feeling)

Disease stages...

Early and Late Symptoms of Lyme Disease

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	Skin	Multiple erythema migrans	
(< 3 months)*	Systemic	Fever	
		Arthralgias	
		Headache	
		Lymphadenophathy	
	Heart	Atrioventricular block	
		Tachyarrhythmias	
		Myopericarditis	
		Myocardial dysfunction	
	CNS	Aseptic meningitis	
		Cranial neuropathy (especially facial nerve palsy)	
	Ocular	Conjunctivitis (rare)	
Late disseminated disease	MSK	Oligoarticular arthritis	
(> 3 months)*	CNS	Encephalopathy	
		Axonal polyradiculoneuropathy	
		Chronic encephalomyelitis	
	Ocular	Retinitis (rare)	

Lyme Disease Clinical Course



Ticks and Tick Surveillance





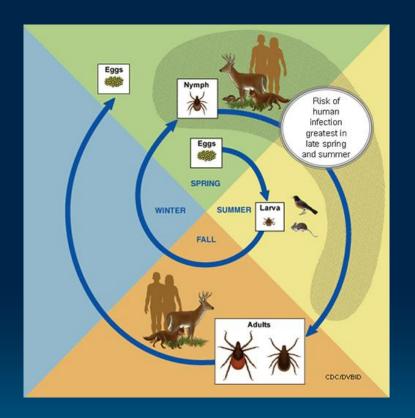
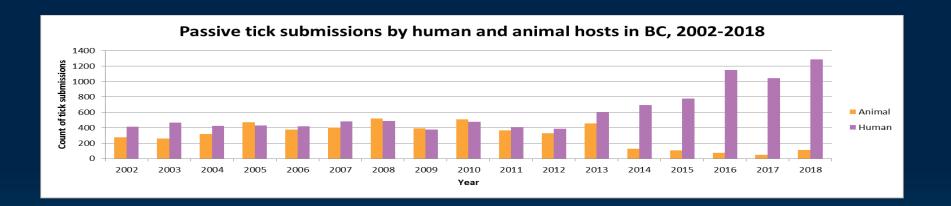


Diagram shows the lifecycle of blacklegged ticks that can transmit Lyme disease



Morshed et al, Vector Borne Zoonotic Dis. 2021 Apr 7. doi: 10.1089/vbz.2020.2743

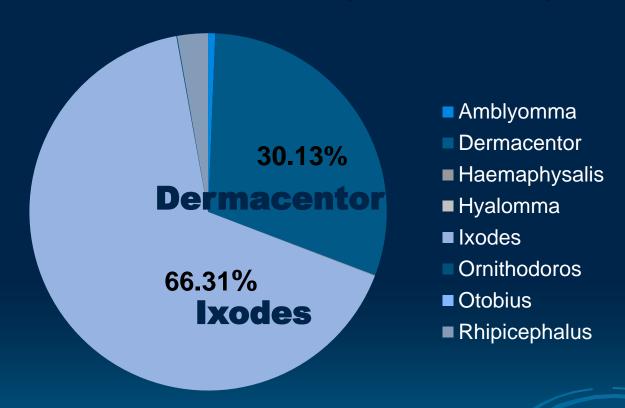
Geographic distribution of major ticks in BC

Geographic distribution of Ixodes pacificus, Ixodes angustus and Dermacentor andersoni: (A) all submissions during 2002-2018, and (B) over 3 consecutive years. The distribution of I. pacificus and I. angustus (blue dots) are predominantly within southwestern BC; whereas, the distribution of D. andersoni (black dots) is predominantly in the interior region of the province.

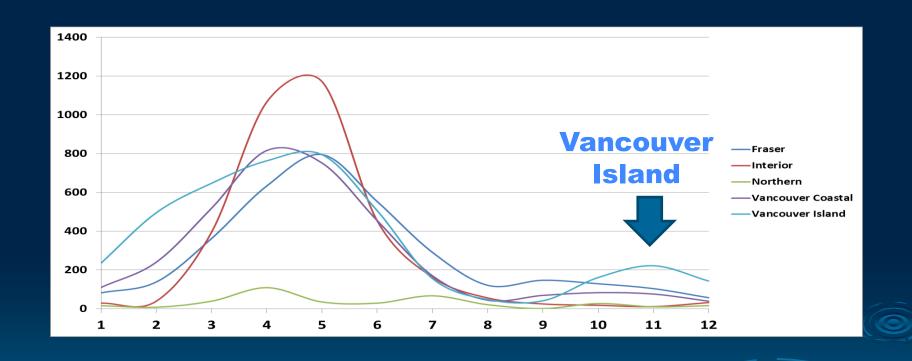
Morshed et al, Vector Borne Zoonotic Dis. 2021 Apr 7. doi: 10.1089/vbz.2020.2743

Courtesy: Sunny Mak

Tick Genus in BC (2002-2018)



Health Authority Specific Tick Seasonality

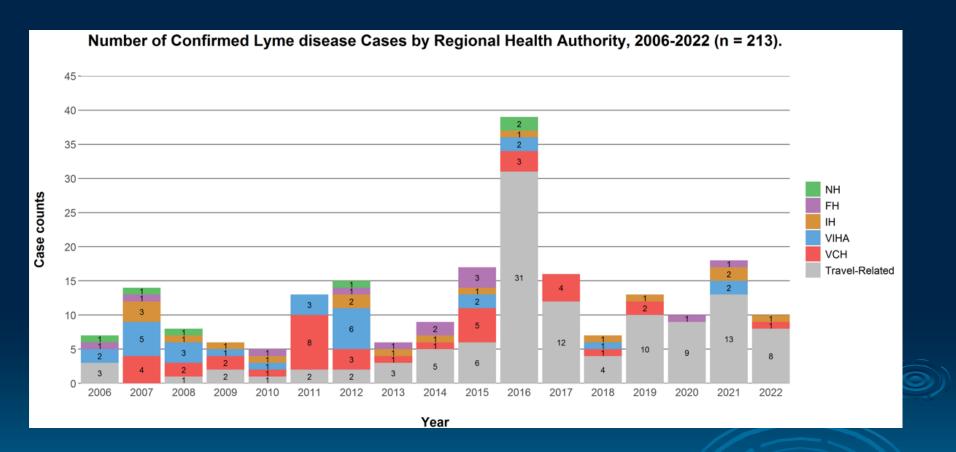


B burgdorferi positive ticks by species, British Columbia, Canada, 2002-2018

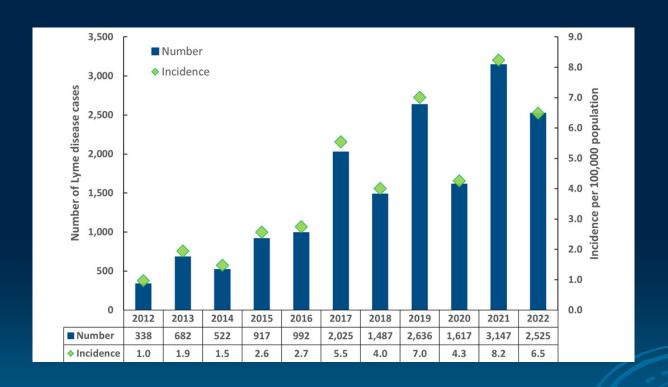
Tick species	Docitive for P. huradorfori	Source and No. of ticks positive for B. burgdorferi			Total No. of ticks
	Positive for B. burgdorferi, n (%)	Human	Dog	Other ^a	Total No. of ticks tested
Ixodes					
pacificus	16 (0.2)	2	9	5	8927
angustus	6 (0.6)	1	3	2	974
scapularis	4 (1.0)	1	3		19
auritulus	4 (6.1)			4	66
Rhipicephalus					
sanguineus s.l.	1 (5.2)	1			387
Other species	0 (0)				782
Total	31 (0.28)	5	15	11	11,155

^aBird (n=4), cat (n=3), squirrel (n=2), unknown animal (n=2).

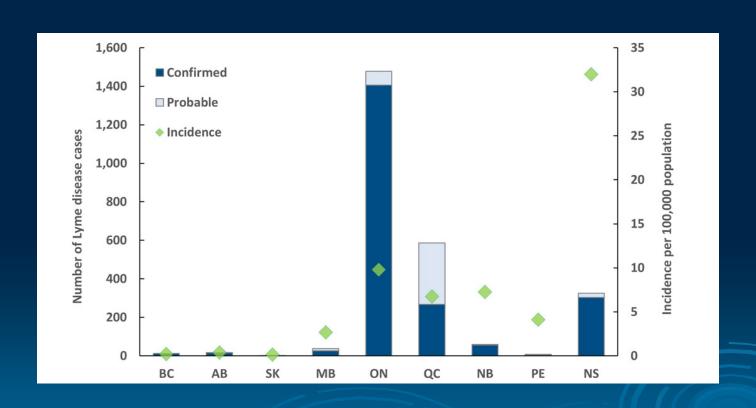
Lyme Disease Epidemiology in BC and Canada



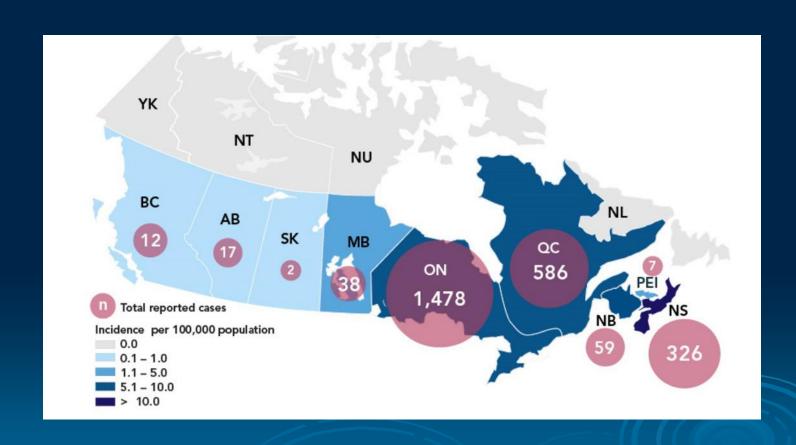
Lyme disease cases in Canada from 2012 to 2022



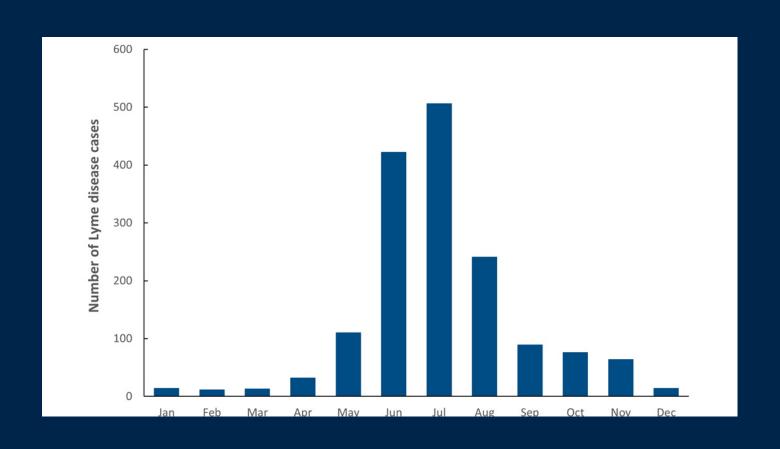
Lyme disease cases in Canada by province of residence, 2022



Geographic distribution of all reported Lyme disease cases, 2022



Month of reported illness onset of Lyme disease cases acquired in Canada, 2022



Laboratory Diagnosis of Lyme disease

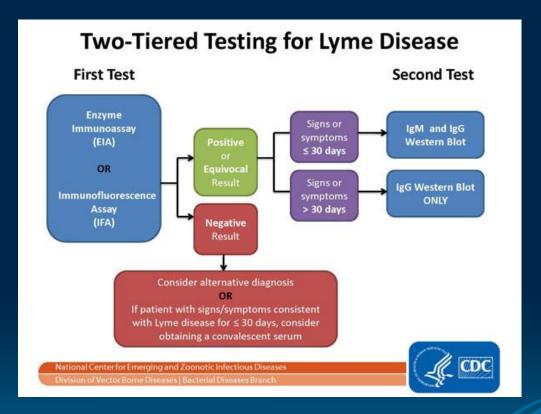
Effect of disease prevalence on predictive values of diagnostic tests a

Prevalence = 1%				
	Test positive	Test negative	Total	
Disease	10	0	10	
No disease	20	970	990	
Total	30	970	1000	
Predictive value of a	a negative result = 970/970 =	= 100%		
Predictive value of a	a positive result = $10/30 = 33$	3% (67% false positives)		
Prevalence = 40%				
	Test positive	Test negative	Total	
Disease	392	8	400	
No disease	12	588	600	
Total	404	596	1000	
Predictive value of a	a negative result = 588/596 =	= 99%		
	a positive result = 392/404 =			

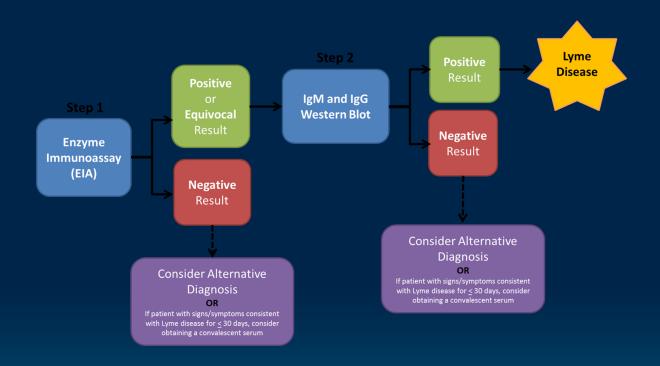
alllustration assumes that test sensitivity and specificity are each 98%.

Ref: Barbra Johnson, CDC. Laboratory Diagnostic Testing for Borrelia burgdorferi Infection. Ed. JJ Halperin. Lyme Disease: An Evidence-based Approach. 73-88

CDC Test Algorithms (STT)

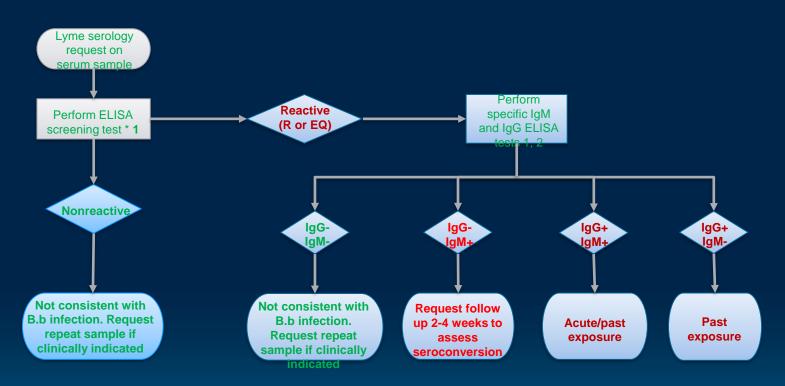


BCCDC PHL Test Algorithms (old STT)



Euro-blot done on cases if travelled in Lyme endemic areas in Europe

Lyme Disease Diagnosis Algorithm in BC, Current (MTTT)



^{1:} The ZEUS ELISA Borrelia VIsE1/pepC10 IgG/IgM. 2. ZEUS ELISA Borrelia burgdorferi IgM; ZEUS ELISA Borrelia burgdorferi IgG Ref: https://www.zeusscientific.com/products/zeus-elisa-test-systems/zeus-elisa-borrelia-vIse1-pepc10-igg-igm-test-system

^{*} Screening test positive, specific IgM and IgG negative; however have history of European exposure \rightarrow send to NML for Euro Lyme test.

Other Methods of Laboratory Diagnosis: Not a routine

Test

> Culture

> PCR

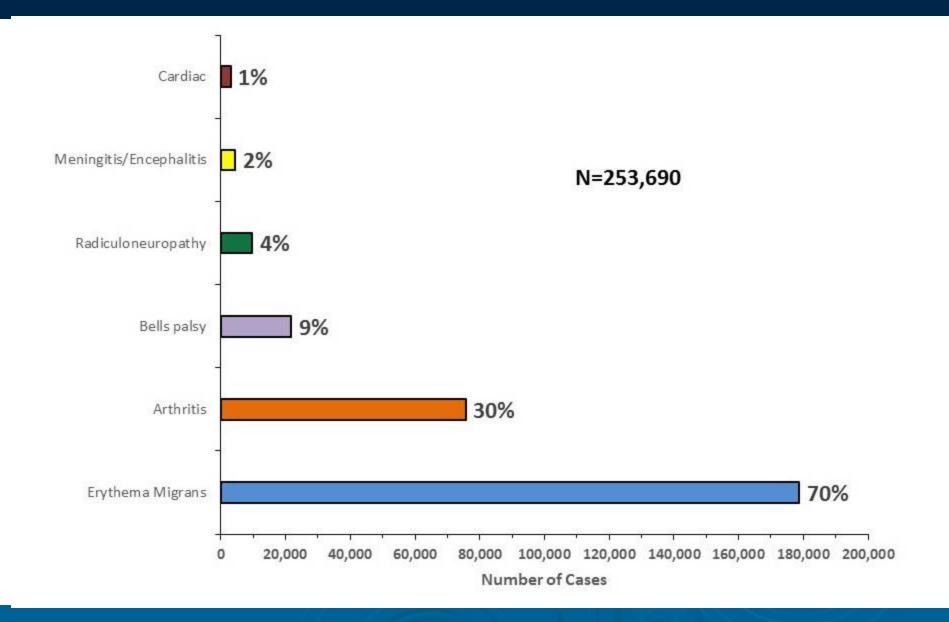
> IHC

Sample

- Skin biopsy from true EM; Time consuming take 3-5 weeks
- Skin biopsy from True EM; Synovial fluid-Available at BCCDC PHL

Few Lab has capacity.

Diagnosis - Clinical



Erythema migrans

- An expanding skin lesion in the shape of a target (over days-weeks)
- "Pathognomonic" for Lyme Disease
- Classically > 5 cm in diameter (usual 10-16 cm), can grow as large as 70 cm in diameter
- Occurs in 80-90% of infected individuals at site of infection, but often not detected
- If multiple often suggests disseminated infection



Rashes – Lyme or Non-Lyme

Lyme	Non-Lyme
No	Yes (Hours)
Almost always	Unusual
No (expands)	Yes
No or mild	Often
No or mild	Often
Often	Unlikely
Up to 80%	Unusual
	No Almost always No (expands) No or mild No or mild Often

- * Time from engorged tick removal if tick detected
- Tick is required to be on skin at least 36 hours for transmission to occur

Early Disseminated

- Occurs weeks to months after exposure...
 - Neurologic (15% of untreated individuals)
 - Lymphocytic meningitis
 - Encephalitis
 - Cranial neuropathy
 - Peripheral neuropathy
 - Radiculoneuropathy
 - Myelitis
 - Cardiac (5% of untreated individuals)
 - Conduction defects
 - Mild cardiomyopathy
 - Myopericarditis

Early Disseminated (cont'd)

- MSK (60% of untreated individuals)
 - Migratory polyarthritis/polyarthralgias
- Other
 - Erythema nodosum
 - Regional or generalized lymphadenopathy
 - Conjunctivitis
 - Iritis
 - Chorioditis
 - Vitritis
 - Retinitis
 - Hepatitis
 - Microhematuria
 - Proteinuria
- May have no history of preceding early disease

Late Lyme Disease

- Months to a few years after exposure and initial infection
- MSK:
 - Intermittent (60% of untreated patients) or persistant (10% of untreated patients) arthritis
 - Involves one or a few large joints (esp. knee)
 - Possibly preceded by migratory arthralgias
- Neuro:
 - Subtle encephalopathy or polyneuropathy (rare)
- > Skin:
 - Acrodermatitis chronica atrophicans
 - Morphea/localized scleroderma-like lesions (Europe only)









Arthritic Knee: Joint may become red, swollen, painful Lyme arthritis is generally periodic, but may become chronic in about 10% of people

Management



Quality of Data Supporting Treatment Recommendations – Group 1

- There are many well designed studies that provide sufficient evidence to support treatment guidelines, even though as with all guidelines there are questions which remain inadequately studied
- > The IDSA guidelines are representative
- No recommendations are for more than 4 weeks of therapy
- There is substantial improvement and usually cure on these regimens

Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease

Paul M. Lantos, Jeffrey Rumbaugh, Linda K. Bockenstedt, Yngve T. Falck-Ytter, Maria E. Aguero-Rosenfeld, Paul G. Auwaerter, Kelly Baldwin, Raveendhara R. Bannuru, Kiran K. Belani, William R. Bowie, John A. Branda, Javid B. Clifford, Francis J. DiMario Jr, John J. Halperin, Matthew H. Liang, H. Cody Meissner, Lise E. Nigrovic, James (Jay) J. Nocton, Mikala C. Osani, Amy A. Pruitt, Jane Rips, Lynda E. Rosenfeld, Margot L. Savoy, Sunil K. Sood, Allen C. Steere, Franc Strle, Robert Sundel, Jean Tsao, Elizaveta E. Vaysbrot, Gary P. Wormser, and Lawrence S. Zemel

Treatment recommendations are essentially unchanged from 2006

Process started in 2015 – delays mainly due to Lyme advocates and their efforts

Drug	December Adulta	December for Children
Drug	Dosage for Adults	Dosage for Children
Oral Regimens		
Preferred		
Amoxicillin ^a	500 mg 3 times daily	50 mg/kg divided 3 times daily (maximum 500 mg per dose)
Doxycycline ^b	100 mg twice daily or 200 mg once daily ^b	4.4 mg/kg divided twice daily (maximum 200 mg daily)
Cefuroxime axetil ^{a,c}	500 mg twice daily	30 mg/kg divided twice daily (maximum 500 mg per dose)
Alternative		
Azithromycin ^d	500 mg once daily	10 mg/kg once daily (maximum 500 mg per dose)
Intravenous Therapy		
Preferred		
Ceftriaxone	2000 mg once daily	50-75 mg/kg once daily (maximum 2000 mg per dose)
Alternative		
Cefotaxime ^a	2000 mg three times daily	150–200 mg/kg divided 3–4 times daily (maximum 6000 mg daily)
Penicillin G ^a	18–24 million units divided every 4 hours	200 000-400 000 units/kg divided every 4 hours (maximum 18-24 million units daily)

Table 4. Treatment of Specific Manifestations of Lyme Disease

Disease Manifestation	Route	Medication	Duration, days (range) ^a
Erythema migrans ^b	Oral	Doxycycline	10
		Amoxicillin or cefuroxime axetil	14
		Azithromycin ^c	7 (range: 5-10)
Meningitis or radiculopathy	Oral	Doxycycline	14–21
	IV^d	Ceftriaxone	14–21
Cranial nerve palsy	Oral	Doxycycline	14–21
Carditis	Oral ^e	Doxycycline, amoxicillin, or cefuroxime axetil	14–21
	$ V_{\theta} $	Ceftriaxone	14–21
Arthritis			
Initial treatment	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	28
Recurrent or refractory arthritis	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	28
	IV	Ceftriaxone	14 ^f
Acrodermatitis chronica atrophicans	Oral	Doxycycline, amoxicillin, Or cefuroxime axetil	21–28
Borrelial lymphocytoma	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	14

Quality of Data Supporting Treatment Recommendations – Groups 2, 3, and 4

- None of several traditionally designed studies have clearly demonstrated significant benefits of longer courses of antimicrobials
- Many of these folk are "treated" according to ILADS or similar guidelines
- For these non-IDSA "treatments", there are no studies demonstrating efficacy of those "treatments", let alone studies including assessments of real or potential harm, and overall cost-benefit of the studies.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MARCH 31, 2016

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Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease

Anneleen Berende, M.D., Hadewych J.M. ter Hofstede, M.D., Ph.D., Fidel J. Vos, M.D., Ph.D., Henriët van Middendorp, Ph.D., Michiel L. Vogelaar, M.Sc., Mirjam Tromp, Ph.D., Frank H. van den Hoogen, M.D., Ph.D., A. Rogier T. Donders, Ph.D., Andrea W.M. Evers, Ph.D., and Bart Jan Kullberg, M.D., Ph.D.

We assessed whether longer-term antibiotic treatment of persistent symptoms attributed to Lyme disease leads to better outcomes than does shorter-term treatment.

CONCLUSIONS

In patients with persistent symptoms attributed to Lyme disease, longer-term antibiotic treatment did not have additional beneficial effects on health-related quality of life beyond those with shorter-term treatment. (Funded by the Netherlands Organization for Health Research and Development ZonMw; PLEASE ClinicalTrials.gov number, NCT01207739.)

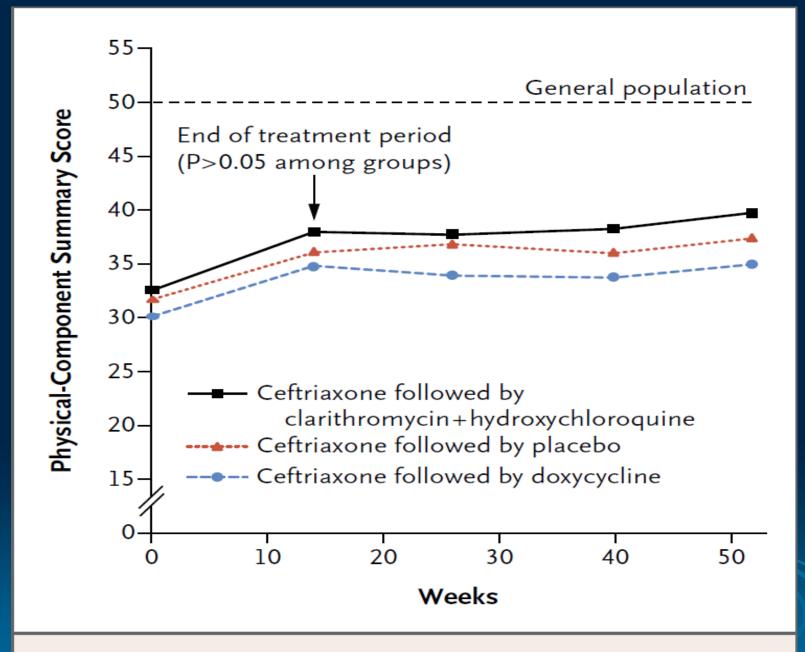


Figure 2. Physical-Component Summary Scores.

Unconventional "treatments" for Lyme disease not supported by scientific evidence

Table 1. Examples of Patients for the Treatm	Alternative Medical Therapies Marketed to ent of Lyme Disease	Nutritional supplements	Vitamins C and B12 Herbs Garlic, cilantro, Chlorella, Sarsaparilla,
Categories of Therapy	Examples	Andrographis, Turmeric, Olive leaf, Cat's claw	
Oxygen	Hyperbaric oxygen Hydrogen peroxide Ozone		Burnt mugwort (moxibustion) Glutathione Fish oil Magnesium
Energy and radiation	Ultraviolet light		Salt
	Photon therapy "Cold" lasers Saunas and steam rooms "Rife" therapy (electromagnetic frequency treatments) Magnets	Biological and pharmacologic	Urotherapy (urine ingestion) Enemas Bee venom Hormonal therapy Dihidroepiandrostenedione, Pregnenolone, Cortisone, Hydrocortisone
Metal/chelation	Mercury chelation and removal Dimercaptosuccinic acid (DMSA) 2,3-Dimercapto-1-propanesulfonic acid (DMPS) Alpha lipoic acid (ALA) Ethylene diamine tetraacetic acid (EDTA) Removal of dental amalgam Colloidal silver Bismuth		Synthetic thyroid hormone Lithium orotate Olmesartan Cholestyramine Naltrexone Sodium chlorite (bleach) Intravenous immune globulin (IVIG) Apheresis Stem cell transplantation

Lantos PM et al, Clinical Infectious Diseases 2015; 60: 1776-1782

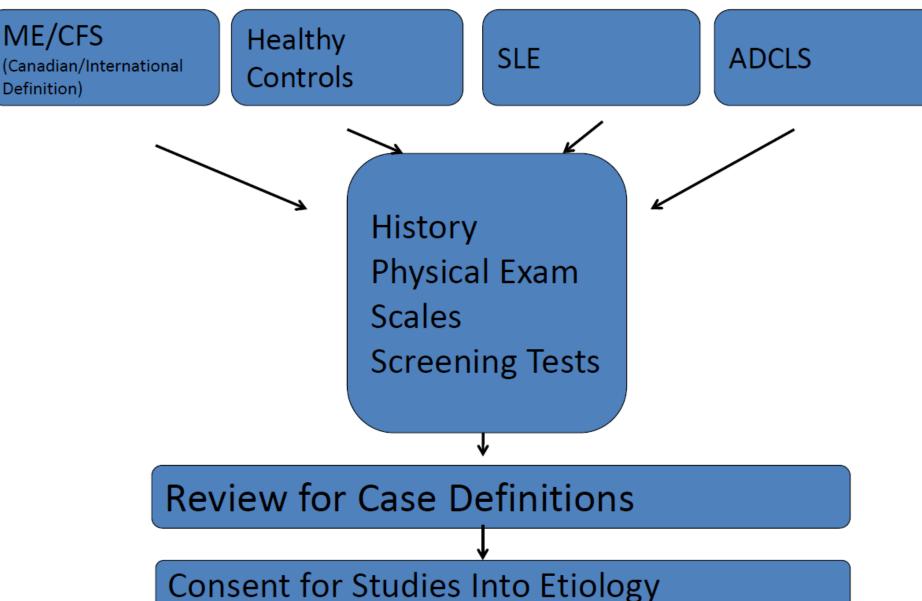
Non Evidence Based "Treatment" Can do Harm

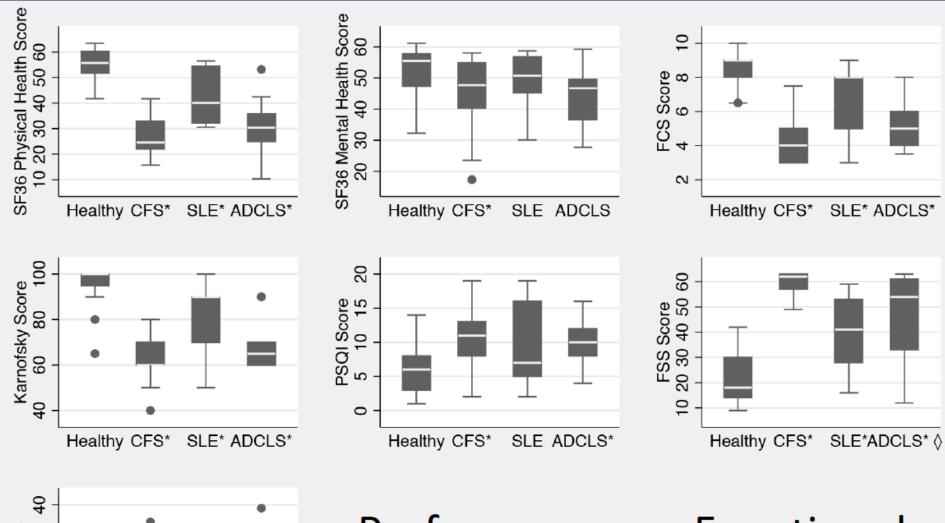
- Desperate and vulnerable individuals are given an incorrect label and subjected to unproven "treatment" for which there is no valid evidence of benefit, let alone of benefits that exceed risk
- Focuses on Lyme rather than pursuing other possibilities
- Risk of antimicrobials to oneself
 - Reactions, other toxicity, superimposed infection, antimicrobial resistance
- Risks to others
 - Antimicrobial resistance
- Undermines medicine and public health
- Scares people who have readily treatable acute Lyme disease

Moving Forward

- Many of the people in categories 2 to 4 have profoundly debilitating and life altering symptoms
- ➤ They deserve formal evaluation of "treatments" given to them, as well as efforts to better understand the etiology of what for most is very similar to presentations of chronic fatigue
- Focusing purely on a perceived diagnosis of Lyme disease has the potential to be highly detrimental

UBC Complex Chronic Disease Study





Performance on Functional Scales

Healthy CFS* SLE* ADCLS*

By Group

AMMI Canada Recommendation

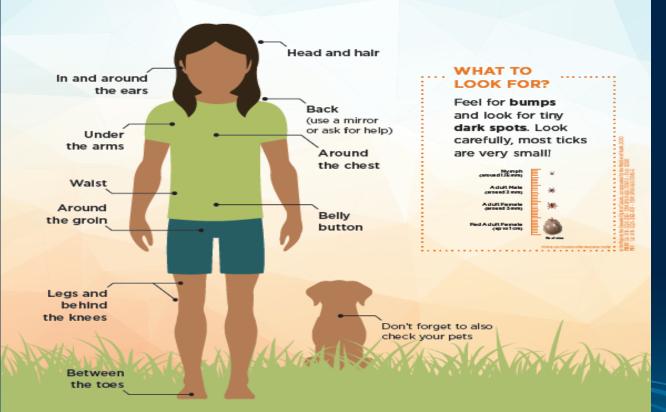
5. Providing Comprehensive Care to Patients with Complex Chronic Health Conditions Many health care providers provide excellent care for people with complex chronic symptoms. However, some people with persistent symptoms, with or without a defined etiology, may have a difficult time getting adequate care and feel poorly served by the health care system. AMMI Canada does not support the use of prolonged antimicrobials to treat patients with persistent symptoms that have been attributed to Lyme disease. Instead, AMMI Canada strongly encourages evidence guided care of these patients in a compassionate and comprehensive manner to identify the underlying cause and an approach to help alleviate symptoms.

Prevention

- Risk assessment allows tailored messages for prevention: no tick bite=no Lyme disease
- To prevent tick bites the following measures are strongly recommended:
 - Walk on cleared trails;
 - Wear a hat, long sleeves and pants and light coloured clothing;
 - Tuck pant legs into socks or boots;
 - Use an insect repellant containing DEET on clothing and exposed skin

TOP 10 TICK HIDING SPOTS ON YOUR BODY

Tick checks are one of the ways you can prevent Lyme disease and other infections spread by ticks. Check your entire body, especially:



Found a tick?

Remove it immediately to reduce the risk of infection.

Canada.ca/LymeDisease



Government of Conada Gouvernement du Canada Canada

ENJOY THE OUTDOORS, WITHOUT A TICK

Lyme disease is spread by the bite of infected blacklegged ticks. These ticks are often found in and near areas with trees, shrubs, tall grass or piles of leaves.

Follow these tips when heading outside:



- Wear light coloured long-sleeved shirts and pants.
- Tuck your shirt into your pants, and your pants into your socks.
- Wear closed-toe shoes.
- Use bug spray with DEET or loaridin (always follow label directions).
- $\overline{\mathbf{v}}$ Walk on cleared paths or walkways.
- You can also wear permethrin-treated clothing, now available in Canada (always follow label directions).



- Shower or bathe as soon as possible after being outdoors.
- Do a daily full body tick check on yourself, your children, your pets and your gear.
- Put your clothes in a dryer on high heat for at least 10 minutes.



- ✓ Use clean fine-point tweezers to immediately remove attached ticks by slowly pulling them straight out. Try not to twist or squeeze the tick.
- Wash the bite area with soap and water or alcohol-based sanitizer.
- Keep the tick in a closed container and bring it with you if you go see your health care provider.
- Contact your health care provider if you're not feeling well or if you are concerned after being bitten by a tick.

For more information, visit

Canada.ca/LymeDisease

Canada

Do Not Ignore Other Tick Borne Diseases

- Definitely in BC
 - Relapsing fever due to other Borrelia species
- Not proven to be in BC, but well documented in many areas where Lyme is present, and which can be confused with Lyme, or co-existent with Lyme
 - Babesiosis
 - Human granulocytic anaplasmosis (previously known as human granulocytic ehrlichiosis)

Post Tick Bite Management - IDSA

- Routine antimicrobial prophylaxis or serologic testing is not recommended
- Single dose doxycycline if all of the following:
 - Attached tick reliably identified as an adult or nymphal
 I. scapularis that has been present at least 36 hours
 - Prophylaxis initiated within 72 hours of tick removal
 - Local rate of infection with Bb in ticks is >= 20%
 - Doxycycline is not contraindicated
- NOTE: in BC, no one would qualify because rates of infection are exceedingly low in Ixodes pacificus

Vaccine Update

Update on Vaccine (Human)

Background

- The only vaccine previously marketed in the United States, LYMERix®, was discontinued by the manufacturer in 2002
- Company cited insufficient consumer demand.
- > Lawsuit???

Current update

- Valneva and Pfizer have developed a Lyme disease vaccine candidate, VLA15, that is currently with 2 Phase 3 human trials in age 5 Years of age and older.
- Pfizer is currently aiming to submit a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) and Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) in 2026, subject to positive Phase 3 data.

Update on Vaccine (Human)

- The University of Massachusetts Medical School's MassBiologics has developed a human monoclonal antibody designed to be used as pre-exposure prophylaxis (PrEP) for Lyme disease. Trial will begin soon.
- > Yale School of Medicine working vaccine against tick saliva
- > Moderna recently started mRNA based vaccine-Initial stage

Conclusions

Conclusions (WRB)

Early Lyme Disease

- Be aware that there is Lyme Disease in BC, albeit at very low levels
- Be aware of erythema migrans
 - Document tick bite, duration of tick contact, engorgement, time course and appearance of the rash
 - If you are uncertain, have a low threshold to offer recommended curative treatment, but make it clear that treatment is offered because the diagnosis cannot be excluded, not that you are specifically diagnosing Lyme Disease
 - Report all treated individuals to BCCDC or your health department

Later Stages

- Follow standard guidelines, and carefully document the history, P/E and findings (positive and negative), test results, treatment(s) and response
- However, guidelines are only "guidelines" and if there is sufficient evidence that the person you are seeing might have Lyme Disease, offer a standard treatment, but make it clear that you are treating for possible, not proven Lyme
- If you are uncertain, seek advice

Conclusions Contd....

- Lyme disease is present in BC in low levels
- If you diagnose and treat a case of possible erythema migrans, report it
- Follow guidelines for management of cases, but remember that guidelines are only "guidelines" that must be interpreted in the light of the person in front of you
- Be very leery of diagnosing and treating people for chronic Lyme or post Lyme Disease if there is no evidence for the diagnosis or if the "diagnosis" is only based on "positive" testing from a laboratory that does not subject itself to standard external quality control and uses non-validated tests or interpretations
- ➤ If you feel compelled to "treat" someone with repeated courses of therapy, or with unconventional treatments, remember that you are essentially experimenting, likely with no formal mechanism to evaluate response or to systematically learn from the episode

Conclusions contd...(MM)

- Borrelia burgdorferi present in very low level in BC ticks
- Tick activity peaks from March and continue till June in BC
- Serology is the test of choice for Laboratory Diagnosis of Lyme disease
- BC is using most acceptable MTTT for Lyme disease
- > Vaccine for human may available by 2026???