Challenges in Lyme Disease Diagnosis and Treatment

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Faculty/Presenter Disclosure

- Faculty:
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- Relationships with commercial interests:
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  - Other: None
Learning Objectives:

• Upon completion, participants will be able to assess Lyme disease risk following tick exposure and decide upon the need for antibiotic prophylaxis.

• Upon completion, participants will be able to explain the clinical assessment of early localized or early disseminated Lyme disease, the appropriate role of laboratory testing and antibiotic treatment of these two Lyme disease clinical presentations.

• Upon completion, participants will be able to describe the elements of risk exposure and clinical history necessary to distinguish between post-treatment Lyme disease syndrome and chronic Lyme disease.
Combatting Lyme Disease Through Collaborative Action

Ontario’s 10-Step Education and Awareness Plan

July 2016
Our 10-Step Education and Awareness Plan Supports Patients First

This Plan supports Patients First: Action Plan for Health Care, Ontario’s plan for changing and improving its health system. Patients First exemplifies our commitment to put people and patients at the centre of this strategy by focusing on four pillars:

ACCESS

1. Improve the availability of the information, tools and supports people need—when and how they need them
2. Strengthen intergovernmental co-ordination of Lyme disease initiatives and prevention
3. Support the availability of consistent signage and information at all provincial parks in risk areas

CONNECT

4. Engage a broad range of voluntary and non-governmental groups/organizations
5. Facilitate effective patient-health care provider interactions about care, treatment and support options available
INFORM

6. Launch a comprehensive, province-wide awareness and education campaign
7. Expand health care provider education to strengthen the focus on care, treatment and support

PROTECT

8. Increase awareness of Lyme disease risk areas and the possibility of infected ticks being found outside known risk areas
10. Contribute to the development of an Ontario Lyme research agenda
Lyme Disease Diagnostic/Treatment Challenges

• Although incidence increasing, infrequently seen clinically
• Risk areas are not static, new areas discovered/expansion of existing risk areas
• Most Lyme disease contracted in known risk areas, but not all
• Travel-related Lyme, especially Europe/United States
• Risk area awareness + decision rules for antibiotic prophylaxis
• Non-specific nature of early/late clinical presentations
• Limitations on serological testing, especially early localized disease
• Diagnostic/treatment controversies, Lyme advocacy
Lyme Disease in Ontario

Number of cases of Lyme disease and incidence rate per 100,000 population: Ontario, 2005–2015


2012 Canadian Data/100,000:
 Nova Scotia: 5.4
 British Columbia: 0.4

2014 Data/100,000
 USA: 7.9
 Connecticut: 47.8
 Massachusetts: 54.1
 California: 0.1

European Rates/100,000:
 Estimated based on 2006 data:
 Austria: 130
 Slovenia: 155
 Netherlands: 43
 United Kingdom: 0.7
Common Goals with Lyme Advocates

- Better understand the emerging epidemiology of Lyme disease and other tick-borne infections
- Optimize resources and methods for prevention
- Monitor evolving science and translate into resources and guidelines, with a focus on prevention, diagnosis and treatment
- Improve early diagnostic tests and ability to monitor response to treatment
- Improve understanding of the causes and management of post-treatment symptoms
- Increase public and clinician education re. awareness, prevention, diagnosis and treatment
Points of Divergence

Key issues of disagreement/divergence between Lyme advocates and vast majority of clinical/public health organizations:

• Pathophysiology of disease processes, especially “persistent” Lyme disease

• Recommended lab diagnostics for Lyme disease

• Diagnosis and treatment of “chronic Lyme disease”
Questions

1. Why designate risk areas for Lyme disease when infected ticks can be anywhere in the province?
2. What are the clinical presentations of Lyme disease, are they clear-cut and straightforward?
3. Why doesn’t Canada support the use of U.S. tests for Lyme disease?
4. Do I have chronic Lyme disease?
Question 1

Why designate risk areas for Lyme disease when infected ticks can be anywhere in the province? Infected ticks attach to migratory birds and can end up anywhere!
Risk areas for Lyme disease

• Risk for exposure to blacklegged ticks/Lyme disease varies markedly across the province
• Risk map allows clinicians to understand the likelihood a patient has had exposure to Lyme disease
• Years of tick/human surveillance show the majority of Lyme disease cases is contracted in known risk areas
• While the risk of acquiring Lyme disease is not zero in non-endemic area, the likelihood of acquiring Lyme disease from a tick falling off a bird is very low; other possible causes of symptoms should be investigated
Passive Surveillance

- Tick surveillance – ticks are submitted by the public or physicians
- Tick testing – blacklegged ticks tested for Anaplasma phagocytophilum, Babesia microti, Borrelia burgdorferi and Borrelia miyamotoi
- Human case surveillance – cases reported through the public health reportable disease system (iPHIS)
Active Surveillance
(looking for ticks in the environment)

• Tick dragging – determine estimated risk areas
• Small mammal trapping – trapping rodents to test them and their ticks for B. burgdorferi
Ontario Lyme Disease Map 2016
Estimated Risk Areas

- The estimated risk areas are calculated as a 20 kilometre radius from the centre of a location where blacklegged ticks were found through drag sampling.
- While low, there is a probability of encountering blacklegged ticks almost anywhere in the province.
- Within estimated risk areas, blacklegged ticks are mainly found in woody and/or brushy areas.
- The closer to an estimated risk area, the higher the estimated risk of encountering a blacklegged tick.

Public Education

- Increased awareness in risk and prevention
- Digital and printed media
- Signage in public areas (e.g. parks)
- PHO support for MOHLTC and PHUs to develop and implement strategies
Importance of Assessment of Exposure Risk

- Black-legged tick habitats increasingly well-understood
- Essential not only to ask where people were, but:
  - What they did, what activities did they engage in?
  - Were they aware that it was a Lyme disease risk area?
  - Did they take personal protection precautions, especially clothing and insect repellants?
  - Did they do tick checks after the activities?
Tick Habitat
Seasonality

http://www.tickencounter.org/education/

Adult Tick
Abundant October to May

Nymphal Tick
Abundant May to Late July

Larval Tick
Abundant August to October
Probability of transmission

Probability of Transmission

Hours Tick Attached

Sood SK et al 1997, JID; Nadelman RB et al 2001 NEJM
Submitting Ticks for Identification and Testing

- Tick identification and testing should play no role in diagnosis/clinical management
- Contributes to surveillance, evolving understanding of LD
- Importance of reporting clinically-diagnosed cases without lab testing/with negative lab results
- Standardized case investigation form and its purposes/benefits
Labstract - June 2016

Tick Surveillance: New Tick Identification Requisition Form

To Healthcare Providers and Public Health Professionals:

As of June 1, 2016, submitters are required to complete and submit the new “Surveillance Form for Tick Identification” which is available at www.publichealhtontario.ca/Requisitions when submitting ticks for identification by the Public Health Ontario Laboratory (PHOL).

The new, simplified form replaces three separate forms (Parasitology Patient’s History Form, PHO General Test Requisition Form, and Public Health Agency of Canada (PHAC) Passive Surveillance for Blacklegged Ticks Form).

As per Infectious Disease Society of America (IDSA) guidelines, tick testing should not be used for diagnosis and management of Lyme disease. PHOL’s tick identification service, and subsequent PCR testing on blacklegged ticks to detect various humans pathogens performed at PHAC’s National Microbiology Laboratory (NML) is for surveillance purposes only. The tick testing program is primarily used to monitor emerging tick populations in Ontario. Certain parts of Ontario, including Long Point Provincial Park, Thousand Islands National Park and Point Pelee National Park are known areas for established tick populations. Therefore, submitting ticks from areas where ticks are already established does not provide additional information. For further information on known risk areas, please refer to the PHO’s Ontario Lyme disease estimated risk areas map, which provides data on the geographical distribution of blacklegged ticks (*Ixodes scapularis*).
What are the clinical presentations of Lyme disease, are they clear-cut and straightforward?
Diagnosis of Lyme disease

Post-exposure prophylaxis

Acute: Clinical presentation with epidemiological link

Late: Clinical presentations with laboratory testing

Post-treatment Lyme Disease Syndrome (PTLDS)
Symptoms

Signs and Symptoms of Lyme Disease in Humans

- Within one month:
  - Erythema migrans (rash)
  - Systemic reaction
  - Fatigue, chills, fever, headaches, muscle and joint aches, swollen lymph nodes
  - Facial (Bell’s) palsy
  - Multiple erythema migrans (rash)

- Three to many months:
  - Arthritis
  - Meningitis
  - Heart block

- One to three months:
  - EKG with heart block
  - EKG - normal

PublicHealthOntario.ca
www.cdc.gov
Prevention of Lyme disease after a tick bite

Routine antibiotic prophylaxis and serological testing is not recommended

A single dose of doxycycline can be offered if:

• Tick can be identified as black legged tick
• Attached for at least 24-36 hours
• Prophylaxis can be started within 72 hours
• Known prevalence of *B. burgdorferi* infection rate
• Doxycycline is not contraindicated
• Patients advised to monitor for development of signs and symptoms for up to 30 days.
Case study #1

• 73 year old male was hunting with his son in a meadow near Brockville
• Developed a “flu-like illness with fever and myalgias
• Has an 2 cm erythematous lesion on his left lower leg
• See on day 5: No other physical findings
• Treated with doxycycline
• Serology (acute and convalescent) negative
Case study #2

- 67 year-old male recent 4 week holiday at Martha’s Vineyard
- Presents with flaccid paralysis below T12
- No leg movement, no reflexes and normal sensation
- Had no “tick bites” but had spent every night using tweezers to remove ticks from his dog
- Treated with Cetrixaxone IV
- Serology was very positive
- Some neurologic recover after 7 days of treatment
- Full recovery by 4 weeks post diagnosis
Common Clinical Symptoms of Lyme Disease

- Erythema migrans: 70%
- Arthritis: 31%
- Bell's palsy: 9%
- Radiculoneuropathy: 4%
- Meningitis/Encephalitis: 1%
- Cardiac: 1%

N=154,405

http://www.cdc.gov/lyme/stats/graphs.html
Erythema Migrans

- Occurs in 70% of cases
- More common in USA strains
- Begins with red macule or papule and expands over a period of days or weeks into large round or oval lesion
- Only 20% of patients will have central clearing (bull’s eyes rash)
- Commonly accompanied by “flu-like” symptoms

Differential diagnosis

- Insect bite
- Parvovirus
- Syphilis
- Epstein-Barr Virus
- Cellulitis
- Ring worm
Early disseminated stage (several weeks post-tick bite)

- Development of additional EM rashes at other parts of the body
- Facial palsy
- Neurological involvement: severe headache, stiff neck, lymphocytic meningitis
- Cardiac involvement: AV blockage, rhythm disturbances
- Joint involvement: swelling and pain primarily large joints
- Residency or travel to high risk areas with history of tick bites in last few weeks could provide some clues
- Laboratory testing could be useful in diagnosis of Lyme Disease. Serological testing is usually positive. Follow up with convalescent serology (2-4 weeks) if initial testing negative
Early-disseminated disease

- ~20% of patients will have multiple EM
- 10-15% of untreated EM patients will have neuroborreliosis
  - Occurs in June/July – October
  - Lymphocytic meningitis with headache and stiff neck is common
  - Cranial neuritis occurs in 50% of patients with facial palsy is the most common manifestation
  - In kids, less frequent cranial pain but more common headache and clinical signs of meningitis. Onset is insidious with low grade fever, loss of appetite, and weight loss

- Carditis:
  - 4-8% of patients may have signs of cardiac involvement
  - Acute onset, rapidly fluctuating AV conduction disturbances
  - A small number may have 2\textsuperscript{nd} degree AV block and may require a temporary pace maker
Late-disseminated disease

• Up to 60% of patients with EM may develop brief, recurrent episodes of arthritis, often accompanied by arthralgia and myalgia

• Involves large bone joints (knees and elbows) involving swelling and pain

• Up to 30% will recall history of tick bite or EM

• Laboratory testing results are highly sensitive and can support clinical diagnosis

• Patients in this group must have IgG antibodies as only IgM reactive results are considered false positive
European vs. North American Lyme Disease

Predominantly due to *B. afzelii* or *B. garinii*

Highest tick infection rates in central Europe – Austria, Czech Rep, southern Germany, Switzerland, Slovakia, Slovenia

Early localized disease → EM

Early disseminated disease → neuroborreliosis (10%)
  - Facial palsy
  - Lymphocytic meningitis
  - Radiculoneuritis

Late disseminated disease → acrodermatitis chronica atrophicans

If suspected, request European Lyme serology from PHOL
Acrodermatitis Chronica Atrophicans

Background

Acrodermatitis chronica atrophicans (ACA) is the third or late stage of European Lyme borreliosis.\(^1\)\(^2\) This unusual progressive fibrosing skin process is caused by an ongoing active infection with *Borrelia afzelii*. First delineated in 1883,\(^3\) it was described in 1902 as a tissue paper-like cutaneous atrophy.\(^4\) See the image below.
# Treatment guidelines

- Preferred choice: doxycycline 100 mg twice daily
- Alternative: amoxicillin 500 mg 3 times per day
- Other treatments may be considered
- IV therapy for neurolymes or failed arthritis

<table>
<thead>
<tr>
<th>Length of treatment (range)</th>
<th>Indication*</th>
</tr>
</thead>
</table>
| 14 days (10-28 days)        | • Erythema migrans  
                            • Early neurologic disease  
                            • Meningitis or radiculopathy (parenteral)  
                            • Cardiac disease (oral or parenteral)  
                            • Late recurrent arthritis after oral regimen (parenteral) |
| 21-28 days                  | • Late arthritis without neurologic disease  
                            • Late recurrent arthritis after oral regimen |

* Unless otherwise indicated, all treatment is oral

Wormser et al, 2006 CID
### Recommended Antimicrobial Regimes for Treatment of Patients with Lyme disease: IDSA Guidelines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage for adults</th>
<th>Dosage for children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred oral regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>500 mg 3 times per day&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50 mg/kg per day in 3 divided doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(maximum, 500 mg per dose)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg twice per day&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not recommended for children aged &lt;8 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For children aged ≥8 years in 2 divided doses (maximum, 100 mg per dose)</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>500 mg twice per day</td>
<td>30 mg/kg per day in 2 divided doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(maximum, 500 mg per dose)</td>
</tr>
<tr>
<td><strong>Alternative oral regimens</strong></td>
<td>For recommended dosing regimens, see footnote d in table 3</td>
<td>For recommended dosing regimens, see footnote in table 3</td>
</tr>
<tr>
<td>Selected macrolides&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preferred parenteral regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 g intravenously once per day</td>
<td>50–75 mg/kg intravenously per day in a single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(maximum, 2 g)</td>
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<tr>
<td><strong>Alternative parenteral regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>2 g intravenously every 8 h&lt;sup&gt;d&lt;/sup&gt;</td>
<td>150–200 mg/kg per day intravenously in 3–4 divided doses (maximum, 6 g per day)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>18–24 million U per day intravenously, divided every 4 h&lt;sup&gt;d&lt;/sup&gt;</td>
<td>200,000–400,000 U/kg per day divided every 4 h&lt;sup&gt;d&lt;/sup&gt; (not to exceed 18–24 million U per day)</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Although a higher dosage given twice per day might be equally as effective, in view of the absence of data on efficacy, twice-daily administration is not recommended.

<sup>b</sup> Tetracyclines are relatively contraindicated in pregnant or lactating women and in children <8 years of age.

<sup>c</sup> Because of their lower efficacy, macrolides are reserved for patients who are unable to take or who are intolerant of tetracyclines, penicillins, and cephalosporins.

<sup>d</sup> Dosage should be reduced for patients with impaired renal function.
Question 3

Why doesn’t Canada support the use of US tests for Lyme diagnosis?
Laboratory methods for detection of organisms/antibodies

Direct Method

- Culture
- PCR

Indirect Method

- Serology
Diagnostic Testing Depends on the Time of Presentation

- Early (e.g., recent exposure, erythema migrans or other localized compatible rash): Diagnosis made through clinical assessment along with level of exposure to ticks/Lyme disease risk areas

- Later (e.g., disseminated rash, joint, heart or brain involvement or persistent symptoms): Diagnosis based on clinical assessment and laboratory testing
Laboratory-based Diagnosis of Lyme Disease

Serological testing is the most common and useful test used worldwide:

- Detects Lyme disease-specific antibodies produced by the immune system – indirect marker of infection
- Commonly-used method for diagnosis of many diseases including HIV, hepatitis, syphilis, chickenpox, etc.
- Can take days to weeks for antibodies to be produced
- Antibodies can be present for long period of time (years)
- Serological testing results are used to support clinical suspicion of Lyme disease
Laboratory Testing

- Canada uses two-tier testing which is recommended by the CDC, initial ELISA (highly sensitive) followed by Western blot (highly specific)
- Ontario uses the same testing algorithm and interpretations as all public health labs and reference labs in the United States
- Early testing is not recommended as patients may not have produced enough Lyme disease-specific antibodies
- Serology is highly sensitive during the later stages of Lyme disease
Unvalidated testing has a very high false positivity

Fallon et al 2014 (Clinical Infectious Disease)

- Tested 40 healthy individuals using CDC criteria and also sent them to private labs using unvalidated diagnostic test methods
- 57.5% of patients positive based on private laboratory unvalidated tests vs. none via CDC criteria
- These unvalidated tests are not “better”, or “state-of-the-art”
- Implication is that people using these tests can be told they have Lyme when they do not
Lyme Disease Diagnostics Research

There is a great need to develop simple and rapid tests to determine whether people are infected with *Borrelia burgdorferi*, the bacterium that causes Lyme disease. NIAID is committed to improving Lyme disease diagnostics by supporting innovative research projects. Priorities include finding potential targets—substances that new diagnostic tools might measure in patient samples—and improving the sensitivity and specificity of currently available diagnostic tests, thereby leading to more accurate results.

Important Considerations

Lyme disease can be difficult to diagnose for a number of reasons. Many of the common symptoms associated with the disease, such as headaches, dizziness, and joint/body pain, also occur with other diseases. The most distinct symptom of Lyme disease—the circular red rash known as erythema migrans (EM)—does not appear in at least one quarter of people who are actually infected with Lyme bacteria. Also, current diagnostic tests do not always detect early Lyme disease. Because treatment is generally more effective in early stages of the disease, it is important to develop new tools that can help doctors make an early diagnosis.

Doctors need to know whether a patient has an active infection, or has been exposed to the Lyme bacteria earlier in their life. Today's diagnostic tests have some limitations that make a clear, quick diagnosis difficult.
Need for Improved Lyme Disease Diagnostic Tests

Important to acknowledge the limitations of serological testing, especially the need for the development of reliable and valid test methods that:

• Can detect and confirm early localized Lyme disease
• Reliably detect *Borrelia* originating from other parts of the world, especially Europe
• Is associated with severity
• Can assist in monitoring effectiveness of treatment
• Does not persist after successful treatment
• Ability to detect re-infection
What is Chronic Lyme disease?

- “I have symptoms of Lyme Disease and my doctor won’t treat me”; or:
- “My symptoms are still present, even after antibiotic treatment”;
- “Do I have ‘Chronic Lyme disease’”?
Post-Treatment Lyme disease Syndrome (PTLDS)

- Persistent or recurring symptoms for at least six months following appropriate treatment in patients with confirmed case of Lyme disease (CDC definition)
- Risk Factors: delay in diagnosis, severity of initial symptoms, presence of neurological symptoms, underlying co-infection that has not been treated
- The exact cause of PTLDS is not yet known – symptoms may be due to tissue injury and excessive inflammatory response
- There is no credible scientific evidence that PTLDS is caused by persistent infection.
Chronic Lyme disease

• Often used to refer to a constellation of symptoms which may include: chronic pain, fatigue, neurocognitive and behaviour symptoms

• “Chronic Lyme disease” might be any one of:
  • Post-Lyme disease treatment syndrome
  • Symptoms of unknown cause with antibodies against B. burgdoferi but no objective clinical findings consistent with Lyme disease
  • A well-defined illness unrelated to B. burgdoferi infection
  • Symptoms of unknown cause, with no evidence of B. burgdoferi infection
Infectious Diseases Society of America (IDSA) Guidelines

• Developed in 2006, endorsed by many national speciality bodies/PH/healthcare agencies in North America and Europe

• Challenged in 2009 by Connecticut Attorney-General, updated literature review undertaken, recommendations confirmed in 2010

• Current updating of the literature review/recommendations by IDSA in conjunction with American Academy of Neurology (AAN) and American College of Rheumatology (ACR) + numerous other national/international organizations (Canada and Europe)

• Draft guidelines expected in 2017: prevention, diagnosis and treatment of Lyme disease and other tick-borne infections

• Current IDSA guidelines removed from the National Guidelines Clearinghouse website due to lack of currency (5+ years old)
IDSA vs. ILADS Guidelines

Long-Term Antibiotic Treatment:

• The National Institute of Allergy and Infectious Diseases (NIAID) has funded three placebo-controlled clinical trials on the efficacy of prolonged antibiotic therapy for treating PLDS.

  “Carefully designed, placebo-controlled studies have failed to demonstrate that prolonged antibiotic therapy is beneficial.” NIAID


• Berende A et al., “Randomized Trial of Longer-term Therapy for Symptoms Attributed to Lyme Disease”
  NEJM 2016;374:1209-20
Treatment of Chronic Symptoms/PTLDS

• Individuals who have long-term non-specific symptoms from any cause suffer from pain, disability, lack of function, depression and frustration, often shared by their personal and professional caregivers.

• Often no single explanation for these symptoms.

• A multidisciplinary approach may assist in sorting out these complex presentations.

• Established in academic centres, supported by laboratory testing and staffed by ID, neurology, rheumatology, and other healthcare professionals, multidisciplinary centres could provide comprehensive assessment and care as well as conduct research into the causes and management of PTLDS and other syndromes.
**Laboratory**

**HUMAN TESTING**
Testing Information

**TICK IDENTIFICATION AND TESTING**
Abstract: New tick Identification surveillance form
Surveillance form for tick identification

**Resources**

Blacklegged tick life cycle

**Systematic reviews**
- Blacklegged tick surveillance in Ontario
- Human Lyme disease surveillance in Ontario

**Surveillance**
- Ontario Lyme disease estimated risk areas map, 2016
- Ontario blacklegged tick surveillance: quick guide for Public Health Units
- Tick dragging standard operating procedure

**Data & Analytics**

Infectious Disease in Focus - Lyme disease

**Vector-Borne Disease Surveillance Reports**
- 2015 Summary Report
- 2014 Summary Report
- 2013 Summary Report

**Related Links**

**ONTARIO MINISTRY OF HEALTH AND LONG-TERM CARE**
- Lyme disease Information for Health Care Professionals
- Lyme disease Information for the Public
- Infectious Diseases Protocol: Appendix A: Disease Specific Chapters
- Infectious Diseases Protocol: Appendix B: Case Definitions

**RESOURCES FOR PROVIDERS**
- Clinical Presentation

**ADDITIONAL RESOURCES**
- PHAC Lyme disease Information
- CDC Lyme disease Information
- IDSA Lyme disease Guidelines
- Tick Management Handbook
- Tick Identification Guide

**Research**

**Standardized Questionnaires**