Treatment of Lyme disease

Dr. Joyce Pickering, MD, FRCPC, FACP
General Internal Medicine, McGill University Health Centre
J.D. MacLean Centre for Tropical Diseases
Associate Professor, McGill University
May, 2022

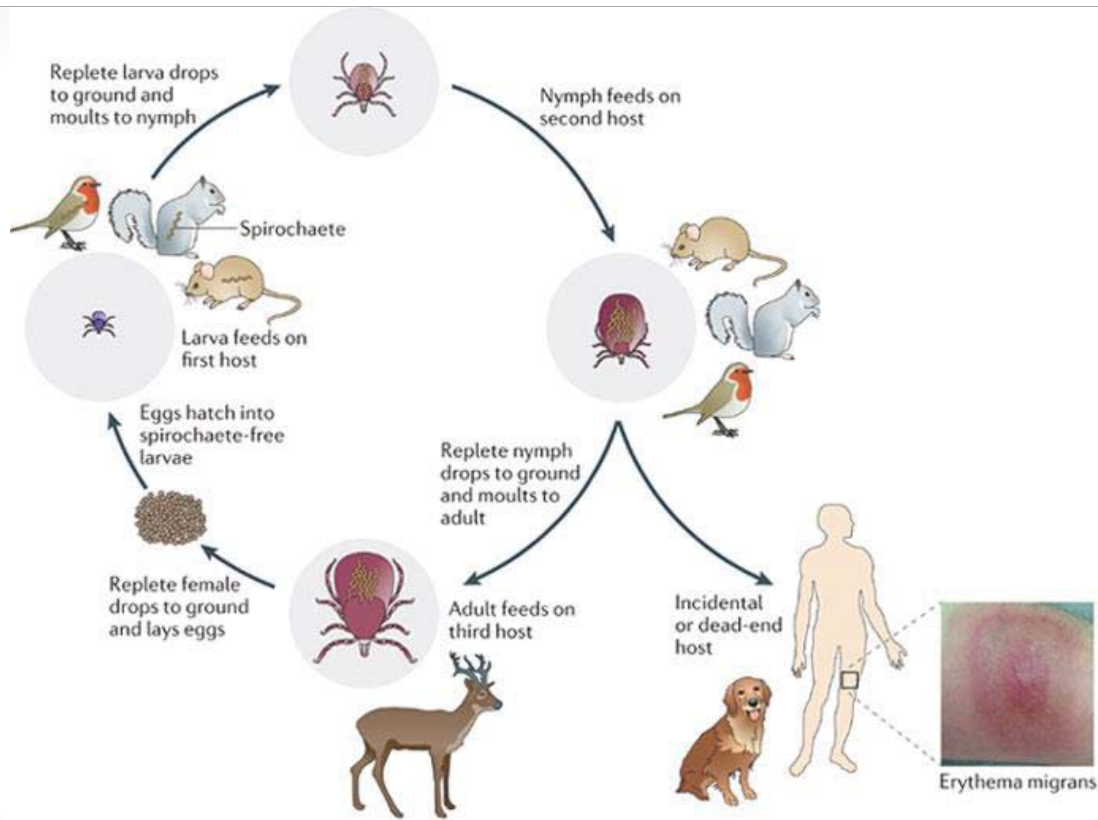
- I have no conflicts of interest to declare.

Objectives

- Know what to do if someone comes in with a tick or tick bite
- Be able to recognize early localized Lyme disease and treat it.
- Be able to recognize early disseminated Lyme disease and treat it.
- Be aware of issues with non standardized testing for Lyme disease.

Lyme disease

- Caused by Borrelia burgdorferi in N. America (other Borrelia species in Europe and Asia)
- Transmitted by the tick Ixodes scapularis or Ixodes pacificus

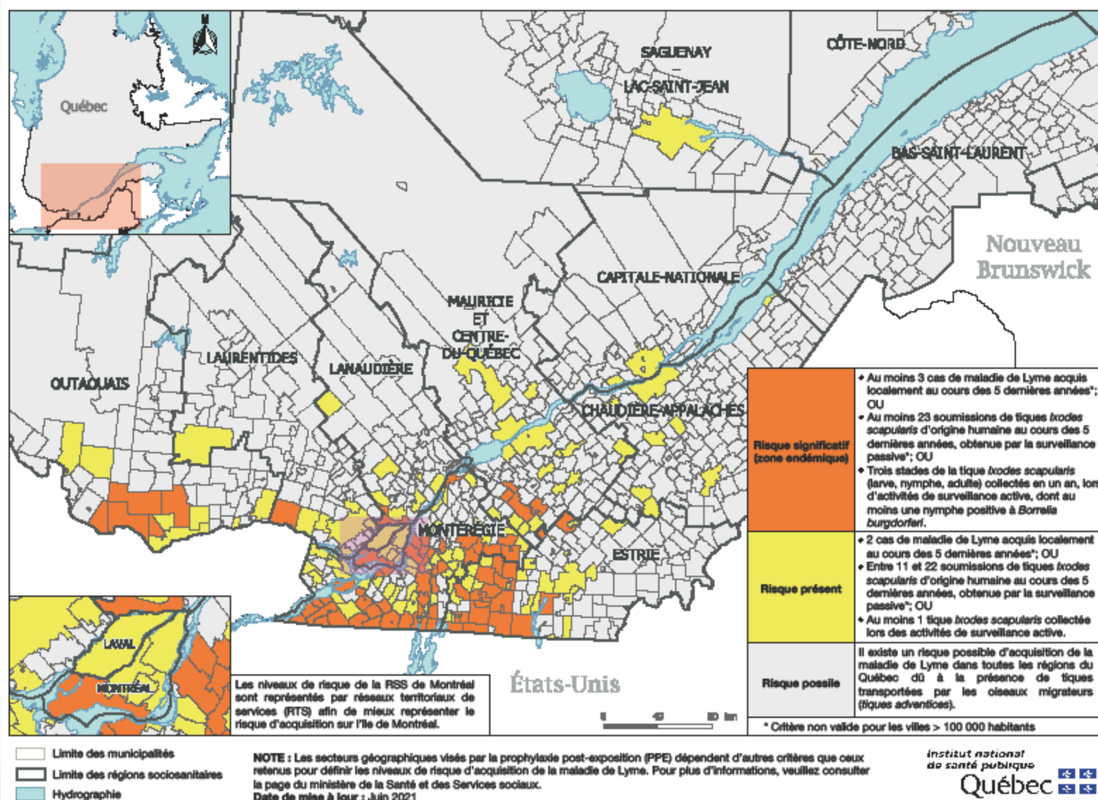


Lyme disease is increasing in Quebec

- http://www.msss.gouv.qc.ca/professionnels/zoonoses/maladie-lyme/evolution-de-la-maladie-au-quebec/
- Lyme disease reportable since 2003.

	2016	2017	2018	2019	2020	2021
Cases acquired in Quebec	126	251	223	381	250	597
Cases acquired elsewhere or unknown	51	78	81	125	24	
Total cases reported in Quebec	177	329	304	506	274	

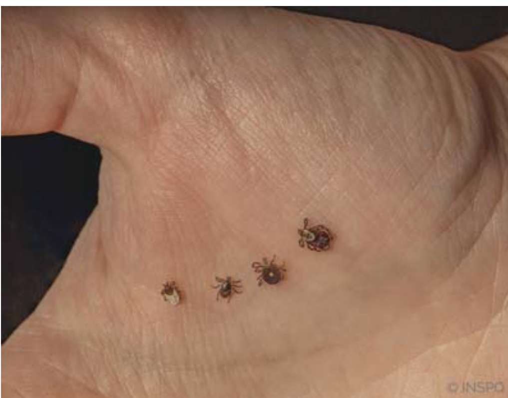
- In Quebec, Ixodes Scapularis ticks infected with Borrelia burgdorferi are found in:
  - the north and west of Estrie;
  - a large part of Montérégie;
  - Lanaudiere
  - the south-west of the Mauricie-et-Center-du-Québec region;
  - the southwest of the Outaouais.
- In most regions, <20% of ticks are infected.
- Tick activity starts in April, ends in November, so acute infections tend to be in this period.
- An interactive map, indicating risk by municipality in Quebec is available at https://www.inspq.qc.ca/zoonoses/maladie-de-lyme



- For areas in Canada outside Quebec see:
- https://www.canada.ca/en/public-health/services/diseases/lyme-disease/risk-lyme-disease.html
  - (links you to provincial health ministry sites)

What to do if someone comes in with a tick

- Try to identify the tick
  - You can use your smart phone, zoom in, and refer to: https://www.inspq.qc.ca/guide-d-identification-des-tiques-du-quebec



Identification of ticks

- Physicians in Quebec can send ticks to the LSPQ for identification. See

https://www.inspq.qc.ca/lspq/repertoire-des-analyses/maladie-lyme-analyse-tiques

- They will tell you if it is ixodes scapularis within about 5 days.
- They will NOT tell you if it is infected with borrelia.

  They do test many ticks for this, but it is for epidemiological purposes and not for patient management.

When to prophylax a tick bite (that is probably ixodes scapularis):

- Did the patient likely acquire the tick in an area at risk?
  - **Must be yes**
- Does the patient currently have signs of Lyme disease?
  - **Must be no**
- Is the tick still attached or is it less than 72 hrs since the tick was removed?
  - **Must be yes**
- Can you be fairly certain that the tick was attached for at least 24 hrs?
  - **Must be yes**
- Are there any contraindications to giving prophylaxis?
  - **Must be no**
    - (Absolute: allergic reaction Relative: pregnancy, active liver disease, obstructive esophageal disease, decompensated myasthenia gravis. NB < 8 years old is no longer a contraindication)

- If yes to prophylaxis, give 200 mgs doxycycline x 1
  - (4.4 mgs/kg in children)
- If contraindication to doxycycline, no prophylaxis
- If no prophylaxis, ask patient to observe for rash, redness, fever etc. and come back to see you if symptoms develop.
- Optional: Send the tick to Laboratoire de Santé Publique du Québec (LSPQ) – will not change management.
- **Remember: the risk of developing Erythema Migrans after a tick bite in a high risk area in Quebec is only 1-3%.**
- Guide for discussing decision re prophylaxis available from INESSS (gives risks of both side effects of antibiotics and risks of EM in an easy to understand format).

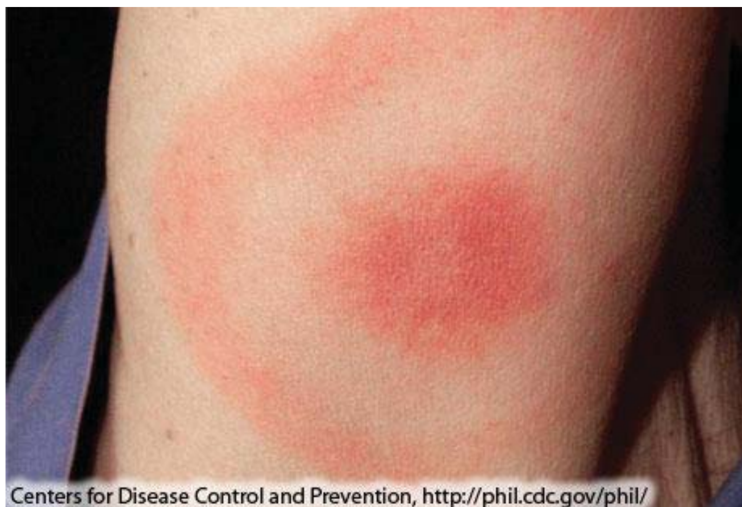
Stages of Lyme Disease

- Early localized
- Early disseminated
- Late disease

- These stages can overlap – for e.g., a patient can have erythema migrans at the same time as they have complete heart block.

Early localized - diagnosis

- Symptoms occur 3 to 30 days after an infected tick bite.
  - Skin lesion – such as erythema migrans in 80%
    - Multiple lesions indicate spirochetemia, not multiple bites, and usually occur in **early disseminated** disease
    - A lesion >5 cms is classical for Lyme disease
    - Lesions are typically not painful, not/or minimally itchy
  - Fatigue
  - Joint and muscle pains
  - Fever
  - headaches



Erythema migrans: commonly not itchy. If > 5 cms, makes it more likely.

- If a red lesion occurs at a tick bite site within 48 hrs of the bite, then it is likely a hypersensitivity to the tick bite, rather than an erythema migrans.
- **Serology is usually negative in the first two weeks of illness, so the decision to treat as Lyme disease needs to be made clinically.**
  - Serology usually only becomes positive 4 to 6 weeks after the tick bite.

Early localized disease - diagnosis

- If typical skin lesion
  - $\geq$ 5 cms
  - Lasting more than 48 hrs after tick bite
    - AND
- Tick bite history within the past 30 days **or**
- Reasonable exposure probability
- Then make a clinical diagnosis and treat with doxycycline 100 mgs BID x 14 days.
- No need for serology

Early localized disease - diagnosis

- If you are in doubt –
  - Skin lesion is not typical
  - No exposure history

- Then ask for serology.

  Indicate date of symptoms and place of likely exposition on request form.

  May need to repeat serology in 4 to 6 weeks.

- If you are not sure if it is a cellulitis or Lyme disease, use cefuroxime 500 mgs po BID x 14 days to cover both.

Early Localized: Treatment:

- Early localized:
  - Doxycycline 100 mgs BID for 14 to 21 day
    - Children, 4.4 mgs/kg/day divided in 2 doses (now approved for children under 8 years old)
  - Amoxicillin 500 mgs tid for 14 to 21 days.
    - Children: 50 mgs/kg/day divided in 3 doses (max 500 mgs/dose)
  - Cefuroxime 500 mgs BID for 14 to 21 days
    - Children 30 mgs/kg/day divided in 2 doses, (max 500 mgs/dose)
  - Macrolides are less effective. Use only if not able to take any of the above regimens.
    - Azithromycin x 7 days
- Note: 15 to 30% of patients will get transient worsening of symptoms (Jarisch-Herxheimer reaction) when treated. Treat this with NSAIDS.

.

Early Disseminated – weeks to months after tick bite (<3 months) - Diagnosis

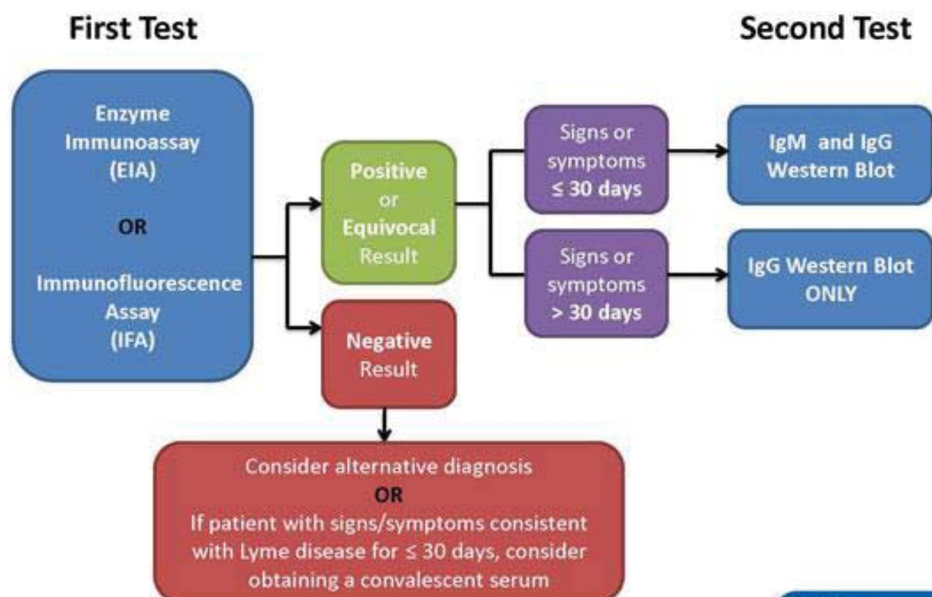
- Carditis
- Lymphocytic meningitis, cranial or other neuropathy
  - Facial paralysis, diplopia, foot drop, facial numbness, loss of hearing
- Migratory arthralgias
- Lymphadenitis
- Conjunctivitis, iritis, choroiditis etc.
- Liver disease
- Kidney disease – microhematuria, asymptomatic hematuria

Think Lyme disease especially if:

- Bilateral 7th nerve palsy
- Heart block in a patient without known heart disease

Early disseminated - diagnosis

- Send blood for antibody testing
  - Specify where they may have been infected, as well as timing of symtpoms
  - (tests are different for Euro/Asian species)
- First screen: Enzyme immunoassay:
  - Test done at Laboratoire Sante Publique due Quebec (LSPQ)
    - Results within about a week
- Confirmatory test: Immunoblot
  - Also done at LSPQ
    - Results take another week.
    - Will test for both IgG and IgM depending on the duration of symptoms.
- Remember: European Lyme will test positive on the screen but negative on the immunoblot that is used here. If European Lyme suspected, specify on the requisition, and give details of trip/exposure.



- Like any test, false positives and negatives can occur
  - If you think you have a false negative:
    - Could be too early – repeat test in a few weeks.
    - If patient was treated before tests drawn may have a negative result.
  - If you think you have a false positive on the enzyme immune assay (EIA), wait for the confirmatory test.
  - **If you clinically suspect Lyme disease, it is reasonable to treat either before any tests are back or with a positive EIA (before the immunoblot tests are back)**
  - If you think you have a false positive on the Western blot (for IgG) use your clinical judgment. (False positives more common on the line blot (IgM)).
  - If positive on IgM and negative on IgG should be considered as negative unless done < 8 weeks from beginning of symptoms – in that case, repeat the tests.
- Antibodies usually decline over time but persistent IgM reported in 10 to 15% of patients and IgG in 25 to 50% of patients up to 10 years after treatment.

Early disseminated disease: Treatment

Suggest: Involve your local internist/neurologist/infectious disease specialist

- Multiple erythema migrans lesions
  - Doxy, amox or cefuroxime x 14 to 21 days
- Joint
  - Doxy, amox or cefuroxime x 28 days
- Neurologic
  - Meningitis
    - Ceftriaxone 2 grams daily x 14 to 28 days
  - Cranial nerve involvement
    - Doxy, amox or cefuroxime x 14 to 21 days
  - Peripheral nerves – radiculopathy
    - Doxy, amox or cefuroxime x 14 to 28 days
- Cardiac
  - AV block, myopericarditis
    - Ceftriaxone 2 grams daily x 14 to 28 days
    - Note: evidence that oral treatment may be equally effective
    - Note: they recover – do not put in a permanent pacemaker

Late disease – more than 3 months to years after the tick bite: Diagnosis

(involve your local internist/infectious disease/rheumatology specialist)

- Intermittent monoarticular or oligoarticular arthritis, usually the knees
- Neurologic disease – rare
- Cutaneous involvement – acrodermatitis chronica atrophicans, morphea – described only in Europe

Late disseminated: Treatment

- Articular
  - Doxy, amox, cefuroxime x 28 days
  - If recurrence after oral treatment, ceftriaxone 2 grams IV daily x 28 days
- Neurologic –encephalomyelitis, peripheral neuropathy
  - Ceftriaxone 2 grams IV daily x 14 to 28 days
- NB: repeated (other than above) or more prolonged treatments have not been shown to be beneficial, and have had more side effects/complications.

The following tests are not validated:

- Capture assays for antigens in urine
- Culture, immunofluorescence staining, or cell sorting of cell wall-deficient or cystic forms of *B. burgdorferi*
- Lymphocyte transformation tests
- Quantitative CD57 lymphocyte assays
- “Reverse Western blots”
- In-house criteria for interpretation of immunoblots
- Measurements of antibodies in joint fluid (synovial fluid)
- IgM or IgG tests without a previous ELISA/EIA/IFA

Post-treatment Lyme disease syndrome
(not the same as late disseminated)

- Compatible symptoms that start within 6 months of treatment for Lyme disease and persist for at least 6 months.
- Surveillance in Quebec showed about 8% of patients had some symptoms more than 6 months after treatment for proven Lyme disease.
- Treatment is expectant – longer courses of antibiotics have been tried in studies and shown not to be effective – in fact, to cause more adverse effects.

(From IDSA guidelines)

- For patients who have persistent or recurring nonspecific symptoms such as fatigue, pain, or cognitive impairment following recommended treatment for Lyme disease, but who lack objective evidence of reinfection or treatment failure, we recommend against additional antibiotic therapy *(strong recommendation, moderate-quality evidence).* **Comment**: Evidence of persistent infection or treatment failure would include objective signs of disease activity, such as arthritis, meningitis, or neuropathy.

"Chronic Lyme Disease"

- Frequently patients with multiple non specific symptoms believe they have "chronic Lyme disease", in the absence of a positive test from a recognized laboratory.
- This is not late disseminated, and it is not post treatment Lyme Disease syndrome.
- My approach:
  - Don't test unless they have compatible symptoms and a history consistent with exposure.
  - If they have already been tested at a non-standard lab, and have a positive result, and possibly compatible symtpoms, test through LSPQ.

Resources

- https://www.cdc.gov/lyme/index.html
- Lantos, Rumbaugh, Bockenstedt et al. Clinical Practice Guidelines by the IDSA, AAN and ACR: 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. CID 2021;72(1) 1-8.
- https://www.canada.ca/en/public-health/services/diseases/lyme-disease/health-professionals-lyme-disease.html
- https://www.inspq.qc.ca/zoonoses/maladie-de-lyme
- http://www.msss.gouv.qc.ca/professionnels/zoonoses/maladie-lyme/
- www.uptodate.com
- http://extranet.santemonteregie.qc.ca/userfiles/file/sante-publique/maladies-infectieuses/Zoo-Traitement-maladie-Lyme.pdf

  (this is an excellent summary sheet).

Training Modules:

- https://www.train.org/cdctrain/course/1093558/
- CDC linked training 4 part training module
  - Free
  - Very good
  - Long