

LYME DISEASE IN ONTARIO- WHEN IS IT REAL?

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Disclosures

- None

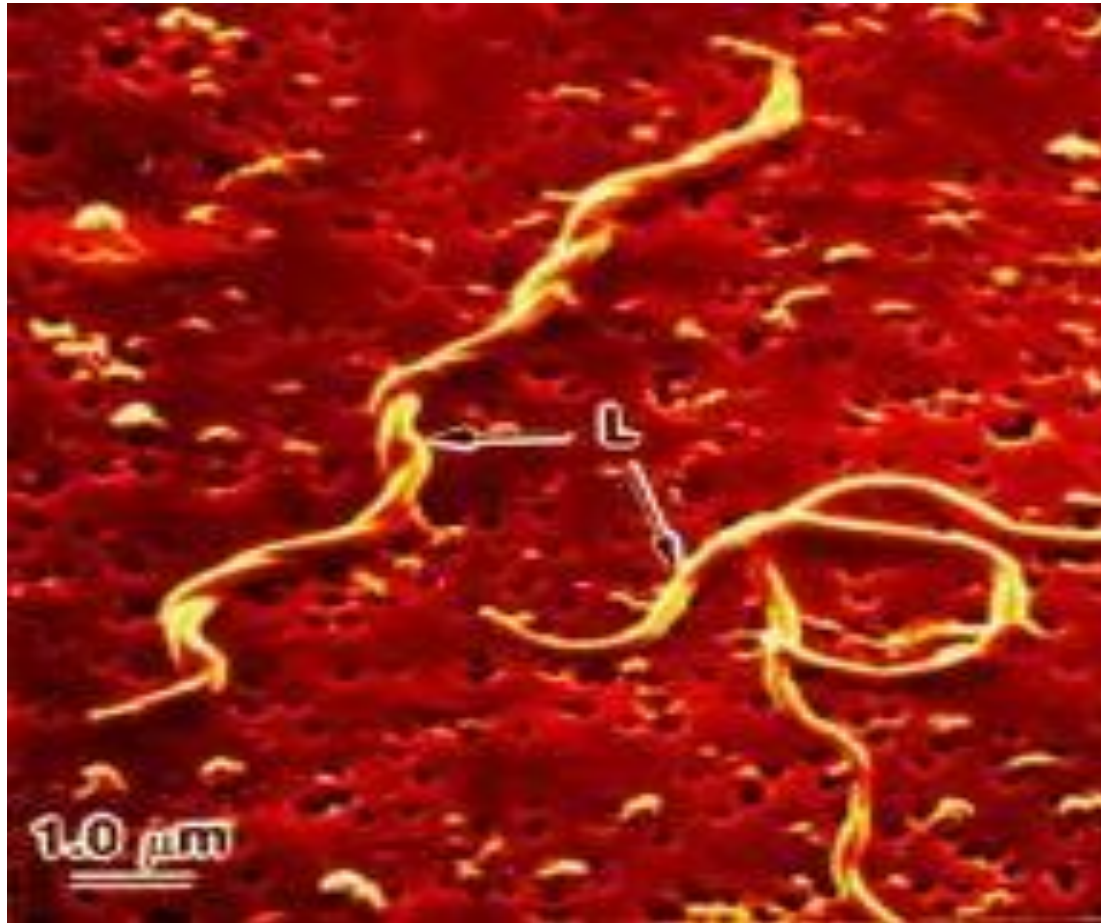
Objectives

- 1) Review epidemiology of Lyme in Ontario
- 2) Clarify clinical manifestations
- 3) How do we deal with all the tests
- 4) What is a realistic approach to treatment

History

- Recognized in Europe but given multiple different names without awareness of their common cause including Erythema Chronicum Migrans (ECM), Bannwarths syndrome, acrodermatitis chronica atrophicans
- 1976 noted clustering of “juvenile rheumatoid arthritis” in Lyme, Connecticut
- 1982 new spirochete found in patients with these syndromes and ticks in the area

spirochete *Borrelia burgdorferi*



Different strains: different presentations

- North America: *B. burgdorferi*
- Central Europe (Germany, Austria+ Sweden)+ rarely Asia: *Borrelia garinii* and *Borrelia afzeli* as well as *B. burgdorferi* so more variable presentations (so they didn't notice the relationship until later)

Blacklegged tick, *Ixodes scapularis*, unfed adult female. Total body length ranges from 2.0 to 3.5 mm



Deer Tick



Differentiating nymphs and larvae are harder than adults- so usually need to send to entomologist and Rx as Ixodes first



American dog tick, *Dermacentor variabilis*, unfed adult female. Total body length ranges from 3.0 to 5.0 mm; This is the tick species most frequently submitted for identification in Ontario; it is not a competent vector for *B. burgdorferi*.



Why has it been increasing

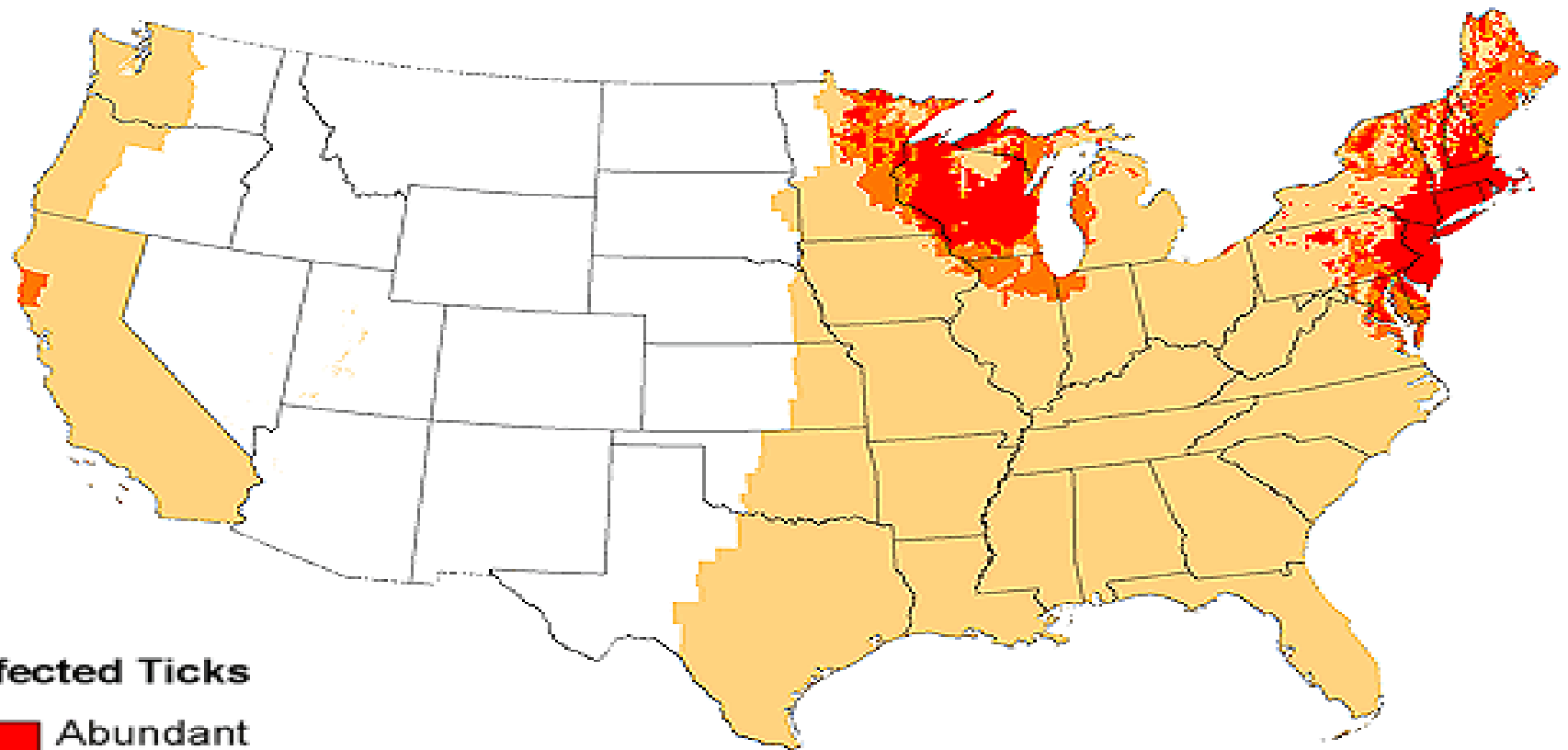
- Likely in North America for millennia
- As Europeans came woodlands cleared and deer hunted to near extinction so reduced prevalence
- Farming decreased in north east and reverted to woodland. Decreased hunting and deer population rose. Large suburban populations living near deer.
- Soil moisture + land cover near rivers/lakes+ along ocean are ideal for ticks
- New more virulent strain *B. burgdorferi* OspC type A may have made symptoms more common

Other Tick borne illnesses

- RMSF (fever + petechiae/purpura- renal failure+ shock)
[throughout US + southern alberta]
- Babesiosis (Atlantic states +acts like malaria- bacteria in RBC's on smear)
- Erlichiosis-southern+ eastern US- fever+ bacteria in WBC's on blood smear- need serology for *Anaplasma*
- Typhus (black eschar+ fever in homeless (lice) from ticks more common in tropics-south africa)
- Tick paralysis (salivary neurotoxin-like Guillain-Barré – **must look for +remove**)
- DOXYCYCLINE is for Ticks!
- Note although Dermacentor does not transmit lyme- it can transmit these other diseases

- Lower New York state ticks-
- 70% carried at least 1 human pathogen, 30% had at least 2, and 5% had at least 3 with some ticks carrying 4 pathogens (Vector borne and zoonotic diseases 2010:10;3,217)

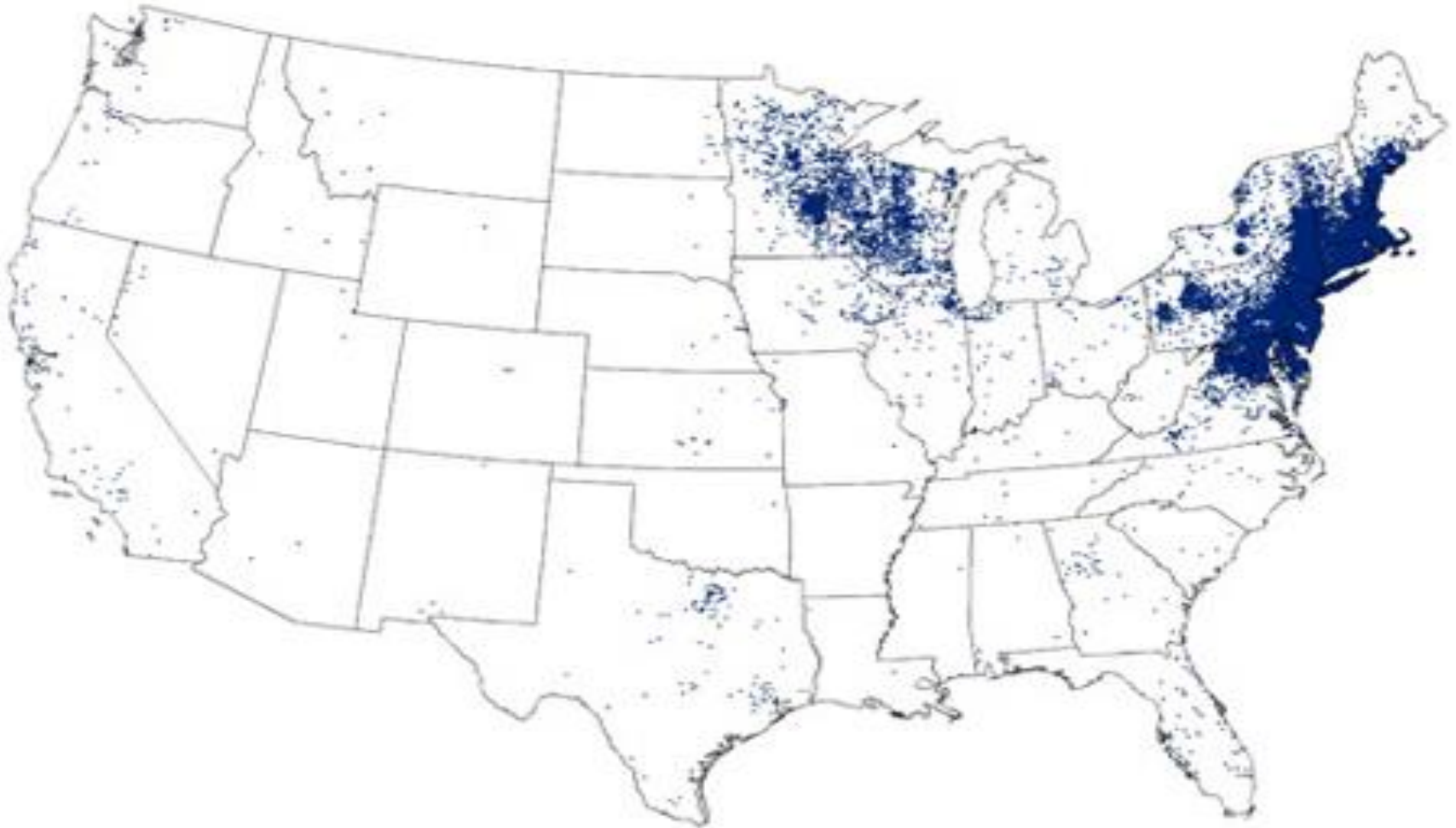
US data (CDC 2008)



Infected Ticks



US Human Cases (CDC 2008)



2002 study across Ontario confirms wide distribution of Infected Ticks

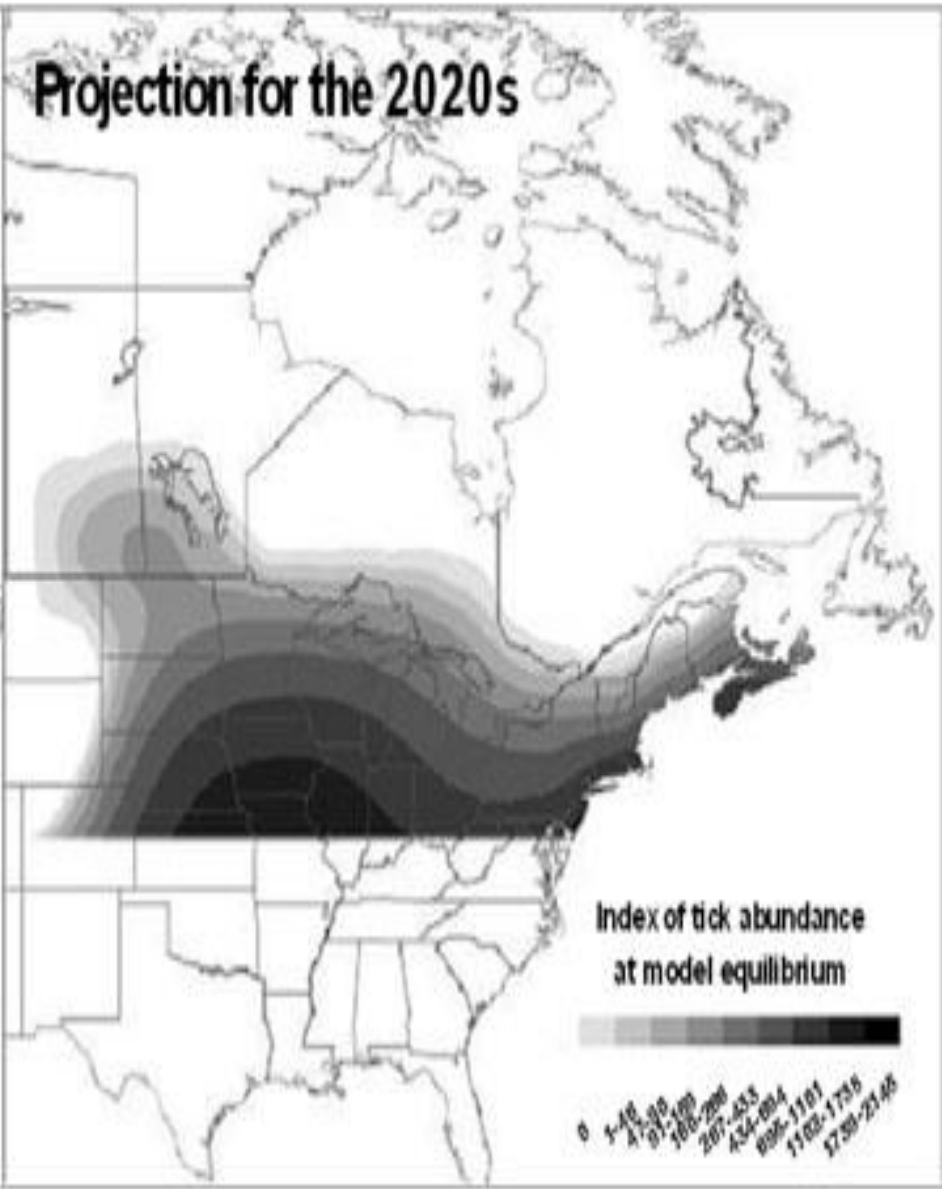
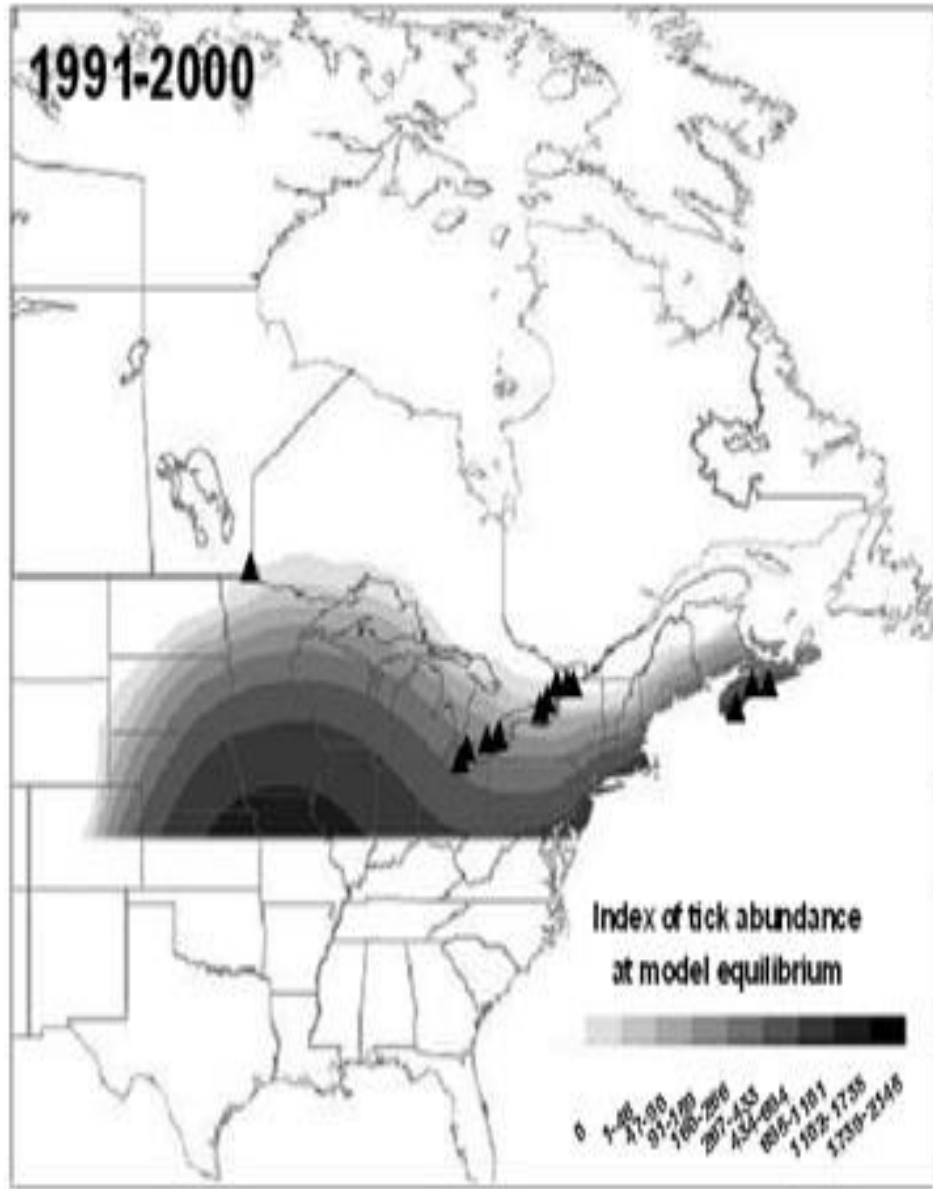


Fig. 1. Distribution of *I. scapularis* tested for *B. burgdorferi* collected from Ontario hosts with no out-of-province travel and the northern detected range, 1993-2002.

WITH GLOBAL WARMING THE RANGE AND NUMBERS OF TICKS HAVE BEEN INCREASING IN ONTARIO- NUMBER OF REPORTED CASES ALSO RISING

Declared an “Emerging Infectious Disease”
by Public Health Agency of Canada

<http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/08vol34/dr-rm3401a-eng.php>



- Once endemic population established (all 3 stages of tick survive) incidence of clinical disease rises
- Many more Nymphs (~20x) than adults (most nymphs end up as food for predators) and only adults “ride the birds” but Larvae and Nymphs also transmit.
- Nymphs are also smaller than adults so more often not noticed

Endemic areas (Ticks undergo full life cycle)- 2012

- Long Point Provincial Park (northwest shore of Lake Erie near Port Rowan)
- Point Pelee National Park (near Leamington)
- Prince Edward Point National Wildlife Area (located at the southeastern tip of Prince Edward County)
- St. Lawrence Islands National Park (near Brockville)
- Rondeau Provincial Park (southeast of Chatham)
- Turkey Point Provincial Park (near Port Rowan)
- Wainfleet Bog Conservation Area (in Port Colborne)
- The black-legged tick also feeds on birds and can be transported to almost anywhere
- therefore, Lyme disease can be acquired almost anywhere in the province.

Spirochetal diseases tend to present in clinical stages (syphilis)

- Stage 1 ECM
Erethema Chronicum Migrans
- Stage 2 Early Infection (Disseminated Infection)
- Stage 3 Late Infection (Persistent Infection)
- “Chronic Lyme Disease syndrome”

ECM

- 70-80% of patients
- Nymphs are very small, so most patients do not remember bite- starts 1-2weeks(3-32 days) post bite
- Thigh, groin +axilla are most common sites, but can be anywhere
- If in scalp may only see a linear streak from hairline
- Without treatment usually fades in 3-4 weeks (but rarely can take a year)
- More mild (less hot + more chronic) in europe

A deep type of gyrate erythema that follows at site of bite. A red papule that expands peripherally as a nonscaling, palpable band that clears centrally. Regional Lymphadenopathy is common



ECM



ECM: may have target appearance (1/3)





ECM

- Not always central clearing- many uniformly erythematous or enhanced central erythema





Early Infection (Stage 2)

- Within days to weeks of initial ECM lesion, secondary lesions may appear from hematogenous dissemination
- Often associated with systemic symptoms such as chills, fever, headache, malaise, nausea, vomiting, fatigue, backache and stiff neck

Stage 2 (secondary lesions)



Similar to secondary syphilis- any system can be involved during dissemination

- **Skin:** Secondary Annular lesions; Malar Rash; Diffuse Erythema or Urticaria; Evanescent lesions
- **MSK:** migratory pain in joints, tendons, bursae, muscle, bone; Brief Arthritis attacks; Myositis; osteomyelitis; panniculitis
- **NEUROLOGIC:** Meningitis; Cranial neuritis- bilateral 7th nerve; motor or sensory radiculoneuritis; encephalitis; mononeuritis multiplex; pseudotumor cerebri; myelitis; cerebellar ataxia

Secondary cont'd

- **LYMPHATIC:** Regional or Generalized lymphadenopathy; splenomegaly
- **HEART:** Atrioventricular Block (transient so usually do not need pacemaker, but rarely 3rd degree)- recent case reports of sudden death with myopericarditis
- **EYES:** Conjunctivitis; Iritis; choroiditis; retinal hemorrhage or detachment; panophthalmitis

Secondary cont'd

- **Liver:** mild or recurrent hepatitis
- **RESP:** sore throat (non-exudative); non-productive cough
- **GU:** Orchitis; microscopic hematuria
- **Constitutional:** severe fatigue+ malaise

Late Infection (Stage 3)

Months after bite

- **Cutaneous:** Acrodermatitis chronica atrophicans; localized scleroderma like lesions
- **EYES:** Keratitis
- **Constitutional:** Fatigue
- **MSK:** Chronic arthritis- 60% of patients- usually 1 or 2 large joints especially knees. Swollen+ hot but not very red or painful
- May relapse + remit over several years.
- May rarely continue after full treatment despite clearance of bacteria by PCR (immune activation after organism dead)

Chronic Neurological (Stage 3)

- **Chronic axonal polyradiculopathy:** Often with localized spinal radicular pain/numbness
- **Chronic Lyme encephalopathy:** Chronic mild cognitive disturbances. May have negative LP for inflammation, localized antibody production occurs. (European strains tend to have more severe encephalomyelitis).

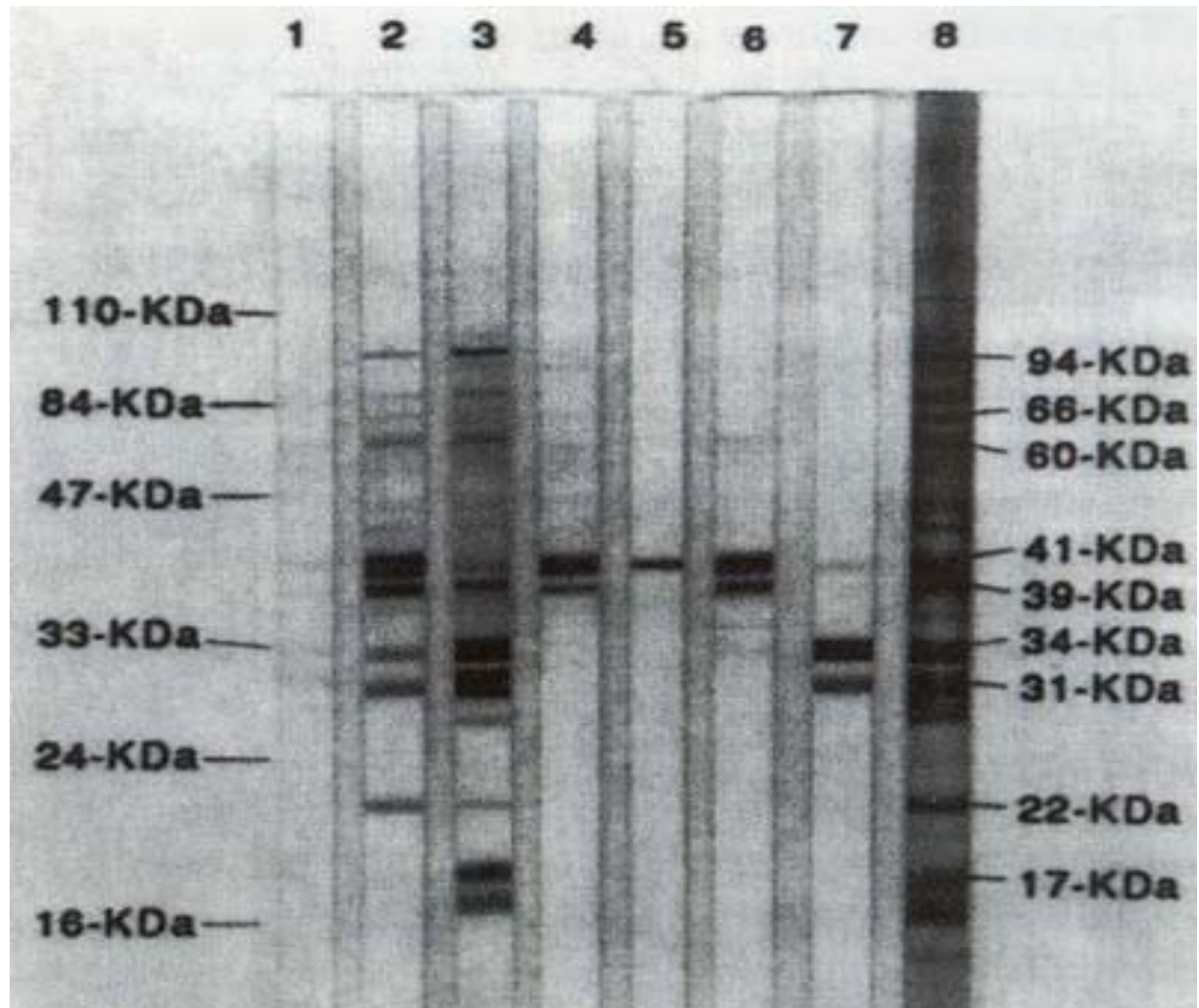
Diagnosis

- Culture- requires specialised medium (BSK) from biopsy of early lesions- not practical as VERY technically difficult
- PCR only way to identify organism directly. Usually only done on CSF (and can be false neg in late infection)
- Most cases diagnosed by clinical presentation + serology- serology takes 4 weeks so 60-75% of ECM seronegative. If Treated early ½ of ECM pt's remain seroneg
- Classic ECM rash=> Treat- no need to wait for serology otherwise serology determines treatment

Serology

- 2 step approach- Screening ELISA – if positive or indeterminate do western blot
- Western Blot- IgM + IgG assays

Western Blot



Western Blot Present recommendations

- **IgM** (turns positive earlier)
needs 2/3 possible bands: may still be false + if 23+41 (39 is third)
- **IgG** needs 5/10 possible bands
- Note: 50% of healthy general population have at least 1 positive IgG band (41kDa)
- May be false negative if symptoms < 4-8 weeks, but after this even IgG should be positive
- A positive IgM alone after 2 months is a false +
- May remain seropositive even for IgM long after treatment (not a sign of treatment failure)

- new Ontario ELISA (antibody to C6 peptide)- more sensitive and specific
- European strains *Borrelia afzelii* and *B. garnerii*- previously missed
- new Ontario ELISA (antibody to C6 peptide) will pick up, but negative western blot
- Need to request “European strain western blot”

- Several private Labs in US “more sensitive” report almost ALL tests as positive as income generating marketing
- “California labs” (IGenX) watch out!- refer to chronic IgM or 2/10 IgG bands as “positive”
- SUNY New York- identical to ours
- CD57- useless

Borrelia miyamoti

- Chronic neurological disease with positive CSF PCR and negative routine serology NEJM Jan 17, 2013 pg 240-5 and Annals Intern Med July 2, 2013 pg 21-7

Differential Dx

- Red papule- can be infected Tick bite (*S.aureus*)
- Rapidly spreading redness- allergy to tick saliva (ECM spreads more slowly ~1cm/day)
- Multiple target lesions; **erethema multiforme** (usually related to HSV or meds)-Lyme doesn't involve mucosa, cause blistering or involve palms or soles
- Facial palsy from Lyme- usually June-September. Often have Hx of ECM and +serology vs Bell's (?HSV) all year
- Reactive arthritis- post chlamydia or campylobacter –HLA B27+. Very high serological titers with Lyme arthritis
- Chronic fatigue/fibromyalgia: Lyme usually involves 1 system at a time (in 3rd stage) and has objective signs+ serology

Treatment

- Oral OK for most- unless neurological or chronic arthritis
- 15% with disseminated will get Jarish-Herxheimer response in first 24 hours (fever/myalgia/arthritis)- consider NSAID
- Doxycycline 100mg PO BID X14-21 days: is best as it also covers other tick borne infections (may have >1 especially anaplasma or babesia if from eastern US)
- **Children ≤ 8 or pregnant women:** Amoxicillin 500mg PO TID X14-21 days
 - **IF Penicillin allergic:** Non-Anaphylaxis: Cefuroxime 500mg PO BID X14-21days
 - Anaphylaxis: Erythromycin 250mg PO QID X14-21 days or Azithro/Clarithro(fourth line- 20% failure rate)

- Note: in vitro sensitive to Penicillin/ 2nd+3rd gen cephalosporins/tetracycline/erythro
- **Resistant to quinolones/aminoglycosides/1st generation cephalosporins (ancef/keflex)**
- For ECM; RCT 10 days of oral doxy Rx equal to 20 days, and adding 1 dose of IM ceftriaxone to 10 days of doxy didn't make a difference (Ann Intern Med, 2003;138:697).
- IV ceftriaxone no better than oral Rx for ECM unless had neuro symptoms (NEJM 1997;337:289)

Neurological

- IV Ceftriaxone 2gm/day (or Pen G 5million Q6h IV) X2-4weeks
- Some use doxycycline if facial palsy alone
- **CARDIAC** 1st degree AV block: doxy alone OK. High degree AV block- IV ceftriaxone for 14-28 days. Monitoring, and may need temporary pacer, but not permanent.

ARTHRITIS

- Usually 30 days of doxy or amoxicillin adequate but some will require IV.
- If fail clinically then 1 month of IV Ceftriaxone
- If still sore joint- test fluid PCR- usually negative (Positive then treat longer)
- If PCR negative can use anti-inflammatory or arthroscopic synovectomy (Arthritis Rheumatism. 2006;54:3079)

Congenital infection

- from dissemination during pregnancy.
Few case reports
- Because of this pregnant asymptomatic patients with positive antibody are often treated with amoxicillin

Reinfection

- Hard to diagnose due to prolonged antibody positivity after Rx
- Unlikely to get positive PCR after episode of arthritis (?immune to reinfection)
- May occur after ECM

Prevention

- Avoid Ticks- can use DEET or permethrin
- Check for Ticks on leaving area (ticks require 24-48 hours to transmit so removing at end of day OK)- Bathe within 2 hours (not well attached yet)
- Nymphs tend to be low near the ground so first attach to legs. Can crawl up and tend to bite in moist areas (groin + axillae)
- In small children may attach on head or neck (rare in adults)
- If Tick already engorged- 200mg PO of Doxy within 72 hours of bite is effective

Environmental Prevention

- Acaracides to kill ticks
- Desiccating barriers between tick infested woods and lawns
- NRA advocates KILL EVERY DEER
- Lyme Vaccine was marketed between 1999-2002. Worked but discontinued (false positive blood tests and not 100% effective)

Post Lyme Disease syndrome also called Chronic Lyme Disease

- Persistent symptoms despite full antibiotic therapy
- Extensive symptoms with no objective findings
- Resembles Chronic fatigue Syndrome or fibromyalgia.
- Often never had clinical signs or diagnostic serology
- Counterculture demanding chronic IV antibiotics- for years- several physician “specialists” catering to this

Chronic Lyme symptoms

- (MSK/Neurocognitive/fatigue) after full treatment
- 3 double blind placebo controlled RCT's failed to show benefit with prolonged courses of IV or Oral Rx (NEJM 2001;345:85+ Neurology 2003;60:1923+ Neurology 2008;70:992)

NEJM 2001 Klempner et al.

- conducted two randomized trials: one in 78 patients who were seropositive for IgG antibodies to *Borrelia burgdorferi* at the time of enrollment and the other in 51 patients who were seronegative.
- intravenous ceftriaxone, 2 g daily for 30 days, followed by oral doxycycline, 200 mg daily for 60 days, or matching intravenous and oral placebos.
- had well-documented, previously treated Lyme disease but had persistent musculoskeletal pain, neurocognitive symptoms, or dysesthesia, often associated with fatigue.
- primary outcome measures were improvement on scales measuring the health-related quality of life - on day 180 of the study.

- After a planned interim analysis, the data and safety monitoring board recommended that the studies be discontinued because data from the first 107 patients indicated that it was highly unlikely that a significant difference in treatment efficacy between the groups would be observed with the planned full enrollment of 260 patients. Baseline assessments documented severe impairment in the patients' health-related quality of life. In intention-to-treat analyses, there were no significant differences in the outcomes with prolonged antibiotic treatment as compared with placebo among either the seropositive or the seronegative patients.

Conclusions: There is considerable impairment of health-related quality of life among patients with persistent symptoms despite previous antibiotic treatment for acute Lyme disease. However, in these two trials, treatment with intravenous and oral antibiotics for 90 days did not improve symptoms more than placebo. (N Engl J Med 2001;345:85-92.

Neurology 2003 L.B. Krup et al.

- randomized double-masked placebo-controlled trial on 55 patients with Lyme disease: had to have had documented Lyme
- severe fatigue at least 6 or more months after antibiotic therapy
- Ceftriaxone vs placebo x28 days
- improvement in fatigue but not cognitive function
- CSF OspA antigen, was present in only 16% of patients at baseline and was not a useful marker of outcome or clinical severity.
- Because fatigue (a nonspecific symptom) was the only outcome that improved and because treatment was associated with adverse events, this study does not support the use of additional antibiotic therapy

Neurology 2008

- Patients had well-documented Lyme disease, with at least 3 weeks of prior IV antibiotics, current positive IgG Western blot, and objective memory impairment. Healthy individuals served as controls for practice effects. Patients were randomly assigned to 10 weeks of double-masked treatment with IV ceftriaxone or IV placebo
- After screening 3368 patients and 305 volunteers, 37 patients and 20 healthy individuals enrolled. Enrolled patients had mild to moderate cognitive impairment and marked levels of fatigue, pain, and impaired physical functioning. Across six cognitive domains
- No patient had a positive CSF PCR.

- Patients reported having been symptomatic with Lyme disease for a mean of 1.7 (SD 3.5) years before diagnosis, and they reported having been ill for a total of 9.0 (SD 6.8) years
- Patients randomized to ceftriaxone had much worse baseline cognitive function than those on placebo or the normal controls. They therefore improved “the most” $p=0.053$ vs placebo at 12 weeks but were not more improved at 24 weeks.
- Those on treatment had less memory than those on placebo at 12 weeks, but had “improved more” (?regression to the mean)

What are the symptoms C/W controls

- Because of persistent symptoms many demand long term treatment
- RCT of doxy vs cefuroxime for ECM showed no difference in outcome
- Also no difference in nonspecific symptoms at 6 months although many had some symptoms
- However compared to a control arm with no history of ECM or positive serology- no difference in new symptoms at 6 or 12 months

- Some physicians providing care as “specialists” surviving on testimonials- large practices in low endemic areas, or family Docs in US- “Canadian Docs ignorant”- Diagnose by “symptoms over email”- mail in fee
- Referrals for 2nd opinion re: patients with chronic neurological illness on Chronic “IV Ceftriaxone + IV Levofloxacin+ IV Metronidazole for 4+ years”
- Consensus opinion is that “Chronic Lyme” does not benefit from antibiotics, and is not an infectious disease ([IDSA+ Ad hoc Lyme advisory group] NEJM 2007;357:1422)

Risks of chronic antibiotics exceed benefits

- C.difficile
- Allergy
- Selection for resistant organisms
- Line complications- Sepsis/ endocarditis. Venous Thrombosis
- Recommendation to advise patient “ don’t go onto the internet”

- Reinfection- hard to rule out- repeat short term Rx if ECM recurs or if synovial fluid or CSF PCR+

