

Tick-Borne Diseases In the United States: A Call to Action

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Disclosures:

- Nothing to disclose

Topics to be Covered:

- Overview and Epidemiology of tick-borne illness in the United States.
- Common ticks, their distribution, and their associated illnesses.
- Lyme Disease
 - Disease presentation
 - Current diagnostic modalities
 - Current treatment options
 - Chronic Lyme Disease and Post-Lyme Disease Syndrome
 - Role for long-term antibiotics

Tick-borne Illness: An Overview

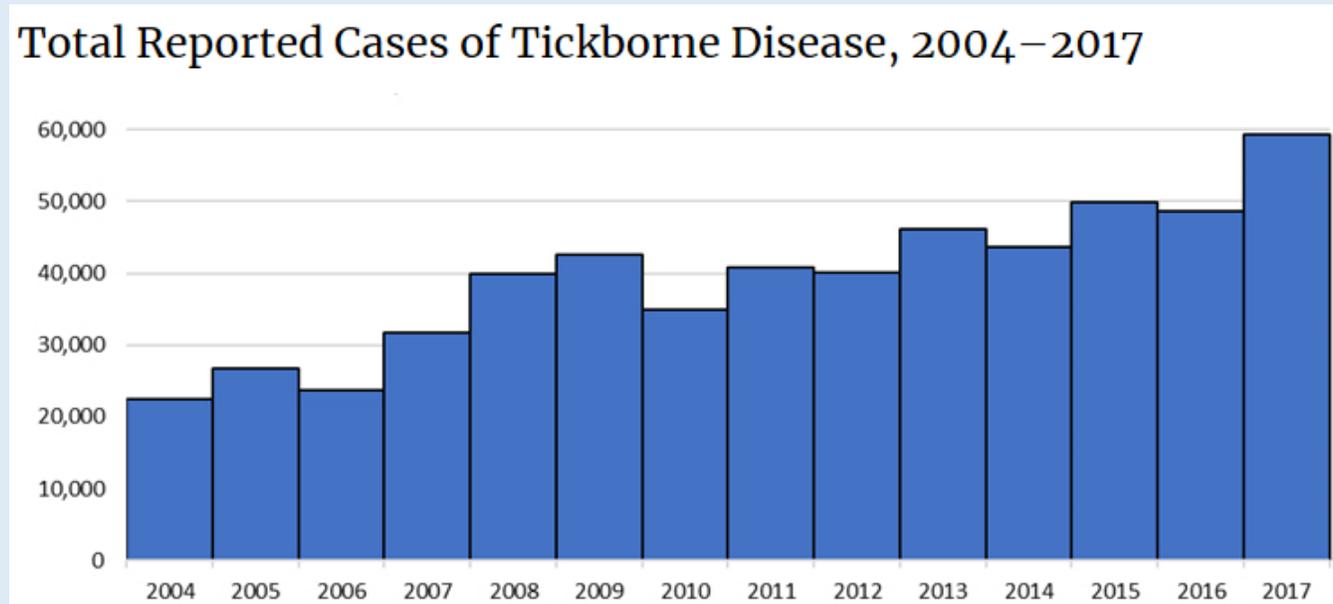
- Infectious disease (bacterial, parasitic, or viral) transmitted by either hard or soft ticks.
- Depending on the tick species, transmission occurs from the bite of a tick at one of the stages in its lifecycle (six-legged larva, eight-legged nymph, or adult).
- Infections are most common from Spring to Summer, but can technically occur any time as long as temperature is above freezing.
- The geographic distribution of tick species dictates the infections for which one is at risk.

Tickborne Illness: Etiologies in the United States

- Lyme Disease
- Anaplasmosis / Ehrlichiosis
- Rickettsial Spotted Fevers (including Rocky Mountain Spotted Fever)
- Babesiosis
- Tularemia
- Powassan Virus (also Bourbon Virus and Heartland Virus)
- STARI (Southern Tick Associated Rash Illness)
- Relapsing Fever
- Colorado Tick Fever

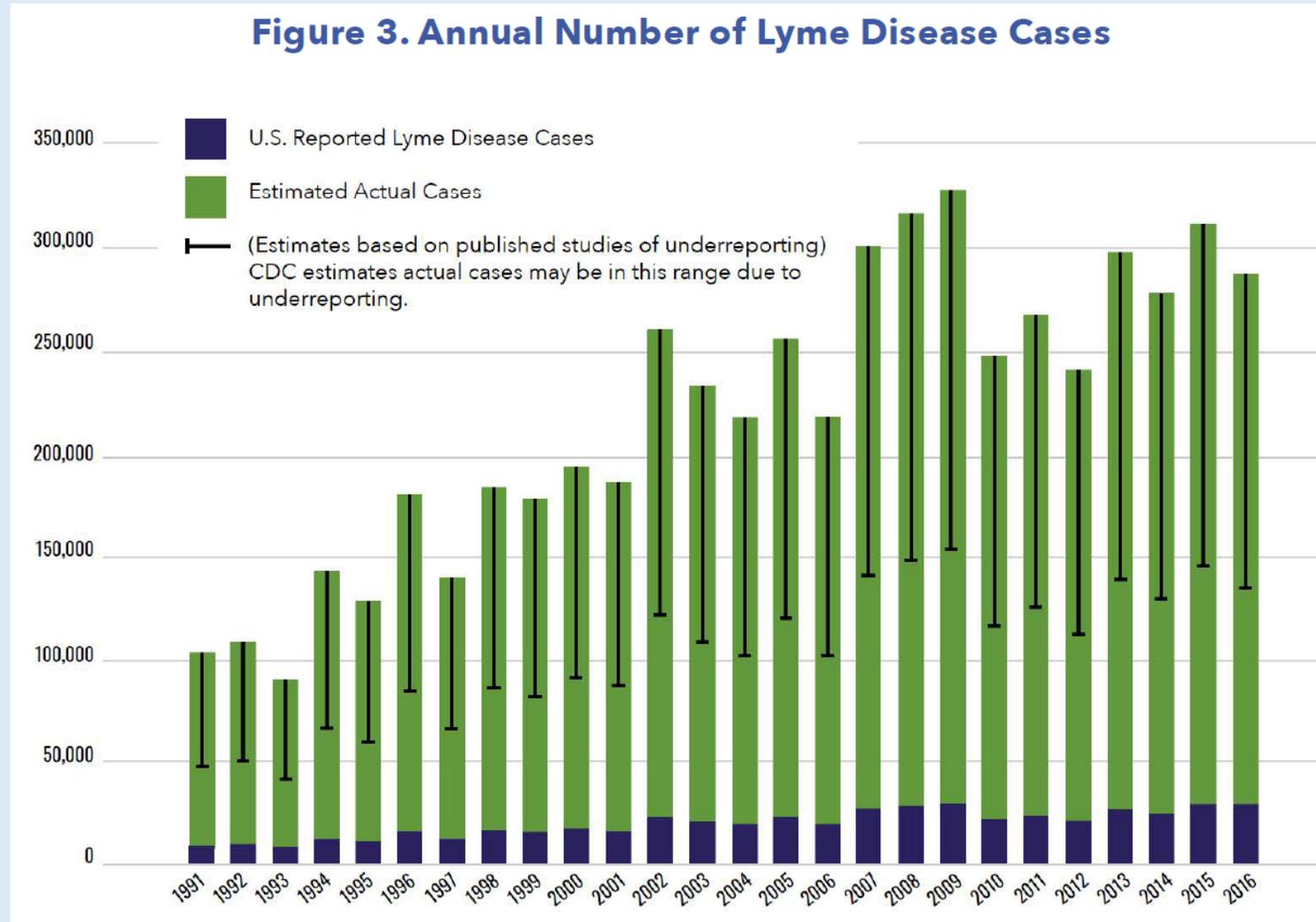
Tick-borne Illness: A Growing Problem

- The number of cases reported to the CDC continues to rise, was at 59,349 in 2017, of which 42,743 were due to Lyme Disease.



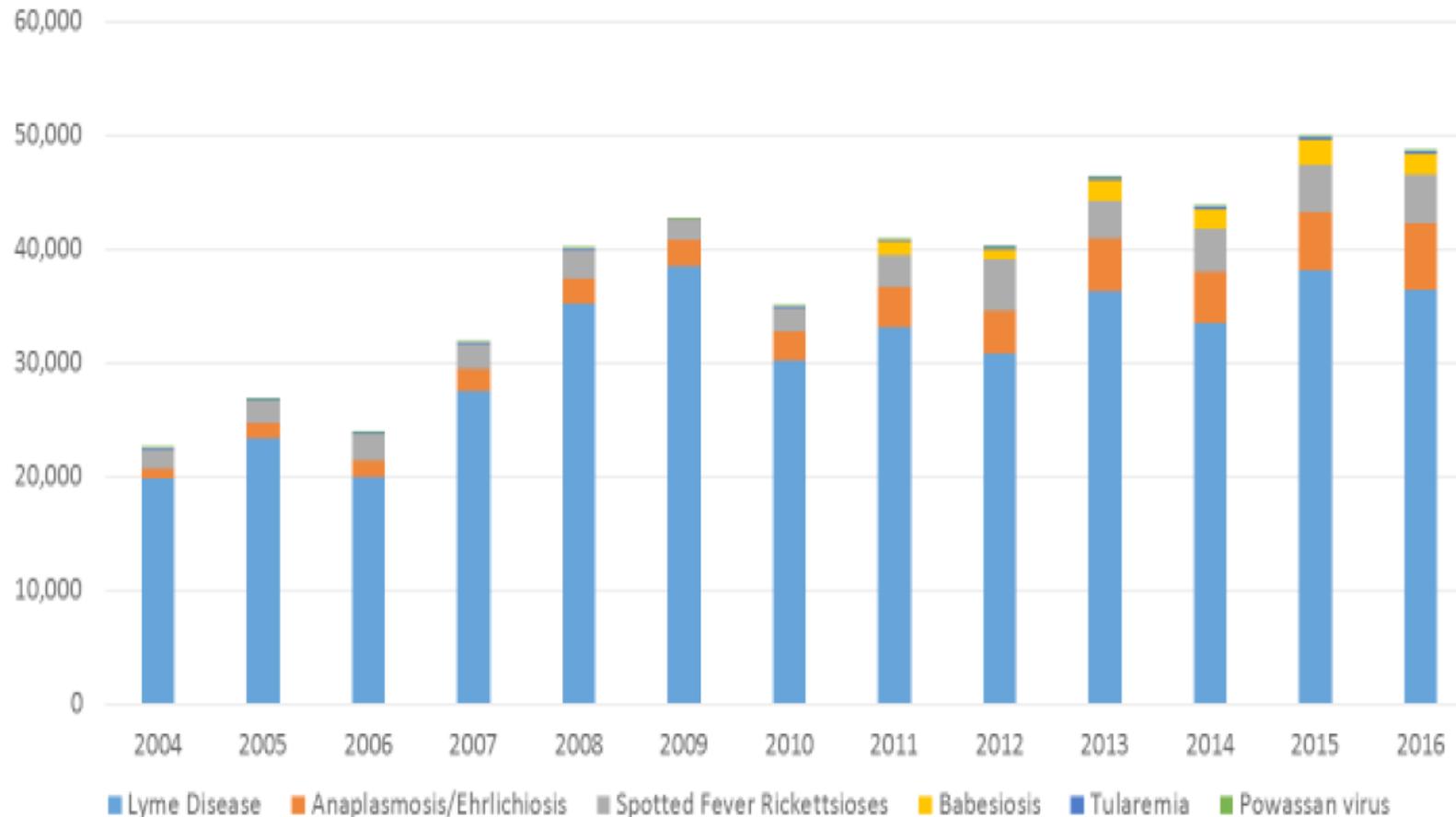
- An average of about 35,000 cases of Lyme Disease are reported annually, however, recent studies suggest the number of actual cases is far greater than reported, possibly over 300,000 cases of Lyme Disease per year. Nelson et al., 2015.

Annual Number of Lyme Disease Cases in the US:



Tick-Borne Disease Cases by Year:

C.2: Annual Reported Tick-Borne Disease Cases by Year, U.S.: 2004-2016



Tick-borne illness: General Presentation

- Common general symptoms include fever, chills, generalized arthralgia and myalgia.
- Rash may be distinctive (erythema migrans seen in Lyme and STARI).
- Disease specific findings may help guide the differential (i.e. heart block suggestive of Lyme, hemolytic anemia suggestive of Babesiosis, relapsing fever suggestive of *B. hermsii*, etc.)

Tick-borne Illness: Diagnostic Approaches

- Need a multifaceted approach.
- First consider the infectious etiologies the patient is at risk for based on geographic exposure and known tick species distribution.
- Evaluate for potential guiding signs, symptoms, or lab abnormalities.
- Send appropriate screening serologies and or serum PCR studies based on the suspected causes. Peripheral smears can be helpful in evaluating for Babesiosis, relapsing fever, and Anaplasmosis/Ehrlichiosis.

Tick-borne illness: General Treatment Themes

- Doxycycline is the standard treatment for many etiologies: Lyme, Anaplasmosis, Ehrlichiosis, Rickettsial illness, relapsing fever, and STARI.
- Ceftriaxone is a standard agent for severe Lyme (with cardiac or CNS manifestations or refractory arthritis), as well as relapsing fever with CNS involvement.
- Viral tick-borne illnesses are all treated with supportive care.
- Babesiosis requires a combination regimen of either atovaquone+azithromycin for mild to moderate disease, or clindamycin+quinine for severe diseases.

Brief Overview of the Major Tick Vectors

Ixodes scapularis – Blacklegged tick

- Eastern United States, Wisconsin, and Minnesota.
- Transmits: *Borrelia burgdorferi* (Lyme disease), *Anaplasma phagocytophilum* (anaplasmosis), *B. miyamotoi* (relapsing fever), *Ehrlichia muris eauclairensis* (Ehrlichiosis), *Babesia microti* (Babesiosis), Powassan virus (Powassan fever).
- All stages can bite humans. Highest risk Spring through Fall.



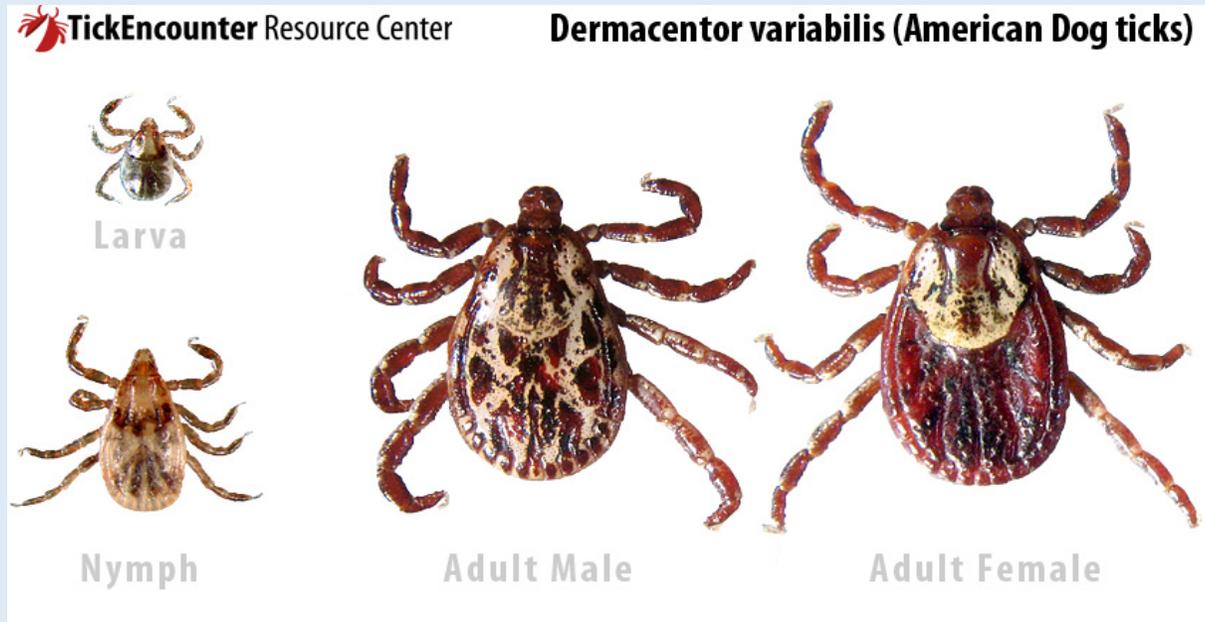
Amblyomma Americana – Lone Star Tick

- Eastern and Southeastern US.
- Transmits Ehrlichia chaffeensis and E. ewingii (Ehrlichiosis), Francisella tularensis (tularemia), Borrelia lonestari (Southern Tick-associated rash illness STARI), Bourbon virus, and Heartland virus.
- Highest risk from Spring through Fall.
- Reports of developing allergic reactions to red meat developing after bites from the Lone Star Tick.



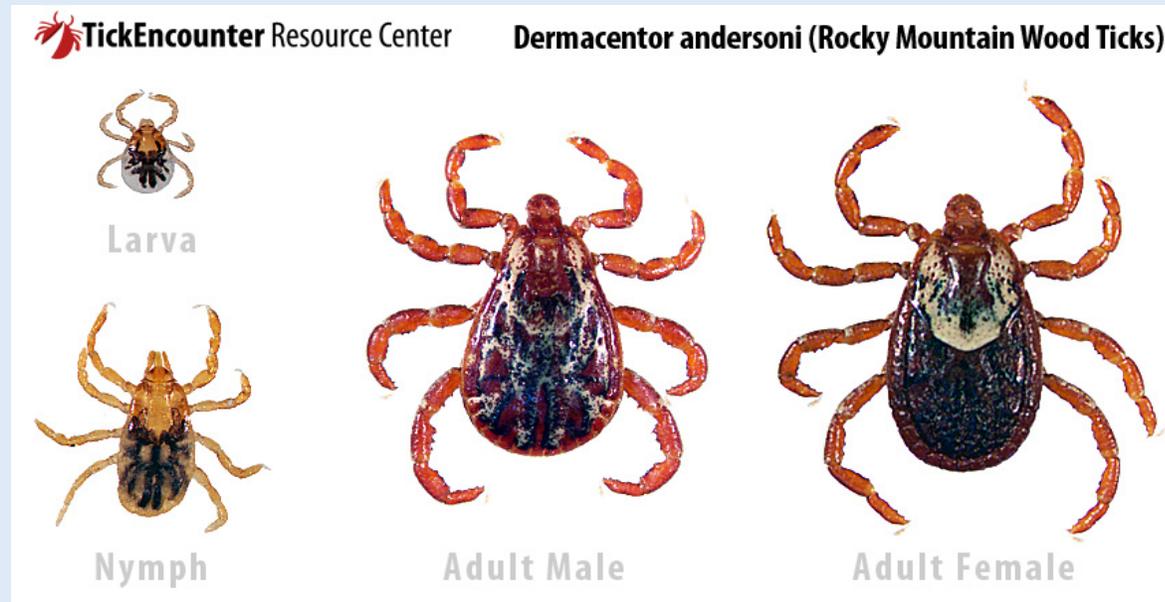
Dermacentor variabilis – American dog tick

- East of the Rocky Mountains. Sporadic areas of the Pacific Coast.
- Transmits *Rickettsia rickettsi* (Rocky Mountain Spotted Fever) and *Francisella tularensis* (tularemia).
- Highest risk during Spring and Summer.



Dermacentor andersoni – Rocky Mountain Wood Tick

- Rocky Mountain states.
- Transmits Rickettsia rickettsi (RMSF), Colorado tick fever virus, and Francisella tularensis (tularemia).
- Adult ticks are the more common vector to humans.



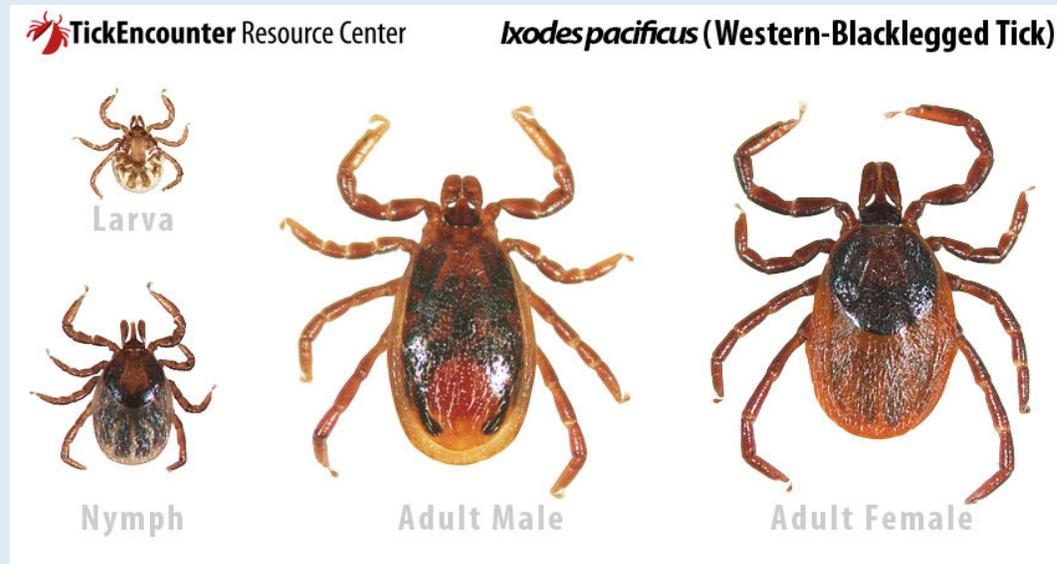
Ornithodoros spp. – Soft tick

- Western United States.
- Often in rustic cabins or rodent infested structures.
- Transmits *Borrelia hermsii* and *Borrelia turicatae* (relapsing fever).
- High risk of exposure in rustic cabins. Often occurs unnoticed at night.



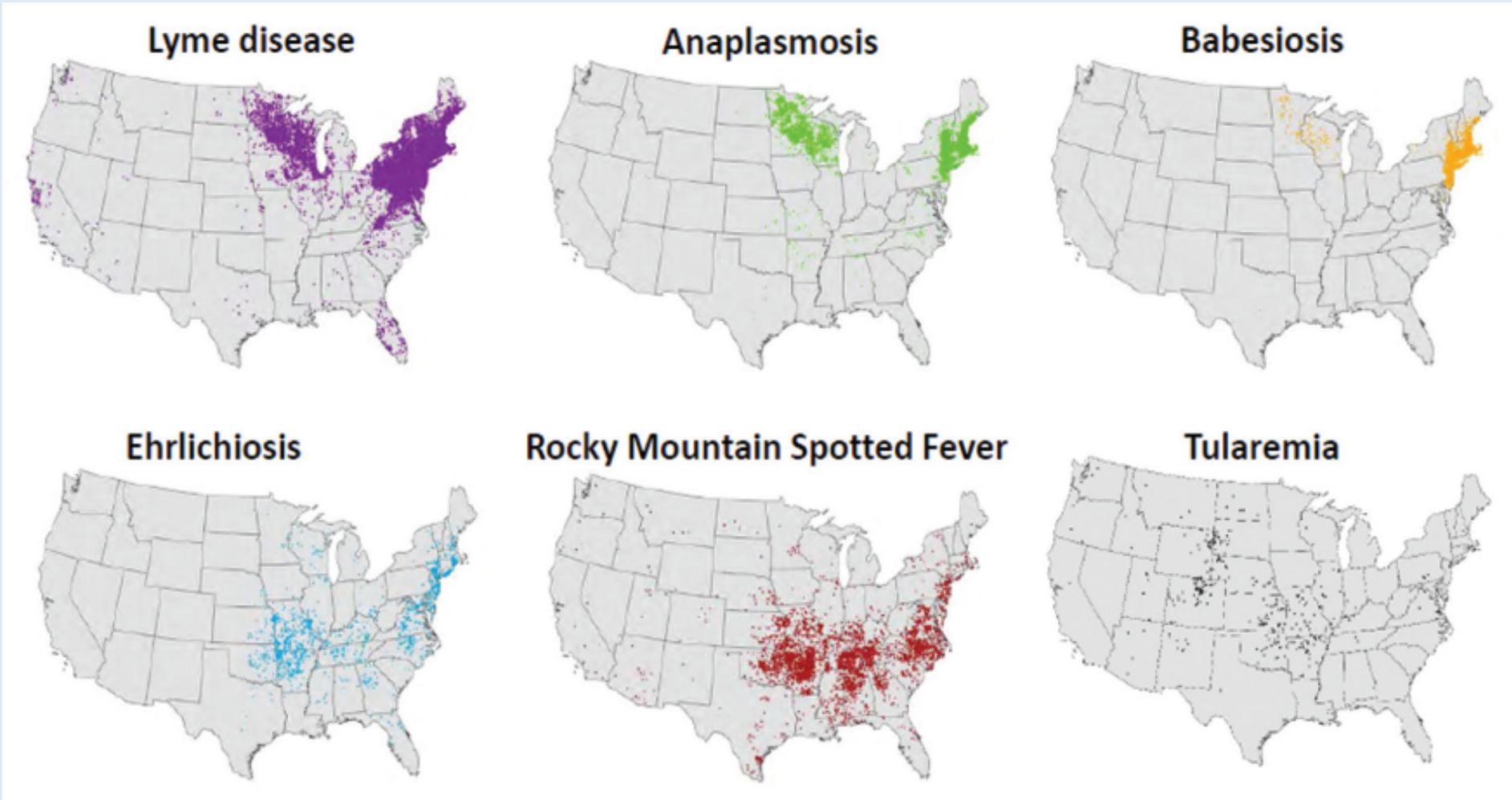
Ixodes pacificus – Western Blacklegged Tick

- Pacific coast states of the United States.
- Transmits *Borrelia burgdoferi* (Lyme disease), *Anaplasma phagocytophilum* (anaplasmosis) and likely *B. miyamotoi* (relapsing fever).



Brief Overview of the Major Tick-Borne Illnesses

Distribution of Major Tick-borne Illnesses in the USA:



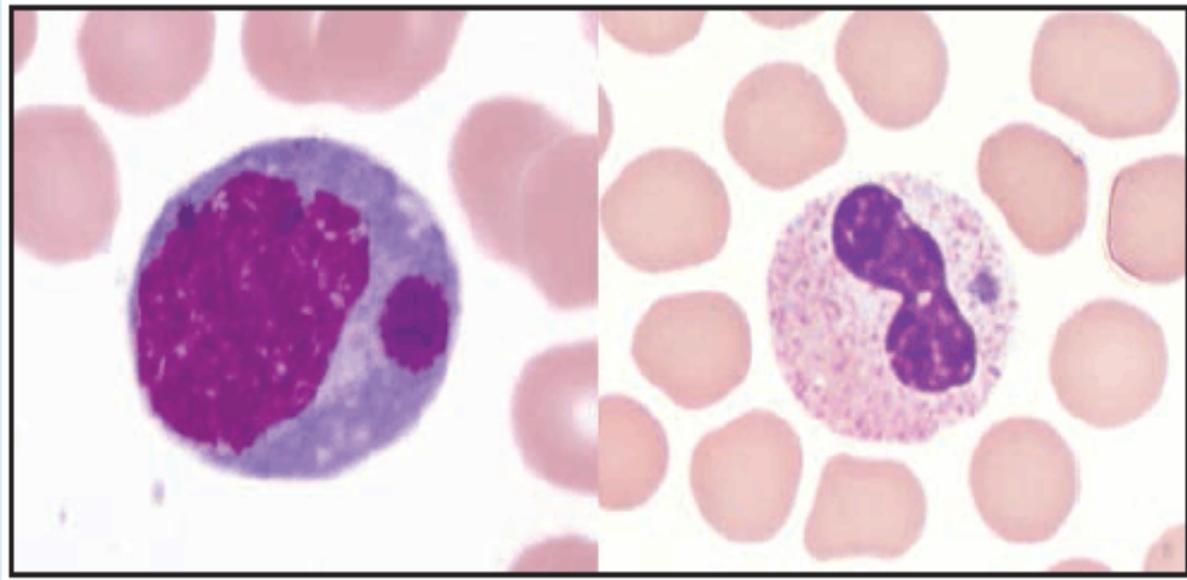
Each dot represents a reported case in the county of residence

Eisen R. Emerging tickborne diseases. CDC Public Health Grand Rounds, March 21, 2017.
www.cdc.gov/cdcgrandrounds/archives/2017/March2017.htm. Accessed June 7, 2017.

Anaplasmosis and Ehrlichiosis:

- Bacterial illness causing similar syndromes with symptoms that may include fever/chills/rigors, headaches, malaise, myalgia, possible GI symptoms (nausea/vomiting) and rash in some cases (more common in Ehrlichiosis).
- May have cytopenias (especially lymphopenia in Anaplasmosis), mild to moderate transaminase elevations.
- Anaplasmosis found in distribution with its vector (*I. scapularis*)
- Ehrlichiosis found in distribution with its vector (*A. americanum*)
- Serum DNA PCR within the first week, four-fold rise in acute to convalescent titers, IHC staining of tissue. May see morulae in granulocytes (Anaplasmosis or *E. ewingii*) or monocytes (*E. chaffeensis*).
- Anaplasmosis treatment: Doxycycline 100mg PO BID for a 10 day course.
- Ehrlichiosis treatment: Doxycycline 100mg PO BID for at least 3 days after resolution of fever and a minimum of 5 to 7 days.

Anaplasmosis and Ehrlichiosis

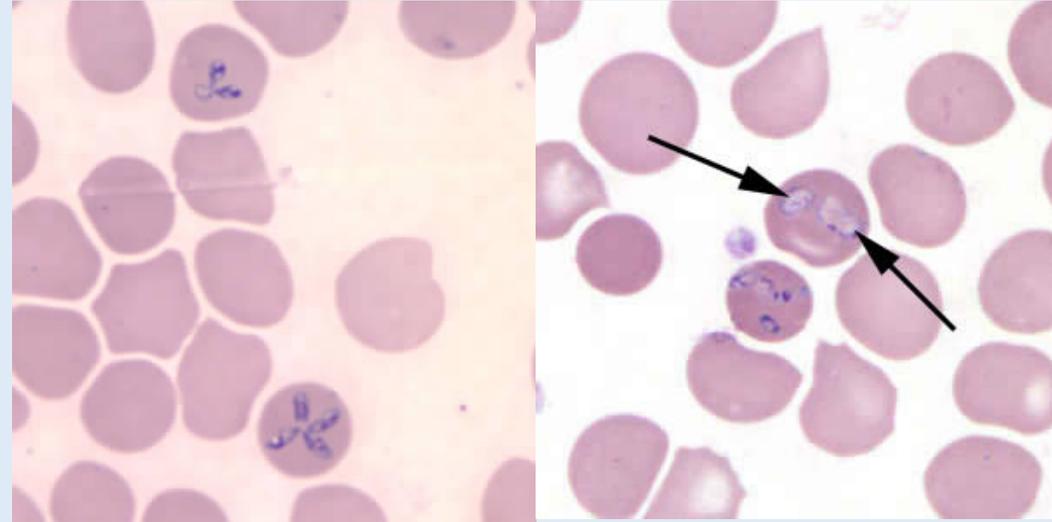


Human Monocytic Ehrlichiosis

Human Granulocytic Anaplasmosis

Babesiosis:

- Intra-erythrocyte parasitic illness with symptoms that may include fever/chills/sweats, malaise, myalgia, nausea, anorexia, dark urine, mild spleno and hepatomegaly, and jaundice.
- Can be asymptomatic.
- May have hemolytic anemia, thrombocytopenia, and mild elevation in transaminases.
- Found in distribution with its vector (*I. scapularis*).
- Diagnose with serum PCR and or blood smear. Positive serology is helpful but does not differentiate from prior disease.
- Treat either with atovaquone+azithromycin or clindamycin+quinine (severe disease) for 7 to 10 days.



Tularemia:

- Transmitted by *Dermacentor variabilis*, *D. andersoni*, and *Amblyomma americanum*.
- Syndromes:
 - Ulceroglandular
 - Oculoglandular
 - Oropharyngeal
 - Pneumonic
 - Typhoidal (generalized symptoms without localizing findings of the other syndromes)
- Diagnosis: Culture, PCR or DFA of tissue, or a 4 fold increase in titers.
- Treatment:
 - Severe disease: Streptomycin 1g IM BID for 10 days.
 - Mild to moderate disease: Doxycycline 100mg BID for 14 to 21 days.



Tick-borne Rickettsioses in the USA:

- *Rickettsia rickettsii*: Rocky Mountain Spotted Fever. Febrile illness with rash (extremities-->trunk). Can be complicated by bleeding, CNS involvement, cardiac involvement, pulmonary edema. Can be fatal without treatment.
- *Rickettsia parkeri*: Spotted fever with headache, myalgia, and eschar.
- *Rickettsia philipphi*: Pacific Coast Tick Fever (California); febrile illness with headache, myalgia, and eschar. Less likely to have spotted rash.
- Primary treatment is with doxycycline for at least 3 days after fever resolves, for a minimum of 5 to 7 days.

Tick-borne Rickettsioses in the USA:

FIGURE. Child with Rocky Mountain spotted fever has the rash that is characteristic but typically does not appear until several days after fever onset



Photo/CDC

Eschar of *Rickettsia parkeri*

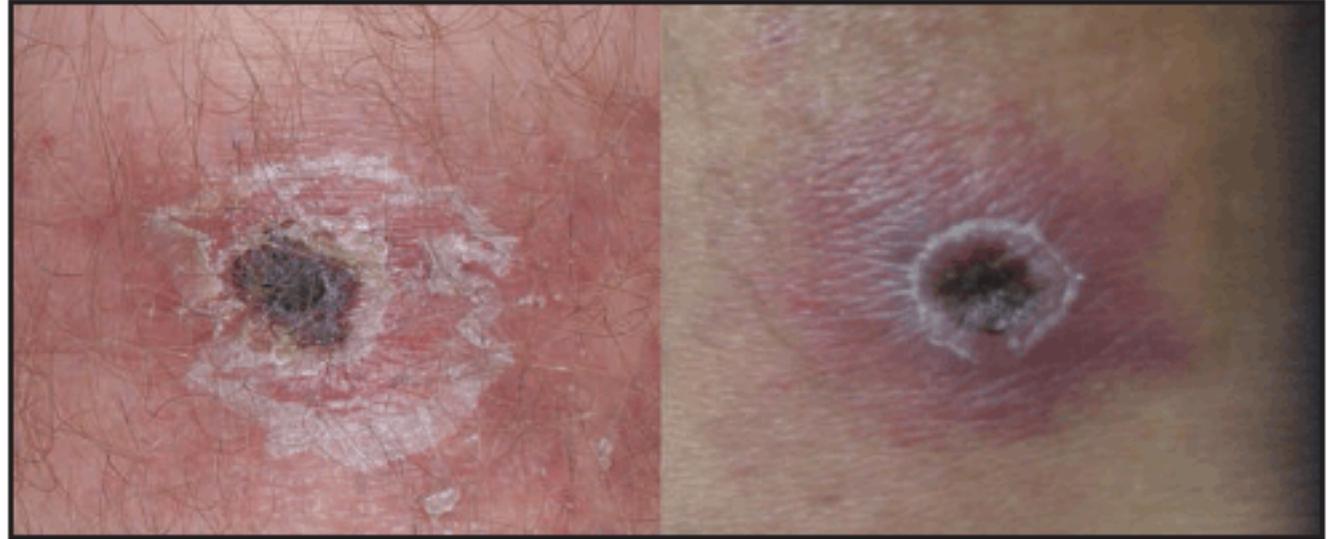
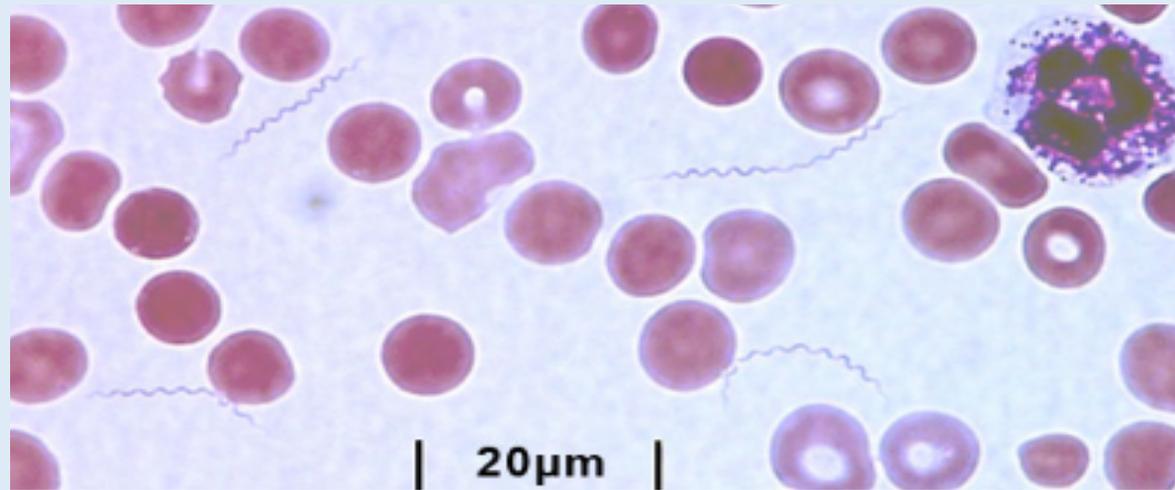


Image Source: CDC

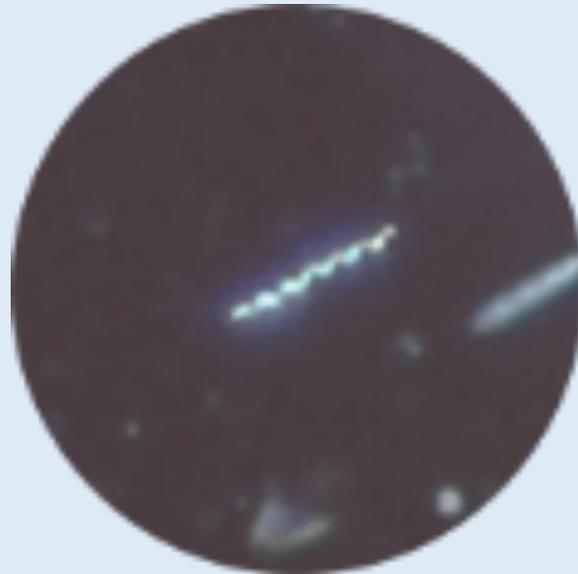
Tick-borne Relapsing Fever:

- Soft tick-borne relapsing fever due to *B. hermsii* and *B. turicatae*.
 - Symptoms often include relapsing fever, chills, fatigue, headaches, arthralgia, nausea/vomiting. Can involve the CNS.
 - May normal to increased WBC count, thrombocytopenia, may have prolonged PT and PTT.
 - Diagnose with observation of spirochetes during febrile episode. Convalescent serologies 10 to 14 days after onset.
 - Treat: If CNS involvement: IV penicillin or ceftriaxone for 10 to 14 days. If no CNS involvement, can treat for 10 days and potentially use doxycycline as alternative.



Tick-borne Relapsing Fever:

- Hard tick-borne relapsing fever due to *B. miyamotoi*.
 - Symptomatically difficult to differentiate from the other mentioned tick-borne illnesses. May present with relapsing fever.
 - Diagnosis with PCR of blood, observation of spirochetes during febrile episode, and convalescent serology.
 - Treat: As per Lyme disease. Most patients respond to 14 days of doxycycline. Ceftriaxone for 14 to 28 days preferred for CNS disease.



Tick-borne Viral Illnesses in the USA:

- Colorado tick fever: Found in the western USA particularly at higher elevations (4k-10k feet). Febrile illness that may be biphasic.
- Powassan Virus Disease: Found in the Northeastern USA and Great Lakes Region. Febrile illness that often progresses to meningo-encephalitis.
- Heartland Virus Disease: Found in the Midwest and Southern USA. Non-specific febrile illness. Fatalities reported.
- Bourbon Virus Disease: Found in the Midwest. Non-specific febrile illness. Fatalities reported.

Southern Tick Associated Rash Illness (STARI):

- A more recently recognized tick-borne illness.
- Presents similarly to Lyme disease, often with erythema migrans-like rash that occurs in distribution with its vector, *Amblyomma americanum*.
- Etiologic agent is unknown, and therefore diagnosis is clinical.
- Treat with doxycycline as one would early Lyme disease.
- Not known to have long-term sequela.



Meat allergy Acquired from Tick bite:

- *Amblyomma americanum* tick bites can induce allergies to non-primate mammalian meat or protein containing products.
- Due to IgE against galactose-alpha-1,3-galactose (Alpha-gal).
- Patients can experience an allergic reaction varying from hives to GI upset, airway obstruction, or frank anaphylaxis that develops from minutes to up to 6 hours after exposure to animal meat or proteins.

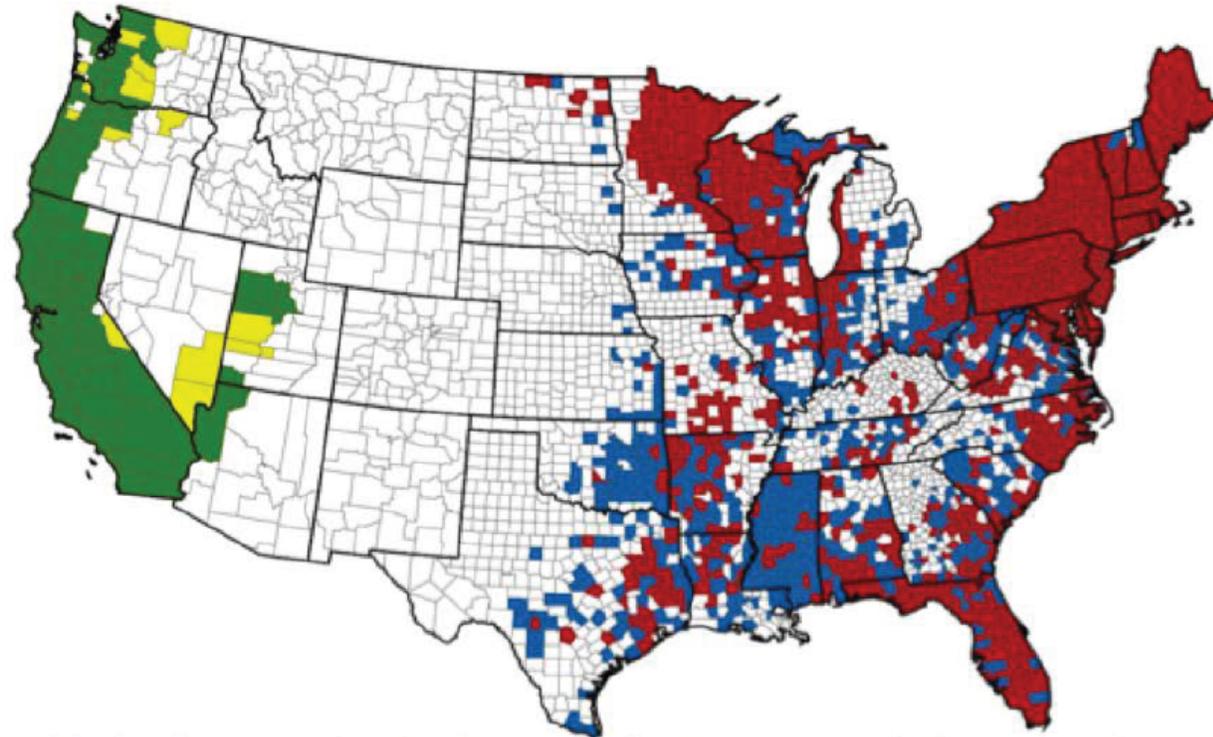
Lyme Disease

Lyme Disease – *Borrelia burgdorferi*

- Transmitted by *Ixodes scapularis* (Northeast and Upper Midwest) and *I. pacificus* (Pacific Coast states). Tick must generally be attached for about 36 hours.
- Infection progresses through 3 stages:
 - Early localized
 - Early disseminated
 - Late disease
- Diagnosis: Screening serologies, confirmatory Western blot, PCR of CSF or synovial fluid.
- Treatment: Doxycycline for uncomplicated cases. Ceftriaxone for severe CNS, cardiac, or arthritic involvement. IDSA Guidelines date back to 2006.
- Post-Lyme Disease Syndrome.

Distribution of the Lyme Disease Vectors: *Ixodes scapularis* and *Ixodes pacificus*

2015 - Distributions of Two Tick Species



- ■ **Established;** ≥ 6 individuals or ≥ 1 life stage recorded in a single year
- ■ **Reported;** < 6 individuals of a single life stage recorded in a single year

Role for Prophylaxis After Tick Bite:

- Routine prophylaxis or serologic testing is not recommended by IDSA guidelines.
- A single 200mg dose of doxycycline can be offered if:
 - The attached tick is identified as a vector of Lyme disease and has been attached at least 36 hours.
 - Prophylaxis can be started within 72 hours of tick removal.
 - Local rate of tick infection with *B. burgdorferi* reported as $\geq 20\%$.
 - No contraindication exists to doxycycline.

Diagnosis of Lyme Disease:

- Early Lyme disease: Diagnosis based on clinical finding of the erythema migrans rash.
- Early disseminated and late Lyme disease:
 - Need presence of a disseminated or late manifestation plus lab confirmed infection.
 - Musculoskeletal: Recurrent brief attacks of joint swelling in one or more joints, may be followed by chronic arthritis.
 - CNS symptoms: meningitis, cranial neuritis, facial palsy, radiculoneuropathy, encephalomyelitis.
 - Cardiac symptoms: acute onset heart block +/- myocarditis that resolve in days to weeks.

Diagnosis of Lyme Disease:

- A recent history of residence or travel to an endemic region.
- Risk factors for exposure to ticks.
- Symptoms consistent with early disseminated or late Lyme disease.
- Do not test people with erythema migrans, asymptomatic patients, or patients with only non-specific symptoms.

Diagnosis of Lyme Disease:

- Initial test with screening Lyme ELISA.
- If positive, a more specific Western Blot test is performed.
 - IgM positive if two of the following: ospC (24), 39, 41
 - IgG positive if five of the following: 18, 23, 28, 30, 39, 41, 45, 58,66, 93
 - The IgM criteria alone should not be considered positive in treatment naïve patients with symptoms ongoing for more than 6 weeks.
- False positive tests due to cross-reactivity with other Borrelia or spirochetes. Also non-specific immune globulin production from EBV or malaria.
- VlsE C6 peptide ELISA: High sensitivity and specificity for even early disease.
- PCR of synovial fluid or CSF: Potentially useful but inconsistent accuracy and high rates of false positivity.
- Not yet validated techniques: Urine antigen, urine PCR, and blood PCR.

Early Localized Lyme Disease:

- Erythema migrans in up to 80% of patients. May be single lesion or can be multiple if spirochetemia is present.
- Usually presents within 1 month of infection.



Early Localized Lyme Disease:

- Many patients will have non-specific viral-like syndrome symptoms including fatigue, anorexia, headache, myalgia, arthralgia, lymphadenopathy, fever.
- Gastrointestinal and respiratory symptoms are uncommon with Lyme disease.
- Elevated ESR and CRP can be elevated. May have mild AST and ALT elevation. Abnormalities in WBC count, platelets, and hemoglobin are less common.
- Treatment: Doxycycline 100mg PO BID for 10 to 21 days.
 - Alternatives: amoxicillin 500mg PO TID or cefuroxime 500mg PO TID for 14 to 21 days.

Early Disseminated Lyme Disease:

- Occurs weeks to months after infection, and may be the presenting manifestation.
- Primary manifestation will be migratory myalgia and/or arthralgia. May also have neurologic or cardiac symptoms.
- **CSN Manifestations:** Lymphocytic meningitis, cranial nerve palsies (especially facial nerve), radiculopathy, peripheral neuropathy, rarely encephalomyelitis or cerebellar ataxia.
- **Cardiac manifestations:** 1st to 3rd degree AV heart block, less commonly mild myopericarditis. Chronic cardiomyopathy has been reported from Europe.
- **Ocular manifestations:** Inflammation of any layer of the eye can occur, most are rare, though conjunctivitis seen in up to 10% of cases of early Lyme disease.
- **Skin manifestations:** Borrelial lymphocytoma of the skin has been reported in European cases.

Early Disseminated Lyme Disease:

- **Neurologic Lyme disease:**

- Isolated cranial nerve palsy, mild radiculoneuropathy, and possibly mild meningitis, can be treated with oral doxycycline for 14 to 21 days.
- Encephalitis or otherwise more severe neurologic disease requires IV therapy with ceftriaxone 2g IV daily for 14 to 28 days.

- **Lyme Carditis:**

- Asymptomatic patients with 1st degree AV block with PR interval < 300 can be treated with oral therapy (doxycycline, amoxicillin, or cefuroxime for 14 to 21 days).
- Symptomatic patients or patients with PR interval > 300, or 2nd or 3rd degree AV block require IV therapy with ceftriaxone 2g IV daily for 14 to 28 days.

Late Lyme Disease:

- Months to years after contraction.
- **Lyme arthritis:** A persistent or intermittent arthritis of one of a few large joints (knee most common, then shoulder, ankle, elbows, and others).
- **CNS Manifestations:** Lyme encephalopathy. Chronic axonal polyneuropathy (spinal radicular pain or distal paresthesia). Rare reports in Europe of a chronic encephalomyelitis with spastic paraparesis, cranial neuropathy, and cognitive impairment.
- **Cutaneous manifestations:** Acrodermatitis chronica atrophicans seen in Europe, mostly in women > 40yo. An often unilateral blue-red swelling followed by atrophy. Fibrous induration or nodular disease over bony prominences (patella, elbow, etc). Can result in nerve or joint damage.

Late Lyme Disease Treatment:

- In general, finite and relatively short courses are recommended.
- Lyme arthritis: Doxycycline 100mg PO BID for 28 days.
 - If persistent or recurrent joint swelling is noted after treatment, retreatment with another 4 week course of oral antibiotics, or a 2 to 4 week course of IV ceftriaxone 2g daily is recommended.
- Late Lyme CNS disease: 2 to 4 weeks of IV ceftriaxone 2g daily.
 - Response may be slow. Re-treatment is not recommended unless objective evidence of relapse is demonstrated.

Coinfection with other tick-borne pathogens:

- *Anaplasma phagocytophilum*
 - Powassan and Deer tick virus
 - *Babesia microti*
 - *Borrelia miyamotoi*
 - Tick-borne encephalitis (Europe and Asia only)
-
- Evaluate for coinfection if fever persists for 48 hours after initiating therapy for Lyme disease or if unexplained cytopenia is noted.

Chronic Lyme Disease:

- Whether or not or to what extent it exists is a very controversial topic.
- **Indisputable:** Chronic Lyme disease can exist in patients with confirmed Lyme disease who never received appropriate antibiotics.
- **Controversial:** Whether or not Lyme disease can persist chronically after receiving appropriate therapy. Whether or not Lyme disease is present in patient's testing negative by conventional diagnostic studies.
- **Majority view:** Lyme disease does not persist chronically once treated with an appropriate course of antibiotics.

Two Schools Of Thought:

- IDSA guidelines: Diagnose Lyme disease using objective manifestations of disease confirmed by two-tiered serological testing. (exception: acute lyme with erythema migrans rash which alone is diagnostic) . Therapy: Generally 10 to 21 days of antibiotic treatment (potentially longer for late/chronic arthritis).
- ILADS: Diagnose using clinical judgment based on reported signs and symptoms of disease and less reliance on objective tests. Recommended antibiotic durations tend to be longer, and there are no restrictions to long-term use of antibiotics.

Post-Lyme Disease Syndrome (PLDS):

- A collection of non-specific symptoms that persist for months to years after appropriate treatment of Lyme disease. Develops in 5 to 15% of patients.
- Headache, fatigue, brain fog, arthralgia, and myalgia are among the common symptomatic complaints.
- Currently felt that symptoms are not due to an active infectious process, but possibly a post-infectious autoimmune process, or unrelated to Lyme disease altogether.

Diagnostic Criteria of PLDS:

- Must have a prior history of Lyme disease treated with an appropriate antibiotic regimen and initial resolution or stabilization of the objective manifestations of Lyme disease.
- Onset of subjective symptoms within 6 months of diagnosis of Lyme disease and persisting at least 6 months after completing antibiotics, including: headaches, fatigue, myalgia, arthralgia, cognitive difficulties/brain fog.
- Exclusion criteria:
 - An active untreated coinfection.
 - The presence of objective abnormalities.
 - Diagnosis of fibromyalgia before onset of Lyme disease.
 - A history of prolonged history of undiagnosed or unexplained somatic complaints before diagnosis of Lyme.
 - Diagnosis of an underlying disease or condition that can explain the patient's symptoms.
 - Lab or imaging findings consistent with an undiagnosed process.
 - A positive culture or PCR for *Borrelia burgdorferi*.

The Question of Long-term antibiotics:

- Chronic suffering from diverse symptoms such as musculoskeletal pain, arthritis/arthralgia, myalgia, neuralgia, sensory disturbances, neuropsych disorders, cognitive disorders, and fatigue have led some to seek benefit from long-term courses of antibiotics.
- Long-term antibiotics are sometimes administered to patients with confirmed Lyme disease who already completed the standard treatment regimen.
- Long-term antibiotics are sometimes administered to patients who have not tested positive for Lyme by conventional accepted methods, but have tested positive by unvalidated measures or by clinical presentation alone.

The Question of Long-term antibiotics:

- There have been several open label non-comparative studies that suggest a possible benefit to prolonged courses.
- However, benefit has not been confirmed with randomized controlled trials.
- In the absence of proven benefit, long-term antibiotics increase risk for adverse events including potentially severe drug side effects, C difficile infection, complications from intravenous catheters, and the development of antimicrobial resistance.

Long-term Antibiotics Not Yet Proven to have Benefit:

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

Berende A., ter Hofstede H., Vos F., et al. N Eng J Med 2016; 374:1209-20

- Recent randomized double-blind controlled trial of 280 patients in the Netherlands assessed the benefit of long-term antibiotics in patients with persistent symptoms attributed to Lyme disease.
- Inclusion criteria: Persistent symptoms attributed to Lyme disease and either temporally related to an erythema migrans rash or otherwise proven case of Lyme by standard IgM or IgG serologic criteria.
 - Musculoskeletal pain, arthritis, arthralgia, neuralgia, sensory disturbances, dysesthesia, neuropsychological disorders, cognitive disorders, with or without persistent fatigue.

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

- All patients received an initial 14 day course of IV ceftriaxone.
- Patients were randomized to receive either 12 weeks of doxycycline, clarithromycin plus hydroxychloroquine, or placebo.
- Primary outcome measured was health-related quality of life as assessed by the physical-component summary score of a standardized questionnaire, the RAND-36 Health Status Inventory (evaluating physical functioning, role limitations due to physical health problems, pain, and general health perception).
- Secondary outcomes measured were physical and mental aspects of health-related quality of life as well as fatigue.
- Outcomes were evaluated at baseline, then 14 weeks, 26 weeks, 40 weeks and 52 weeks after start of treatment.

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

- Baseline duration and symptoms across the 3 groups were comparable

Table 1. Baseline Characteristics in the Modified Intention-to-Treat Population.*

Characteristic	Doxycycline Group (N=86)	Clarithromycin–Hydroxychloroquine Group (N=96)	Placebo Group (N=98)
Female sex — no. (%)	40 (47)	42 (44)	47 (48)
Age — yr	48.1±12.8	48.2±13.0	50.0±9.7
White race — no. (%)†	84 (98)	96 (100)	98 (100)
Current symptoms — no. (%)‡			
Arthralgia	80 (93)	87 (91)	84 (86)
Musculoskeletal pain	72 (84)	77 (80)	76 (78)
Sensory disturbances	62 (72)	72 (75)	79 (81)
Neuralgia	7 (8)	16 (17)	18 (18)
Neurocognitive symptoms	76 (88)	81 (84)	85 (87)
Fatigue	84 (98)	91 (95)	92 (94)
Duration of symptoms — yr			
Median	2.7	2.7	2.1
Interquartile range	1.3–7.7	1.3–5.4	0.9–5.5

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

- Baseline antibiotic treatment history across the 3 groups was comparable

Lyme disease history — no. (%)‡			
Tick bite	47 (55)	46 (48)	60 (61)
Erythema migrans§	25 (29)	26 (27)	27 (28)
Acrodermatitis chronica atrophicans¶	0	1 (1)	2 (2)
Meningoradiculitis	1 (1)	9 (9)	5 (5)
Previous antibiotic treatment — no. (%)	75 (87)	86 (90)	89 (91)
Duration — days			
Median	40	30	31
Interquartile range	27–57	21–44	28–58
No. of courses			
Median	2.0	2.0	2.0
Interquartile range	1.0–2.0	1.0–2.0	1.0–2.5
Intravenous treatment — no. (%)	11 (13)	16 (17)	15 (15)
Positive <i>Borrelia burgdorferi</i> serology — no. (%)			
IgM	25 (29)	21 (22)	35 (36)
IgG	55 (64)	65 (68)	58 (59)

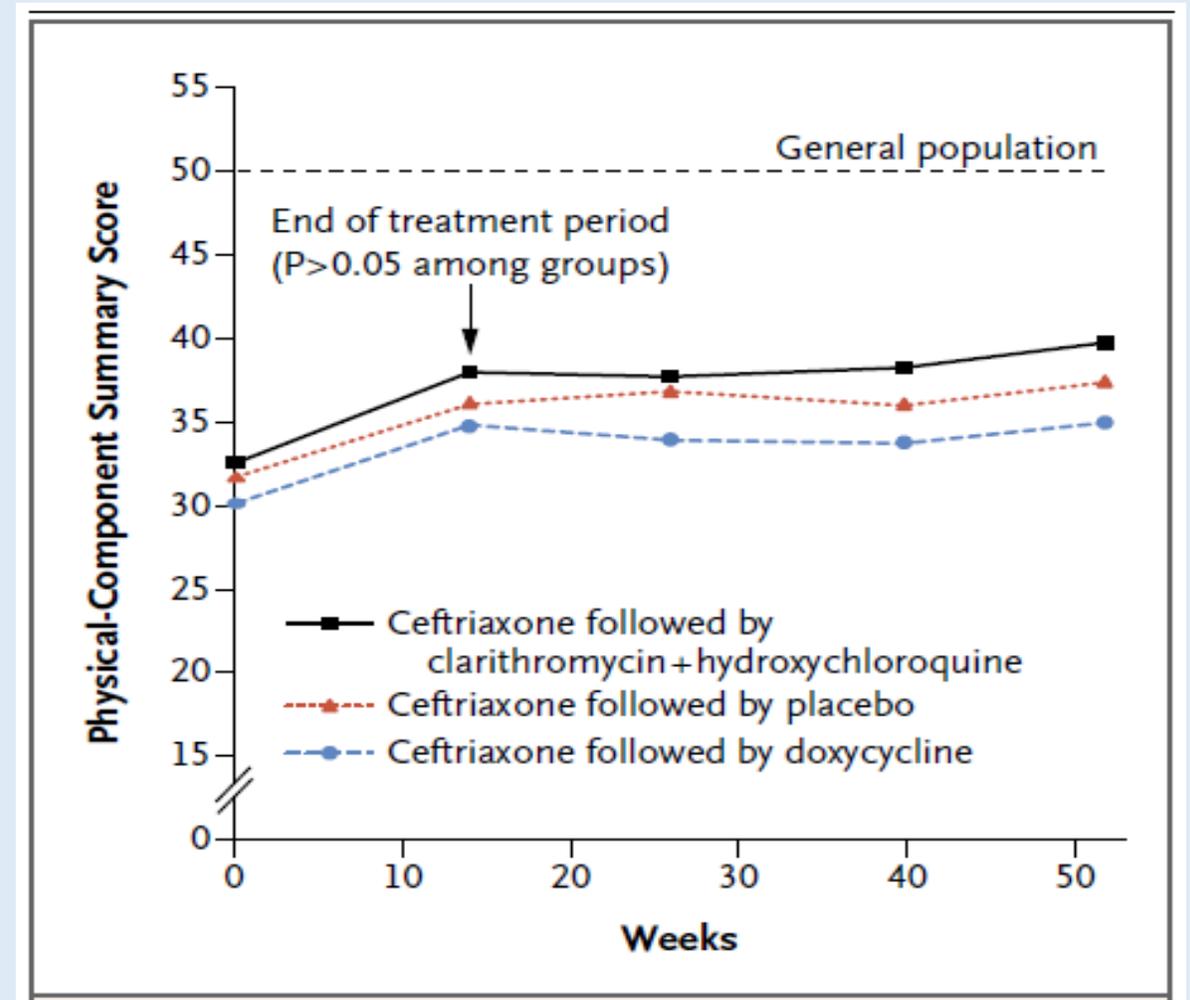
Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease

- Baseline health-related quality of life and fatigue across the 3 groups was comparable

RAND SF-36 score**			
Physical-component summary	30.3±6.3	32.7±7.5	31.8±8.1
Mental-component summary	37.4±9.9	37.1±9.8	37.6±9.6
Global-health composite	32.1±8.0	33.1±8.3	33.0±9.1
Physical-functioning scale	37.3±8.2	40.3±9.9	38.1±9.4
Role-physical scale	28.8±5.9	31.3±9.5	30.3±8.6
Bodily pain scale	35.2±8.3	37.3±8.2	38.1±9.4
General-health scale	35.5±7.7	35.9±7.6	35.9±8.4
Mental-health scale	44.2±9.8	43.6±10.0	44.0±8.5
Role-emotional scale	41.8±15.1	39.9±15.2	42.4±14.8
Social-functioning scale	33.5±12.8	33.8±12.0	34.2±12.2
Vitality scale	38.3±7.1	39.0±7.8	38.3±7.7
Characteristic	Doxycycline Group (N = 86)	Clarithromycin-Hydroxychloroquine Group (N = 96)	Placebo Group (N = 98)
Checklist Individual Strength††			
Total score	101.9±19.4	96.5±20.7	99.3±22.3
Fatigue-severity scale	46.0±8.1	42.7±10.7	43.8±10.6

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

- In all study groups, the RAND SF-36 physical component summary score increased from baseline to the end of treatment.
- Mean scores increased from:
 - 30.3 to 35.0 in the doxycycline group
 - 32.7 to 35.6 in the clarithromycin plus hydroxychloroquine group
 - 31.8 to 34.8 in the placebo group
- No significant continued improvement was noted beyond 14 weeks.
- Quality of life remained below that of general population.



Physical-Component Summary score was based on categories of physical functioning, role limitations due to physical health problems, pain, and general health perceptions)

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

Table 2. Treatment Effect at the End of the Treatment Period in the Modified Intention-to-Treat Population.*

Outcome	Doxycycline Group (N=86)	Clarithromycin– Hydroxychloroquine Group (N=96)	Placebo Group (N=98)	P Value†	Doxycycline Group vs. Placebo Group	Clarithromycin– Hydroxychloroquine Group vs. Placebo Group
	score (95% CI)				difference in score (95% CI)‡	
Primary outcome: SF-36 physical-component summary§	35.0 (33.5 to 36.5)	35.6 (34.2 to 37.1)	34.8 (33.4 to 36.2)	0.69	0.2 (-2.4 to 2.8)	0.9 (-1.6 to 3.3)
Secondary outcomes						
RAND SF-36§						
Mental-component summary	40.2 (38.6 to 41.9)	40.5 (38.9 to 42.1)	40.1 (38.6 to 41.7)	0.94	0.1 (-2.7 to 2.9)	0.4 (-2.3 to 3.1)
Global-health composite	36.1 (34.5 to 37.8)	36.6 (35.1 to 38.1)	36.0 (34.5 to 37.5)	0.85	0.1 (-2.6 to 2.9)	0.6 (-2.1 to 3.2)
Physical-functioning scale	41.9 (40.5 to 43.3)	42.1 (40.8 to 43.4)	41.0 (39.7 to 42.3)	0.44	0.9 (-1.4 to 3.2)	1.1 (-1.1 to 3.4)
Role–physical scale	33.6 (31.6 to 35.6)	34.4 (32.5 to 36.3)	33.9 (32.0 to 35.8)	0.84	-0.3 (-3.7 to 3.1)	0.5 (-2.8 to 3.8)
Bodily pain scale	39.1 (37.5 to 40.7)	40.5 (39.0 to 41.9)	39.4 (37.9 to 40.9)	0.42	-0.3 (-2.9 to 2.4)	1.1 (-1.5 to 3.6)
General-health scale	37.1 (35.6 to 38.6)	38.4 (37.0 to 39.8)	37.5 (36.2 to 38.9)	0.41	-0.4 (-2.9 to 2.0)	0.9 (-1.5 to 3.3)
Mental-health scale	45.1 (43.8 to 46.4)	45.2 (43.9 to 46.4)	45.1 (43.9 to 46.4)	1.00	0.0 (-2.3 to 2.2)	0.0 (-2.1 to 2.2)
Role–emotional scale	44.7 (42.4 to 47.0)	41.4 (39.2 to 43.6)	42.6 (40.4 to 44.8)	0.11	2.1 (-1.7 to 6.0)	-1.2 (-5.0 to 2.6)
Social-functioning scale	36.3 (34.2 to 38.4)	38.5 (36.6 to 40.5)	37.5 (35.6 to 39.5)	0.32	-1.2 (-4.7 to 2.3)	1.0 (-2.4 to 4.4)
Vitality scale	42.5 (40.9 to 44.0)	42.4 (41.0 to 43.9)	41.9 (40.5 to 43.4)	0.85	0.5 (-2.0 to 3.1)	0.5 (-2.0 to 3.0)
Checklist Individual Strength¶						
Total score	88.7 (84.4 to 92.9)	87.1 (83.0 to 91.1)	88.4 (84.4 to 92.4)	0.84	0.3 (-6.9 to 7.4)	-1.3 (-8.3 to 5.6)
Fatigue-severity scale	39.4 (37.3 to 41.5)	38.6 (36.6 to 40.5)	38.3 (36.3 to 40.2)	0.73	1.1 (-2.4 to 4.6)	0.3 (-3.1 to 3.7)

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

- 68.6% of patients reported a drug-related adverse event, though the rate of serious adverse events was low.
- 4 serious adverse events were reported during the initial 2 week ceftriaxone phase (allergic reaction) and no serious drug-related events occurred during the 12 week randomized phase.

Table 3. Adverse Events in the Modified Intention-to-Treat Population.*

Type of Event	Total (N=280)	Open-Label Phase (N=280)	Randomized Phase			P Value
			Doxycycline Group (N=86)	Clarithromycin- Hydroxychloroquine Group (N=96)	Placebo Group (N=98)	
<i>no. of participants (percent)</i>						
Any adverse event†	205 (73.2)	131 (46.8)	47 (54.7)	45 (46.9)	42 (42.9)	0.27
Any drug-related adverse event†	192 (68.6)	127 (45.4)	42 (48.8)	42 (43.8)	34 (34.7)	0.14
Discontinued treatment owing to adverse event†	19 (6.8)	6 (2.1)	3 (3.5)	7 (7.3)	4 (4.1)	0.49‡
Any serious adverse event	9 (3.2)	5 (1.8)	3 (3.5)	1 (1.0)	0	0.08‡
Most common adverse events						
Diarrhea	91 (32.5)	72 (25.7)	4 (4.7)	9 (9.4)	6 (6.1)	0.43
Nausea	44 (15.7)	20 (7.1)	9 (10.5)	10 (10.4)	5 (5.1)	0.31
Rash†	31 (11.1)	23 (8.2)	1 (1.2)	8 (8.3)	1 (1.0)	0.01‡
Mucosal fungal infection	20 (7.1)	8 (2.9)	5 (5.8)	4 (4.2)	3 (3.1)	0.66‡
Photosensitivity	19 (6.8)	2 (0.7)	16 (18.6)	0	1 (1.0)	<0.001
Headache	16 (5.7)	12 (4.3)	0	2 (2.1)	2 (2.0)	0.55‡
Dizziness	16 (5.7)	3 (1.1)	3 (3.5)	5 (5.2)	5 (5.1)	0.88‡
Visual impairment	16 (5.7)	1 (0.4)	1 (1.2)	4 (4.2)	10 (10.2)	0.02‡

The Question of Long-term antibiotics:

- Based on this randomized placebo controlled trial of 280 patients, there is no appreciable benefit to long-term antibiotics.
- There is an increased risk of adverse drug related events.
- Quality of life remained below that of general population despite long-term antibiotic therapy.

The Question of Long-term antibiotics:

Two Controlled Trials of Antibiotic Treatment in Patients with Persistent Symptoms and a History of Lyme Disease

Klempner M, Hu L, Evans J, et al. N Engl J Med 2001; 345:85-92

- Two Randomized double-blind placebo controlled trials, one with 78 patients seropositive for IgG to *B. burgdorferi* and 51 patients who were seronegative.
- Patients had to have at least one of: A history of erythema migrans, early neuro or cardiac symptoms attributed to Lyme, radiculoneuropathy, or Lyme arthritis.
- Patients had to have completed a standard antibiotic regimen.
- At enrollment all patients had at least one or more of: musculoskeletal pain, cognitive impairment, radicular pain, paresthesias or dysesthesia.
- Symptoms had to have begun within 6 months after initial infection and persisted for between 6 months and 12 years.
- At baseline there was no evidence of persistent *B. burgdorferi* infection by culture or PCR.

Two Controlled Trials of Antibiotic Treatment in Patients with Persistent Symptoms and a History of Lyme Disease

- Patients randomly assigned to receive antibiotics or placebo.
- Antibiotic regimen consisted of 30 days of ceftriaxone 2g IV daily followed by 60 days of doxycycline 100mg BID.
- Primary outcome was an improvement in the health-related quality of life measured by the SF-36 General Health Survey assessed at baseline, 30, 90, and 180 days.

Two Controlled Trials of Antibiotic Treatment in Patients with Persistent Symptoms and a History of Lyme Disease

- Interim analysis in the seropositive study at 180 days showed a 1.4% chance that a significant difference in the efficacy of treatment between the antibiotic group and placebo group would be observed at full projected enrollment.
- Interim analysis in the seropositive study at 180 days showed only a 4.0% chance of finding a significant difference.
- The data and safety monitoring board thus recommended early discontinuation of the study.

Two Controlled Trials of Antibiotic Treatment in Patients with Persistent Symptoms and a History of Lyme Disease

- At the time the study was discontinued, no significant differences in the measures of health-related quality of life were noted between the antibiotic and placebo groups in either trial.
- 25% of patients in the combined antibiotic groups experienced one or more adverse events (compared to 17% in the combined placebo groups).
- Only 2 patients had severe adverse events (one with pulmonary embolism and the other with fever, anemia, and GI bleeding).

No Proven Role for Long-Term Antibiotics:

- Some patients with proven Lyme disease report experiencing chronic musculoskeletal pain, neurologic and cognitive symptoms, and fatigue despite completing standard therapy.
- Their quality of life can be significantly impaired relative to the baseline population.
- Despite attempts at long-term antibiotics to treat such chronic symptoms, no randomized controlled trials have demonstrated significant benefit.
- Minor adverse effects to prolonged therapy are common. Though serious side effects are less common, reports of serious allergic reactions and infectious complications (*C. difficile* and blood stream infections) are well noted.
- Long-term antibiotics beyond the standard regimens are not recommended given the potential risks in light of lack of proven benefit.

Summary of the State of Tick-borne Illness in the USA:

- The US population is at an increasing threat of diverse tick-borne infectious syndromes, with an incidence that has more than doubled over the past 13 years.
- Lyme disease counts for more than 80% of the reported tick-borne illnesses, and the endemic region of its tick vector is spreading.
- Most patients with Lyme disease and other bacterial tick-borne illnesses respond well to standard therapies, but up to 20% of patients with a history of Lyme disease have persistent symptoms.
- No randomized placebo controlled trials have shown a benefit to long-term antibiotic therapy, but do highlight the potential for harm.
- Gaps exist in the accurate diagnosis of many tick-borne illnesses including Lyme disease.
- Currently no vaccine available for tick-borne illnesses seen in the US. Prior vaccine against Lyme was withdrawn due to poor sales and concerns over adverse events.
- The best prevention continues to be tick avoidance with long sleeves, repellent, and checking for ticks after possible exposure.

Major References:

- Berende A, ter Hofstede HJ, Vos FJ, van Middendorp H, Vogelaar ML, Tromp M, van den Hoogen FH, Donders AR, Evers AW, and Kullberg BJ. Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease. *N Engl J Med* 2016 Mar 31; 374(13):1209-20.
- Klempner M, Hu L, Evans J, Schmid CH, Johnson GM, Trevino RP, Norton D, Levy L, Wall D, McCall J, Kosinski M, and Weinstein A. Two Controlled Trials of Antibiotic Treatment in Patients with Persistent Symptoms and a History of Lyme Disease. *N Engl J Med* 2001 Jul 12; 345(2):85-92.
- Nelson CA, Saha S, Kugeler KJ, Delorey MJ, Shankar MB, Hinckley AF, and Mead PS. Incidence of clinician-diagnosed Lyme disease, United States, 2005-2010. *Emerging Infectious Diseases* 2015 Sep; 21(9):1625-1631.
- Tickborne Diseases of the United States A Reference Manual for Healthcare Providers. CDC. Fifth Edition, 2018.
- Tick-borne Diseases Working Group. 2018 Report to Congress.
- Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, Krause PJ, Bakken JS, Strle F, Stanek G. The Clinical Assessment, Treatment, and Prevention of Lyme disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006 Nov 1; 43(9):1089-134.