Lyme Disease: 2025 Guidelines on Diagnosis and Treatment

Lawrence Zemel MD

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Maven Project

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MAVEN PROJECT

Objectives

- Identify key clinical features of Lyme disease for accurate diagnosis and management
- Apply the latest guideline recommendations with practical relevance to patient care
- Explore controversies surrounding Lyme disease including diagnosis, treatment, and chronic Lyme debates

Lyme disease: diagnosis and treatment. Schoen, R. **Current Opinion in Rheumatology. May 2020 , Volume 32 (3), p 247 – 254**

Reid MC, Schoen RT, Evans J, et al. The consequences of overdiagnosis and overtreatment of Lyme disease: an observational study. Ann Intern Med 1998; 128:354 – 362

Steere AC, Malawista SE, Snydman DR, et al. Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Arthritis Rheum 1977; 20:7 – 17.

Lantos PM, Pavia AT, Wormser GP, Zemel, L. et al. Clinical practice guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 guidelines for the prevention, diagnosis and treatment of Lyme disease. Clin Infect Dis. 2021;72:1–8.

Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001; 345:85–92

Taylor-Salmon, Emma, Shapiro, Eugene D. Tick-borne infections in children in North America. **Current Opinion in Pediatrics April 2024 , Volume 36 (2), p 156 – 163**

Conclusion

- 1. Lyme disease is straightforward to diagnose, and treatment schedules are relatively well-established

- 2. Lyme Disease is a politically charged disorder, in which a small group of lay lobbyists have dictated health policy, over-riding sound medical evidence.

Lyme Case

- 8 y.o. boy from the CT shore presents with L swollen knee of 2 days duration without prior trauma. There is no history of recent fever, recent strep, rash, or ocular sx.
- He had a “viral” illness in June, 2020, consisting of fever to 102, chills, transient neck stiffness, headaches, and myalgias.

Lyme Case, cont.

At this point, do you:

- Refer to orthopedics
- Aspirate the knee to r/o a septic joint
- Order lab studies, including Lyme screen, and start amoxicillin pending results
- X-ray the knee
- All of the above

Case, cont.

- Lab results:
- CBC nl
- ESR 35
- Lyme screen positive @ 5.2 units
- Lyme Blot 9/10 IgG bands, 2/3 IgM bands

Lyme Disease Case Definition

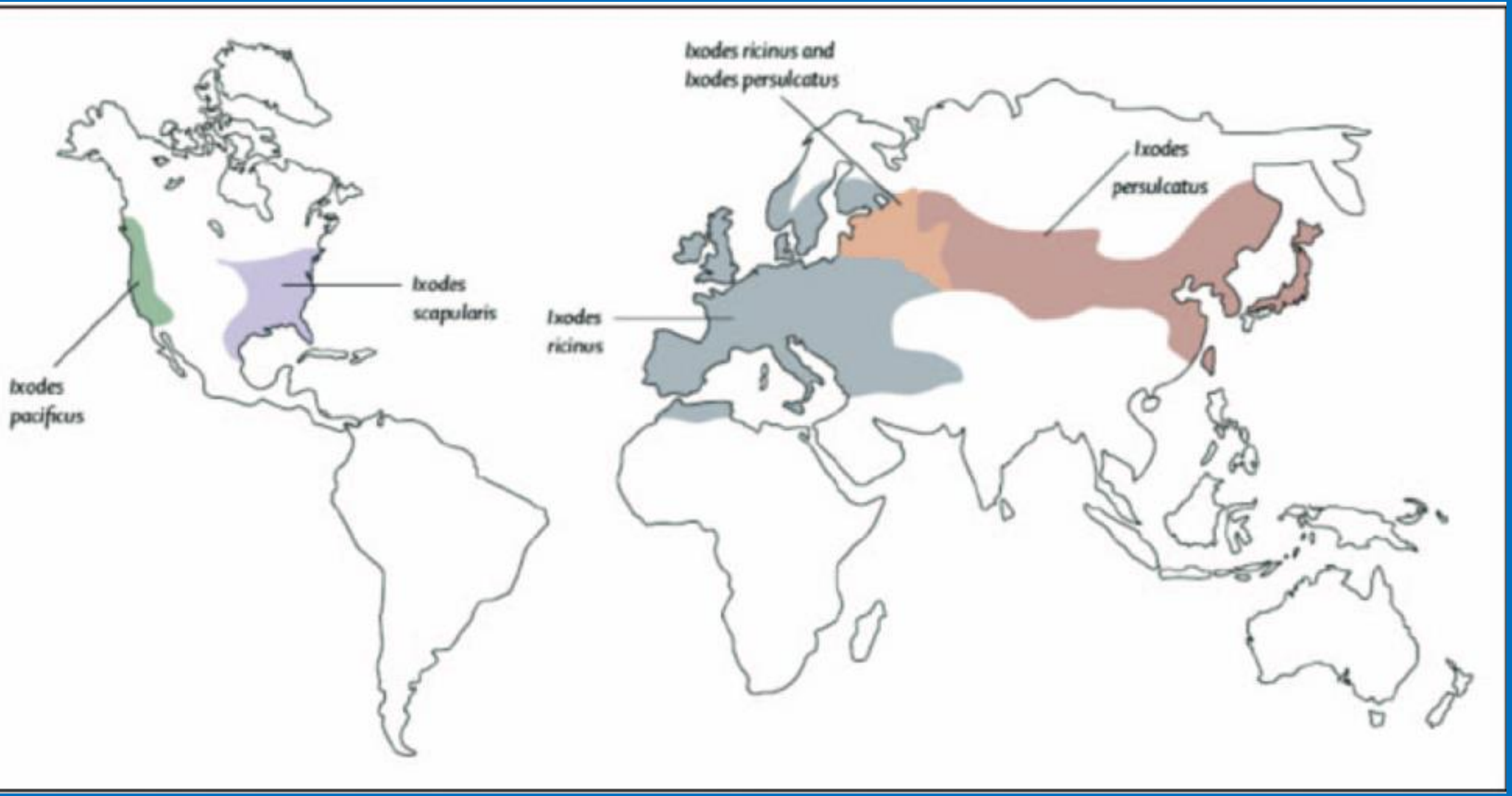
- **Erythema Migrans (at least 5 cm), or**
- **One late manifestation, and laboratory confirmation of infection**

Late manifestations include:

- **arthritis**
- **carditis**
- **neurologic disease**

"IgG seronegativity in an untreated pt. with mos. to years of symptoms essentially rules out the dx of Lyme disease…"

Distribution of ticks carrying Lyme borrelia



Distribution of Lyme disease in US

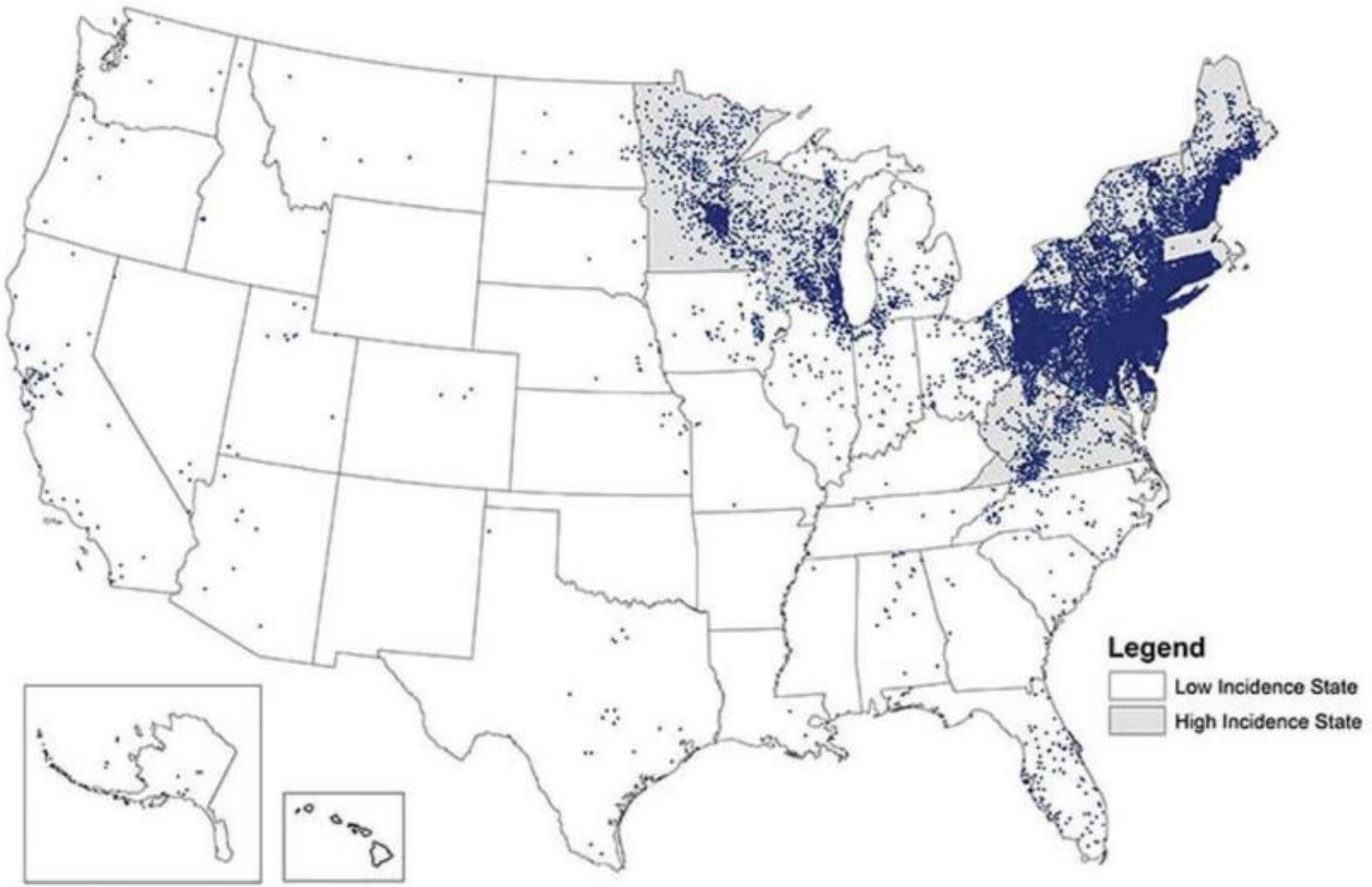
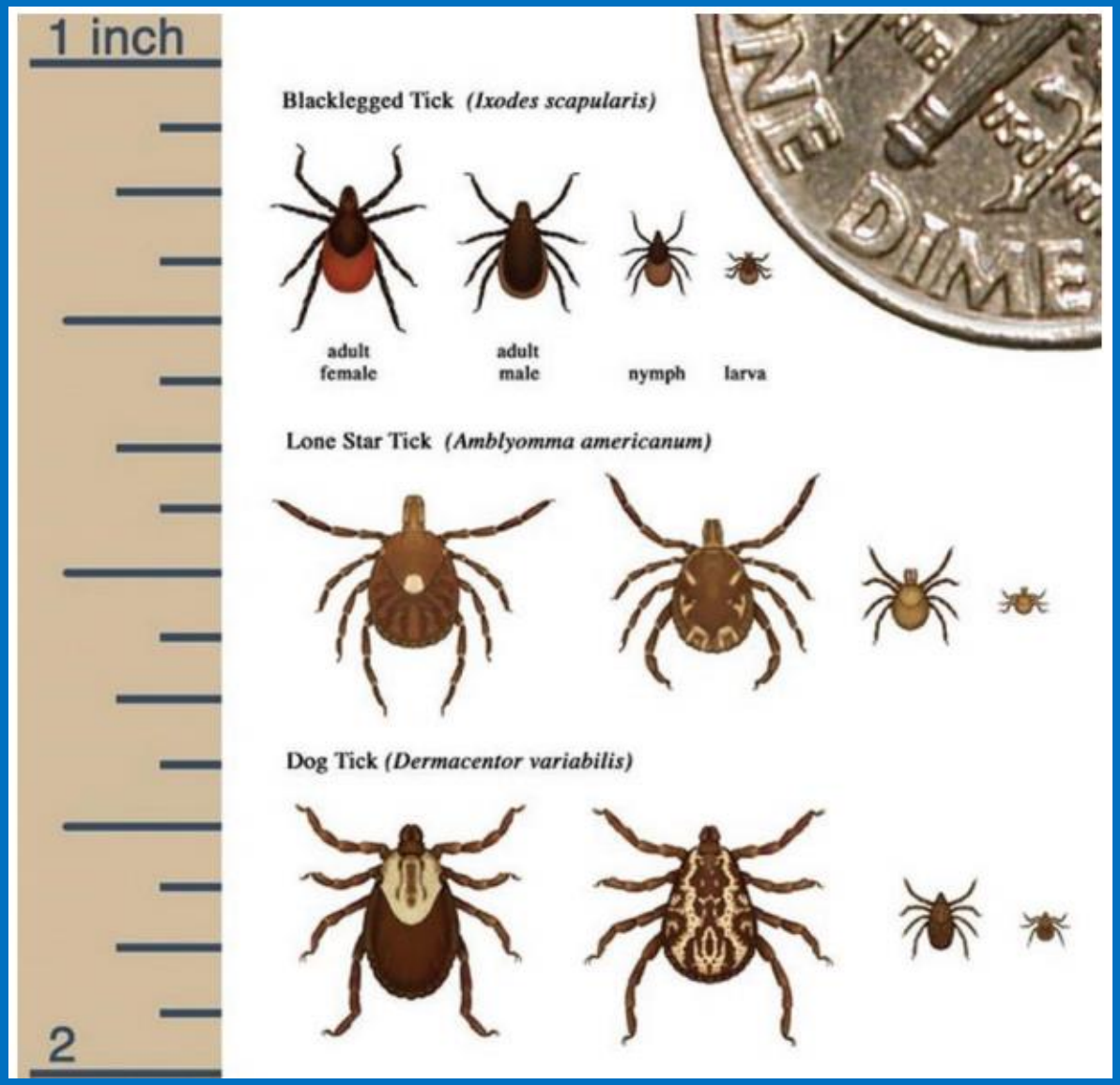


Figure 4. Reported cases of Lyme disease, United States, 2018. Incidence of confirmed Lyme disease cases (2018), by county of residence in the United States and classification of states as high, neighboring, or low Lyme disease incidence states. For the most current map, please see: https://www.cdc.gov/lyme/datasurveillance/maps-recent.html [63].

Tick comparisons



Female adult ixodes tick

B burgdorferi, the causative bacteria of Lyme disease

FIGURE 1

Photomicrograph of the B31 strain of *B. burgdorferi* derived from an early log-phase *in vitro* culture in BSK medium prepared and visualized using dark-field microscopy as previously by us (12, 20, 21). Magnification was 500x. A micro-colony is shown on the left side and four separate organisms are shown on the right side of this image.

Erythema Migrans

Erythema Migrans

- 65-70% of patients with Lyme disease develop EM
- EM occurs 3-25 days after infected tick exposure
- In Connecticut, 40% of deer ticks (ixodes scapularis) are infected with Borrelia burgdorferi. In the west, ixodes pacificus has a much lower infectivity rate
- Patients with classic EM do not need lab confirmation. Atypical cases could be tested by acute and/or convalescent serum. Skin PCR or culture is not advised.

Symptoms of Early Lyme Disease

- headache
- fever
- myalgias, arthralgias
- chills
- neck stiffness
- erythema migrans (60-70 % of the time)
- fatigue
- abdominal pain

Early Disseminated LD

- multiple e. migrans
- meningeal signs
- cranial neuropathies (especially 7th nerve palsy)
- chest discomfort, syncope
- abdominal pain
- fever

Late Lyme Disease

- episodic oligoarthritis of large joints, especially the knee
- chronic arthritis (10-20% of children)
- low-grade encephalopathy
- acrodermatitis chronicum atrophicans (seen mostly in Europe)
- Post-treatment Lyme syndrome

Ruptured popliteal cyst in childhood Lyme disease

MRI of the knee of a 7-year-old boy presenting with a 4-day history of atraumatic, progressive left knee pain, calf swelling, and tenderness. Coronal fat-saturated images demonstrate extensive edema tracking along the posteromedial leg (red arrow, Fig. 1-D). Corresponding axial short tau inversion recovery images show a large knee effusion (Fig. 1-A), with myositis of the medial head of the gastrocnemius with a large fluid collection posteromedially (yellow arrows, Figs. 1-B and 1-C). Subcutaneous edema is noted in the medial shank (red arrow), as well.

Diagnostic testing for Lyme arthritis

- Serological testing is preferred: 2-tier testing or C6 peptide
- 2-step testing: Lyme screen (polyvalent) followed by Western blot if screen is positive or 2nd Elisa
- Virtually all patients should test positive for >5 IgG bands by the time arthritis develops. IgM alone is not diagnostic.
- Synovial fluid analysis not necessary unless septic arthritis or crystal arthropathy needs to be ruled out.
- Rarely, B. burgdoferi PCR can be run on SF

(small joint arthritis is rarely Lyme disease)

Role of MRI in Lyme Arthritis

none

Neurologic Lyme

Peripheral nervous system

- Cranial neuritis
- Radiculoneuritis
- Plexopathies
- Mononeuropathy
- Mononeuropathy multiplex

Central nervous system

- Meningitis
- Raised ICP
- Encephalitis
- myelitis

Steroids and 7th nerve palsy

In patients presenting with acute facial nerve palsy without other objective evidence of Lyme disease, steroids should be started within 72 hours, until Lyme serology comes back positive.

Psychiatric illness and Lyme

In adults with psychiatric illness, the recommendation is not to test for Lyme disease.

In children presenting with developmental, behavioral, or psychiatric disorders, routine Lyme testing should be avoided.

Lyme Prevention

Table 5. Personal Prevention Measures

Before venturing outside	During and/or after exposure to tick habitat[b]
Personal Prevention Measures[a]	• Conduct a thorough tick check of extremities, torso, and areas where ticks may be visually obscured (eg, axilla, nape of neck, hairline, in and around ears, umbilicus, groin, popliteal fossa)
• Avoid risky habitats	• Bathe or shower within 2 hours
• Wear light-colored clothing	• Dry clothes on high heat for at least 10 minutes; if not possible, wash clothes in hot water.
• Wear long sleeves and pants	
• Tuck pants into socks or footwear	
• Wear permethrin-treated clothing	

Lyme Prevention

Use an EPA-approved repellent or insecticide as per manufacturer's instructions

- DEET
- Picaridin
- IR3535
- Oil of lemon eucalyptus (OLE)
- p-methane-3,8-diol (PMD)
- 2-undecanone
- Permethrin (for application to clothing and gear only)

Vaccine development

- Smallpox 1796 - live cowpox vaccine
- Covid 2020 - mRNA technology
- Lyme 1998 - single bacterial antigen (OspA) (GSK)
- Lyme 2017-present - anti-OspA antibodies (Pfizer, Valnexa)
- Lyme 2024-ongoing - mRNA OspA

Lymerix Lyme Vaccine 1998-2002

"The licensure of LYMErix™ confronted Lyme advocacy with the added problem of how to sustain public anxiety (and donations), media attention, and political clout against the evidence-based reality of a bacterial infection that was antibiotic-responsive, non-fatal, non-communicable, geographically focused, and – now – preventable through vaccination.

Unfortunately, what people found online were activist websites filled with misleading information about the vaccine, personal 'vaccine victims' stories, and newsgroup bulletin boards offering a repetitive stream of misinformation, libel and quack treatments. The public opinion battles over LYMErix™ were fought, and lost, in cyberspace."

Edward McSweegan was the program officer for Lyme disease research at the National Institute of Allergy and Infectious Diseases at the National Institutes of Health during the early 1990s.

VLA15 – Valneva's Lyme disease vaccine candidate

- The placebo-controlled Phase 3 study, Vaccine Against Lyme for Outdoor Recreationists (**VALOR**) (NCT05477524), investigates the efficacy, safety and immunogenicity of VLA15 in participants 5 years of age and older. **9,437 participants** were enrolled at sites across the U.S., Europe and Canada in areas where Lyme disease is endemic.
- VLA15 is a multivalent recombinant protein vaccine that **targets six serotypes of Borrelia** representing the most common pathogenic strains found in the United States and Europe.
- Data from the Phase 2 studies continue to demonstrate strong immunogenicity in adults as well as in children, with acceptable safety and tolerability profiles in both study populations [5,6]. The results of two Phase 2 clinical trials of VLA15, were published in the peer-reviewed medical journal, The Lancet Infectious Diseases.
- Valneva and Pfizer reported positive pediatric and adolescent immunogenicity and safety data for VLA15, when given as a booster [7].
- In September 2024, further positive data following a second booster vaccination of VLA15 given one year after receiving the first booster dose were reported [8].
- Valneva and Pfizer entered into a collaboration agreement in April 2020 to co-develop VLA15, with updates to the terms in June 2022 [9].
- Subject to positive Phase 3 data, **Pfizer aims to submit a Biologic License Application to the Food and Drug Administration and Marketing Authorization Application to the European Medicines Agency in 2026.**
- The VLA15 program was granted Fast Track designation by the U.S. Food and Drug Administration (FDA) in July 2017 [10].

Following a tick bite:

- May submit tick for species identification
- Not necessary to test tick for B. burgdorferi
- Asymptomatic patients need not be tested
- Single dose of 200 mg doxycycline (or 4.4 mg/kg in children) may be taken if tick is clearly a deer tick, and attached for 36-72 hours in a highly endemic region

(likelihood of removed deer tick resulting in Lyme disease is 1-3%)

Duration of tick attachment

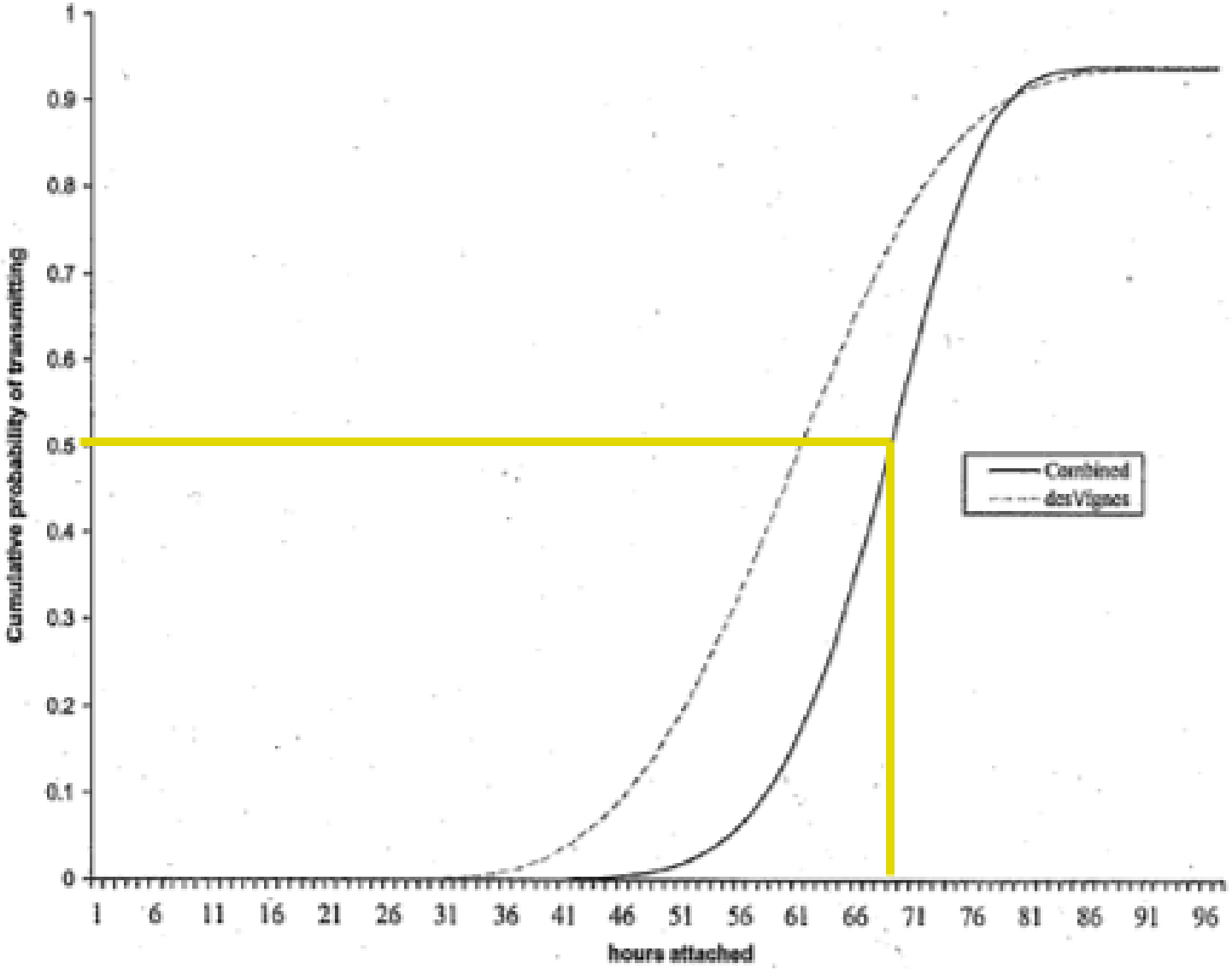
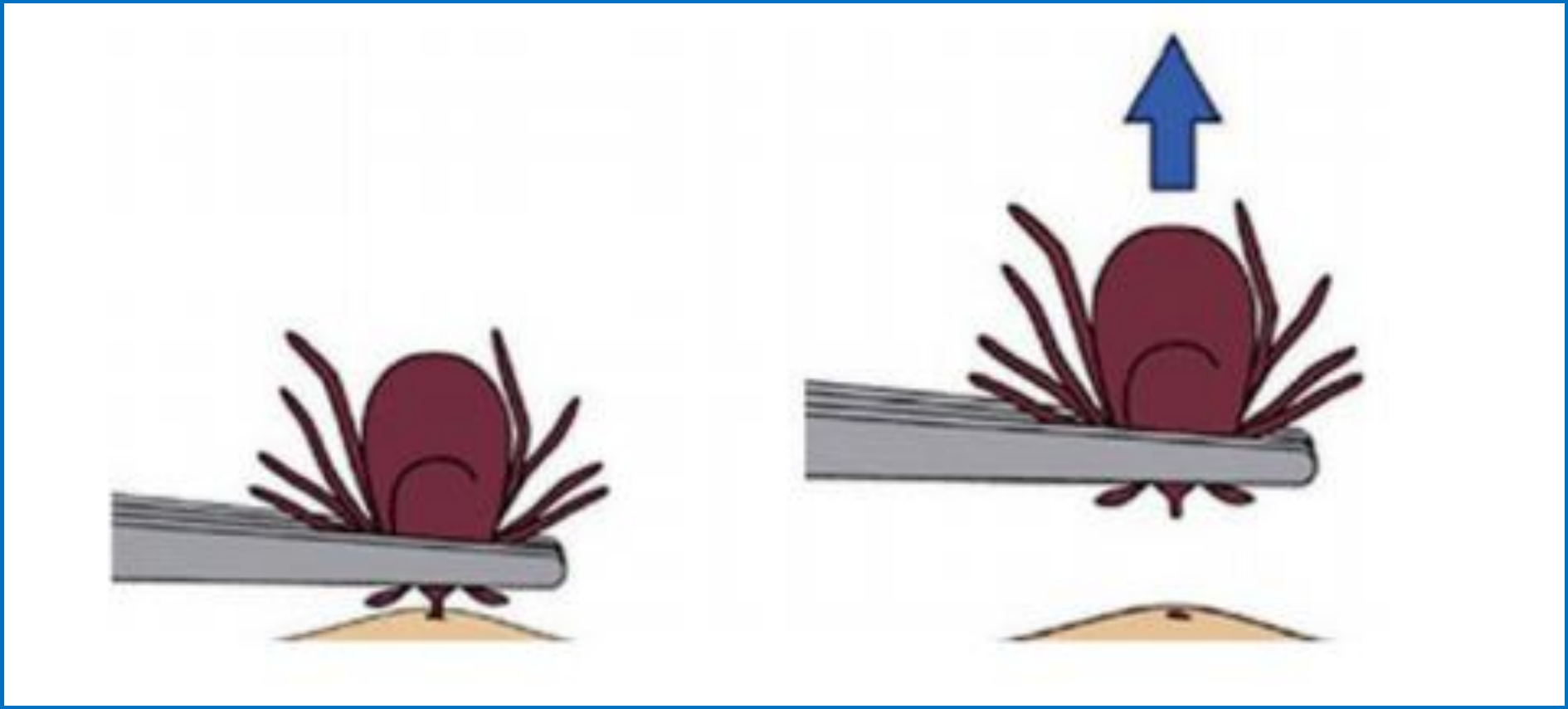


Fig. 1. Cumulative probability of infected *I. scapularis* nymphs transmitting *B. burgdorferi* s.s. by attachment time as estimated in a previous study (dashed-lines; des Vignes et al. 2001) and recalculated using data collected during this study combined with data from des Vignes et al. (2001).

Tick removal



Antibiotic treatment of Lyme disease

Table 4. Treatment of Specific Manifestations of Lyme Disease

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

Abbreviation: IV, intravenous.

[a]Ranges are given where different durations have been studied, and the optimal duration remains uncertain.

[b]This recommendation applies both to solitary and multiple erythema migrans.

[c]Because of concerns for lower efficacy, macrolide antibiotics including azithromycin are considered second line agents, and should be reserved for patients in whom other antibiotic classes are contraindicated. Azithromycin has not been sufficiently studied for manifestations of Lyme disease other than erythema migrans.

[d]The preferred IV agent is ceftriaxone. Cefotaxime and penicillin G are alternatives.

[e]Initial IV therapy is recommended for patients requiring hospital admission. Therapy can be completed orally for the same total 14-day duration. Patients with Lyme carditis who do not require hospital admission can be treated orally.

[f]Repeat IV therapy can be extended to 28 days if inflammation is not resolving.

Young children can safely take doxycycline for up to 14 days

Table 3. Drug Doses

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

Regardless of the treatment regimen, complete response to treatment may be delayed beyond the treatment duration. Relapse may occur with any of these regimens; patients with objective signs of relapse may need a second course of treatment.

[a]Doses of some beta lactam antibiotics (amoxicillin, penicillin, cefuroxime, and cefotaxime) may require adjusted dosing for patients with impaired renal function.

[b]There is increasing favorable information on the safety of short courses of doxycycline in young children, which should impact the risk to benefit ratio of using this antibiotic in patients with various manifestations of Lyme disease; see the General Principles and the individual treatment sections of this guideline for further discussion.

[c]The oral suspension of cefuroxime is currently not available in the USA.

[d]Because of concerns for lower efficacy, macrolide antibiotics including azithromycin are considered second line agents, and should be reserved for patients in whom other antibiotic classes are contraindicated.

Persistence of Lyme arthritis

- For mild residual swelling, 2-4 weeks of observation may be all that is needed
- Consider a 2nd course of oral antibiotics in such patients
- For patients with minimal response to first round of therapy (assuming compliance, no other obvious diagnosis), recommend 2-4 weeks of IV ceftriaxone

Post-antibiotic Lyme arthritis

- Do not give additional antibiotics beyond 2 mos
- DMARDs (disease modifying anti-rheumatic drugs) such as methotrexate
- Intra-articular steroids
- Biologic agents (etanercept, adalumimab, etc)
- Arthroscopic synovectomy
- NSAIDs for pain management if needed

Lyme disese in pregnancy

Pregnant women with Lyme disease can be safely treated with beta lactams and cephalosporins.

“…Lyme disease in pregnancy has not been found to result in congenital infection or a syndrome of congenital abnormalities…” [when appropriately treated].

Several cases of neonatal demise in untreated women

Post Treatment Lyme Syndrome

Inclusion criteria	Exclusion criteria
Documented clinical and laboratory evidence for previous Lyme disease	Evidence for an active infection or coinfection (e.g., Babesiosis)
Documented completed therapy, adequate for the stage	Concurrent other disease, objectifiable on clinical examination, including active and ongoing rheumatologic, neurologic, or psychiatric disease
Subjective symptoms such as fatigue, arthralgia, myalgia, cognitive dysfunction or radicular pain, with onset within 6 months of diagnosis of Lyme disease	A diagnosis of fibromyalgia or chronic fatigue syndrome before the onset of Lyme disease
Persistence or recurrence for more than 6 months after completion of antibiotic therapy	A prolonged history of undiagnosed or unexplained somatic complaints, such as musculoskeletal pains or fatigue, before the onset of Lyme disease
Subjective symptoms of such severity that, when present, resulting in substantial reduction in previous levels of occupational, educational, social or personal activities	A diagnosis of an underlying disease or condition that might explain the patient's symptoms
	Laboratory or imaging abnormalities that might suggest an undiagnosed process distinct from PTLDS

“Chronic Lyme Disease”

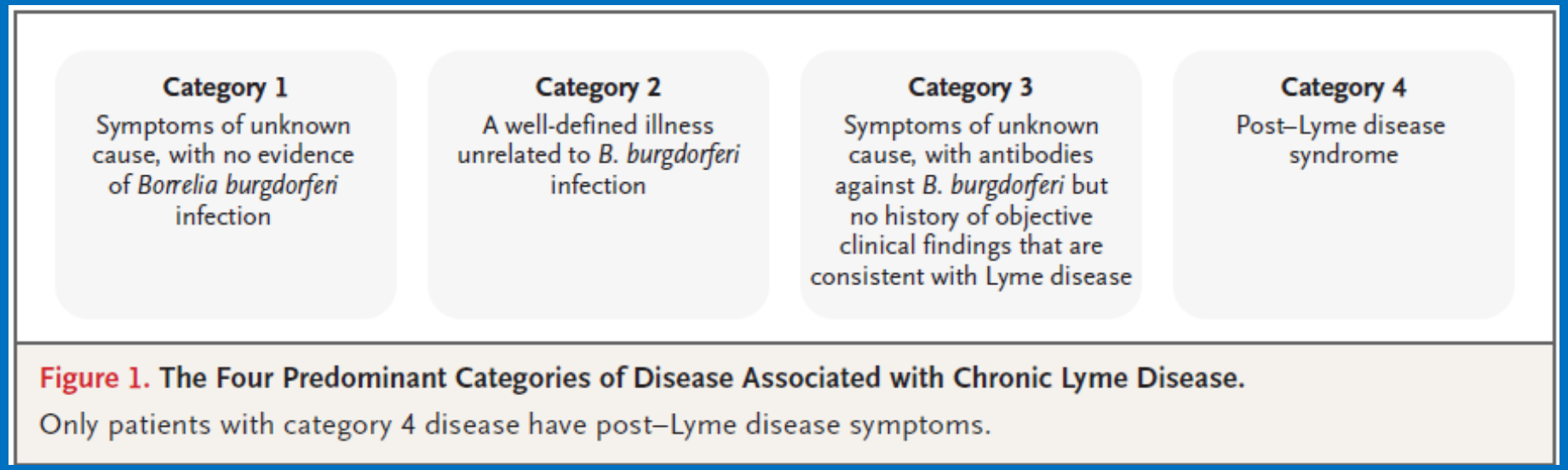


Figure 1. The Four Predominant Categories of Disease Associated with Chronic Lyme Disease.

Only patients with category 4 disease have post–Lyme disease symptoms.

A Critical Appraisal of “Chronic” Lyme Disease. Feder HM Jr, Johnson BJ, O'Connell S, Shapiro ED, Steere AC, Wormser GP; Ad Hoc International **Lyme** Disease Group, Agger WA, Zemel L. N Engl J Med. 2007 Oct 4;357(14):1422-30

Lyme Group Strategies

- Web-based information (unfiltered)
- Public testimony
- Fund-raising and directed granting
- Slanted scientific meetings
- Lobbying NIH and legislators
- Personal attacks
- Referrals to sympathetic physicians
- Protecting “LLD’s” from prosecution

Bay Area Lyme FOUNDATION

Why Care About Lyme Disease?

- **There are over 400,000 new cases of Lyme disease in the US every year** and it is growing rapidly. The revised CDC estimates increased the number of cases by more than ten-fold what was previously believed making Lyme disease one of the fastest-growing infectious diseases in the US.
- **Untreated, Lyme disease can become a severely debilitating disease** affecting joints, the heart, the brain, and/or the central nervous system. There are half a million Americans struggling with late-stage Lyme disease.
- **Persistent Lyme Disease (PLD) causes immense suffering and severe health issues** for thousands of patients with little remedy. Controversy over prolonged antibiotic use, highly variable disease progression and genetic conditions, and masquerading symptoms often impede treatment.

MYTH: Antibiotics cure everyone.

Statistics show that as many as 20% of patients continue to exhibit symptoms even after antibiotic treatment. While there is controversy about the cause of this symptom persistence (e.g., residual bacteria or auto-immune response), for these patients, the suffering continues. As many as a million Americans are estimated to be suffering with this condition, referred to as Persistent Lyme Disease (PLD).

MYTH: If the test is negative, you don't have Lyme.

Not so fast … The current "gold standard" diagnostic for Lyme disease is a two-tiered blood test requiring a positive ELISA result. The ELISA measures infection-fighting or memory antibodies against *Borrelia burgdorferi*, and it misses up to 60% of acute cases of Lyme when antibodies may not be high enough to detect.

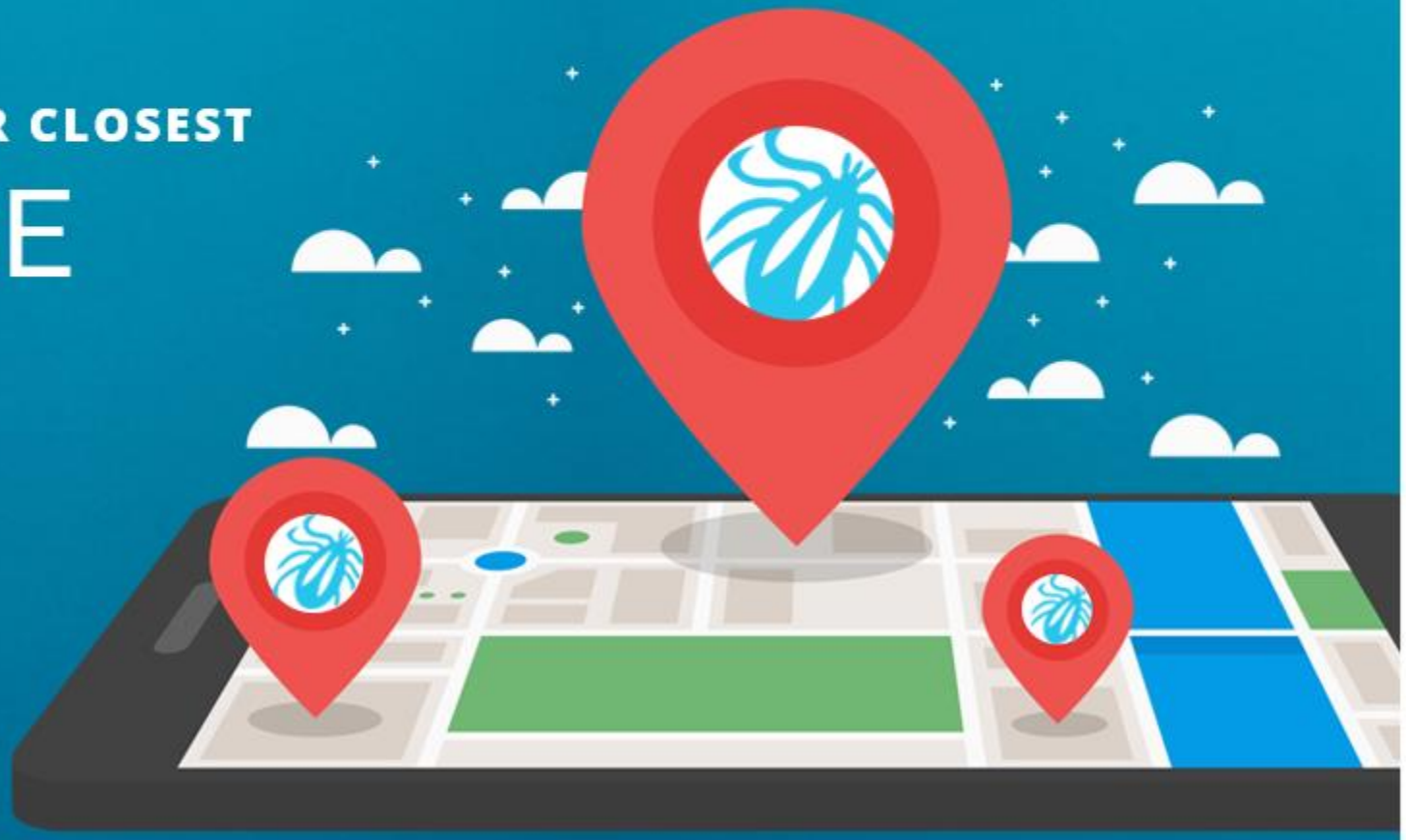
Lyme Disease Physician Referral

CONNECTING YOU WITH YOUR CLOSEST

LYME DISEASE SPECIALIST

For the past 25 years, LymeDisease.org has been connecting patients with Lyme-literate doctors who specialize in caring for patients with Lyme disease.

FIND A LYME DOCTOR



Stalking Dr. Steere

Twenty-five years ago he uncovered Lyme disease. Now he says that it is not the epidemic that many claim, and he's being threatened by people who insist that Lyme—and Steere—have ruined their lives.

Allen C. Steere, MD

Table. Summary of Lyme disease information given by 19 web sites.

	Tick Bites	LD Diagnosis	Serology	Other Tests	Chronic LD	Treatment	Pregnancy	Breast Feeding
www.acponline.org	A	A	A	A	A	A	A	-
www.aldf.com	A	A	A	A	A	A	-	-
www.cdc.gov	A	A	A	A	-	A	-	-
www.fda.gov	A	-	A	A	-	A	-	-
www.healingwell.com	A	A	A	A	-	A	-	-
www.hopkins-arthritis.com	A	A	A	A	A	A	-	-
www.igenex.com	I	I	I	I	I	I	-	I
www.ilads.org	-	I	I	-	I	I	-	I
www.intelihealth.com	A	A	A	A	A	A	A	-
www.kidshealth.org	A	A	A	-	A	A	A	-
www.lyme.org	I	A	A	I	I	I	I	I
www.lymealliance.org	A	I	I	I	I	I	A	-
www.lymedisease.org	I	A	I	I	I	A	I	-
www.lymediseaseassociation.org	I	I	I	I	I	I	I	I
www.lymediseaseinformation.com	A	-	-	-	-	A	-	-
www.lymeinfo.net	-	-	I	A	I	-	-	I
www.lymenet.org	-	I	I	-	I	I	I	I
www.lymesite.com	I	I	I	-	I	-	I	I
www.webmd.com	A	A	A	A	A	A	-	-

Cooper J and Feder H. Ped Infect Dis, Dec 2004