



Lyme Disease aka Lyme borreliosis

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Disclosures of Financial Relationships with Relevant Commercial Interests

- Research: Pfizer (investigational Lyme disease vaccine)
- Consulting: medical-legal, Tonix Pharmaceuticals, Tarsus Pharmaceuticals

Question #1

A 56-year-old man from southern Missouri
Onset in July:

- Myalgia and malaise
- Itchy rash x 2d at tick bite site 1 week ago

Exam: T 37.0°C

- Annular “bulls-eye” ~6 cm
- (same area that engorged tick was removed earlier in the week)



Question #1

Which of the following is the most likely diagnosis?

- A. Lyme disease (*Borrelia burgdorferi* infection)
- B. Human Monocytic Ehrlichiosis (*Ehrlichia chaffeensis*)
- C. *Borrelia mayonii*
- D. Southern tick-associated rash illness (STARI)
- E. *B. lonestarii* infection

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STARI

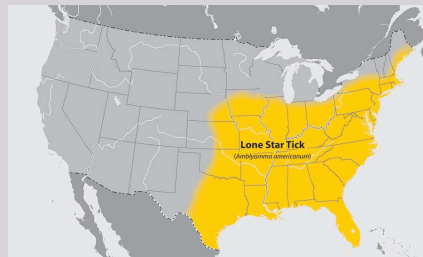
Southern Tick-associated Rash Illness



- Rash variable
 - Expansile from the site of
- Lone Star tick bite
 - Similar to erythema migrans
- Usually, a single lesion
- Multiple described
- Maybe Bull's eye-like

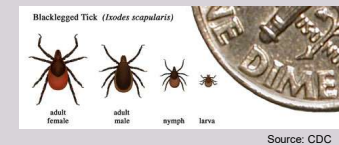
STARI

- No infection yet convincingly documented
 - *B. lonestari* (single case)
 - CDC does not support as cause of STARI
- Symptoms can include fever, headache and musculoskeletal pains
- *B. burgdorferi* tests, including serology negative
- No diagnostic test for STARI. Clinical diagnosis
- **Likely accounts for some reported Lyme disease cases in non-endemic states**
- Unclear if doxycycline is needed, typically given
- No sequelae



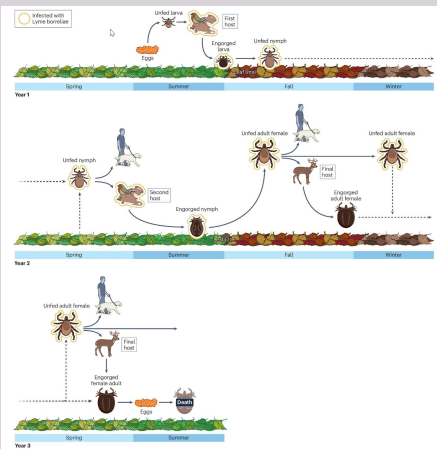
James AM, J Infect Dis 2001;183:1810
Wormser GW, Clin Infect Dis 2005;41:958-65
CDC, STARI (accessed 5/18/25)

B. Burgdorferi Vector-borne Infection



- Spirochetal infection due to *Borrelia burgdorferi* (Bb)
- Tick-borne disease
 - Ixodes species
 - In North America
 - *Ixodes scapularis* (mostly)
 - Black-legged tick
 - *Ixodes pacificus* (uncommon)
 - Western black-legged tick
- Not known as an STD or blood-borne infection

- Commonly called the “deer tick”
 - Small-sized tick, unengorged
 - Adults: sesame seed
 - Nymphs: poppy seed
- Bacterial reservoir:
 - Mice, other small mammals
 - Not: deer, humans



Ixodes spp.

Tick Life Cycle +/- *Borrelia burgdorferi*

Four stages over 2+ years:

Feeding:

- Larvae and nymphs → mammals, birds and lizards
- Adults → deer

Strle, Nat Rev Dis Prim 12(15) 2026

Borrelia burgdorferi sensu lato

USA

• *Borrelia burgdorferi*

- Geographically localized
 - 90% of cases in 15 states + DC
 - Estimates 476,000 cases/yr
 - Especially coastal, lake and river environs
 - New England
 - Mid-Atlantic
 - Upper Midwest

Europe (+ other genospecies)

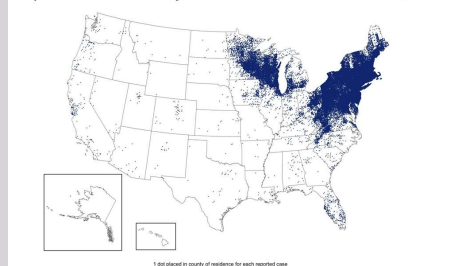
- *Borrelia afzelii* > *B. garinii* >> *Borrelia burgdorferi sensu stricto*, *B. bavariensis*
- Occasionally others
- Genus name: taxonomists prefer *Borrelia* (to distinguish from relapsing fever *Borrelia spp.*)

Most Common Vector-borne Infection in US: A Mostly Regional Disease

Newer States

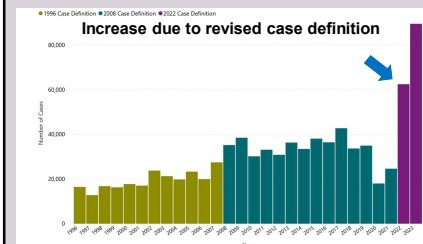
Ohio
Michigan
Indiana
Iowa
Virginia
North Carolina

Reported Cases of Lyme Disease – United States, 2023



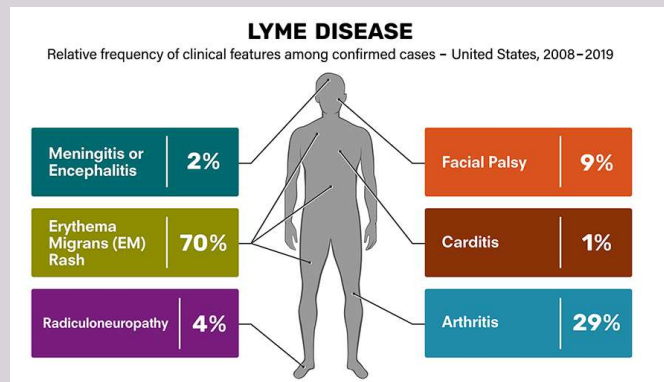
Source: CDC
Accessed 7/18/26

CDC Case Definition (Revised 2020*)



*First applied in the 2022 report. CDC graph last updated 2/11/2025
As of 2022, high-incidence jurisdictions (15): CT, DE, DC, ME, MD, MA, MN, NH, NJ, NY, PA, RI, VT, VA, WV and WI.

- 2022-3 ↑ Lyme disease cases compared to '17-'19
- High incidence states* report based on serology only (w/o clinical information)
- Low-incidence states* require clinical information



(Based on 62% of 311,561 confirmed cases reported-probably favoring later presentations, Source CDC)
<http://www.cdc.gov/lyme/stats/charts/tables/casesbysymptom.html>

Lyme Disease Presentations

- Early, localized
 - Rash: erythema migrans
- Early, disseminated
 - Rash: multiple erythema migrans
 - Cardiac
 - Neurologic
- Late
 - Lyme arthritis
 - Neurologic (rare)
 - Dermatologic (Europe)
- Overlapping presentations possible

Question #2

July, 18M living in suburban Maryland, with this rash growing to ~12 cm, first noted 4d ago, asymptomatic. Landscaper, had tick bite 10d ago. PCP gave cephalexin 2d ago.

Which of the following is true?

- Lack of response to cephalexin is consistent with erythema migrans
- Lack of systemic symptoms makes this unlikely to be Lyme disease
- Ordering *B. burgdorferi* standard 2-tier serology will likely confirm Lyme disease
- Whole blood *B. burgdorferi* PCR is superior to serology in early infection
- Tick should be submitted for detection of *B. burgdorferi* by PCR



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Early, Localized LD: Erythema migrans

Classic: "bull's eye"
With central clearing upon expansion



Most common: homogeneous, pink-red ovoid



Typical Erythema Migrans



Punctum:
site of bite



Lesions: occur typically below neck and above knees & elbows

Spider Bite?

Differential Diagnosis may also be Confused with MRSA, Cellulitis



Less typical erythema migrans: skin punch biopsy *B. burgdorferi* culture positive (research labs only)

Erythema migrans

- Primary lesion: occurs 3-30d [7-14d average] @ site tick bite site
 - 5 cm = more secure diagnosis
 - Ddx: includes cellulitis, tinea, erythema marginatum, tick hypersensitivity reaction (smaller)
 - Diagnosis: characteristic rash + epidemiology
 - Serologic testing not recommended, rash sufficient
 - Acute serology negative 40-70% in early Lyme disease
- Most lesions with minimal local symptoms
 - ~70% experience flu-like problems (fever, HA, myalgia)

Early, Disseminated Lyme Disease 1



- Multiple Erythema Migrans
 - Often smaller and less red than primary lesion
- Always ill:
 - Fever
 - Flu-like symptoms
 - Headache

Early, Disseminated Lyme Disease 2



If suspicious for Lyme disease, and serology negative, repeat in 2-4 wks

- Neuroborreliosis
 - Aseptic meningitis
 - Lymphocytic predominance
 - Cranial nerve palsy
 - CN VII (facial)
 - Most common (if isolated, no LP required)
 - Bilateral CN VII may occur
 - Other CN palsies: seen less
 - e.g., III, VI, VIII
 - Radiculoneuritis
 - Mononeuritis multiplex

Diagnosis: Facial Palsy

- Facial Palsy: up to 25% due to *B. burgdorferi* (Long Island NY)¹
- Serology may take 4-6 wks turn positive
 - (if untreated, recheck if negative and suspicious)
- Lumbar puncture
 - Not required
- Most would recover without antibiotic therapy²
 - Main role of abx: prevent later disease manifestations

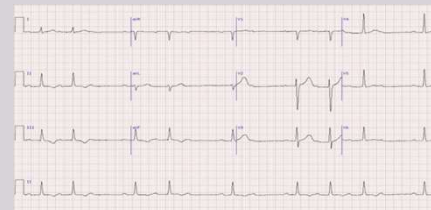
¹Neurology 1992; 41:1268.
²Laryngoscope 1985; 95:1341. Clin Infect Dis. 2006 Nov 1;43(9):1089

Early, Disseminated Lyme Disease 3

- 19M collapsed outside VT college cafeteria
 - Lacrosse athlete, not well for ~ 1 month

Lyme carditis

- 1°, 2° or 3° block
 - May be variable
 - Hospitalize/telemetry for high-grade AV block or PR ≥300 ms
- 3° most commonly identified since symptomatic
 - May need temporary pacer
 - Complete heart block usually resolves within several days of antibiotic; lesser block may take weeks



Question #3

56M Long Island, NY with R knee pain and swelling x 3 weeks. Thought this was a wrenched knee from yardwork.

No fever, rash, tick bite or Lyme disease history. No prior arthritis history. (-) new sexual contacts

PMH: HTN, hyperlipidemia

PE: afebrile, mildly warm knee, moderate effusion, reduced ROM

Labs: nl CBC



Which of the following is usually true for Lyme arthritis?

- A. Knee swelling doesn't remit without arthrocentesis
- B. *B. burgdorferi* PCR synovial fluid ~ 100% sensitivity
- C. Synovial fluid WBCs >50,000 cells/mL
- D. Synovial fluid *B. burgdorferi* culture ~100% sensitivity
- E. Serum *B. burgdorferi* 2-tier testing ~100% sensitivity

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Late Lyme Disease 1: Lyme Arthritis



- Recurrent mono- or oligo-arthritis
 - Knee most common
 - Large, cool effusions
 - Baker's cysts may develop
 - Other large joints possible + TMJ
- Afflicts ~30% untreated patients (historically 50-60%)
- May remit, recur in different joints over period of wks to mos w/o abx Rx

Ann Int Med 1987; 107:725
Lantos, CID Nov 30, 2020

Late Lyme Disease 2: Neurologic

- Encephalopathy:
 - Cognitive dysfunction, objective
 - Due to systemic illness, rather than true CNS infection
- Encephalitis: rare
 - Objective neurological or cognitive dysfunction
 - White matter changes on MRI or abnormal CSF
 - CSF: (+) lymphocytic pleocytosis, Bb antibody
- Peripheral neuropathy: rare (controversial)
 - Pain or paresthesia
 - Diffuse axonal changes on EMG/NCV

Halperin JJ. Brain 2022;145(8):2635-2647
Wormser GW. Diagn Microbiol Infect Dis 2017;87(2):163-167

Late Lyme Disease 3: Dermatologic

Acrodermitis chronica atrophicans (Europe)
Distal extremities most commonly seen



Borrelia Lymphocytoma (Europe)
Earlobes, nipples, genitals favored sites



Question #4

- 49F complains of four years of fatigue, headache, poor sleep and joint aches since trip to London UK
 - PMH: TAH/BSO
 - Medications: hormone replacement
 - SH: Married, accountant. Lives in central Pennsylvania. Two dogs, often sleep in bed.
 - PE: normal
 - Labs: normal CBC, ESR, TSH
 - *B. burgdorferi* serology: EIA (not done), IgM WB 3/3 bands, IgG 1/10

Question #4

What is the best recommendation at this time?

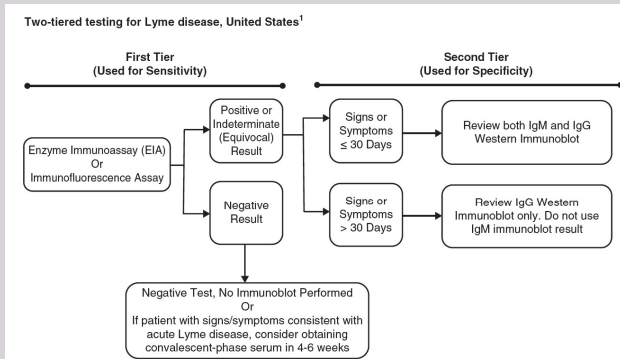
- A. Doxycycline 100 mg twice daily x 14 days
- B. Doxycycline 100 mg twice daily x 28 days
- C. Repeat Lyme serology (two tier: EIA w/ reflex WB)
- D. *Borrelia burgdorferi* PCR (whole blood)
- E. Neither additional Lyme disease testing nor treatment

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Standard Two-tier Testing (STTT)



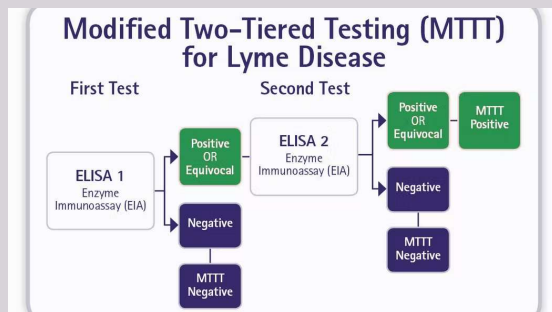
¹Adapted from MMWR 1995

Laboratory Testing

- Standard Two tier (STTT) serology: not needed for erythema migrans
 - First: total Ab screen – ELISA or EIA (for sensitivity)
 - If positive, second tier reflexes to immunoblots (IB, for specificity)
 - IgM: ≥ 2/3 bands, use only if < 4 wks of symptoms
 - High rates false (+)
 - IgG: ≥ 5/10 bands, more reliable
 - Alternative criteria (different bands): less specific
- Often negative in early infection (first 2-3 weeks)
- May need acute/convalescent for confusing rashes or neuroborreliosis
- Serology: may remain (+) for decades including IgM

MMWR 1995;44:590
Clin Infect Dis 2001;33(6):780-5

MTTT: Faster, Cheaper, Better (Early LD)



Modified Two-tier (2-EIA) vs. STTT

- Technically easy, quick
- Less cost
- Appears to provide similar sensitivity/specificity
- Better in early disease

Pooled LD USA	Standard 2-tier	Modified 2-tier	C6 only
Specificity (%)	98.3-100	98.3-100	96.5-100
Sensitivity (%) --Early LD	28-54	38-61	64-68
--Late LD	96-100	98-100	98-100

Branda et al. Clin Infect Dis 2018;66(7):1133-1139

Diagnostics: Lyme arthritis

- Arthrocentesis
 - Synovial fluid: inflammatory
 - 10,000-25,000 WBC average (range: 500 – 100,000)
 - PMN predominant
 - Bb PCR –non standardized
 - Sensitivity 40-96% if prior to antibiotic therapy
 - Specificity 99%
- Serology: ~100% (+) in blood
 - High titer, Bb IgG immunoblot
- Culture: rarely (+)

Arvikar, Steere. Inf Dis Clin N Am 2015;29(2):269-280

FYI: Stats on Lyme Disease Presentations and Routine Diagnostics

Table 1: Sensitivity and specificity of assays for the diagnosis of Lyme disease

Assay	Specimen type	Clinical manifestation	Sensitivity (%)	Selected References	Specificity (%)	Selected References
Standard two-tiered testing	Serum	Early localized	< 40% (acute) 27% (convalescent) 61% (convalescent)	[32] [33] [37] [32] [32]	~99%	[36]
		Early disseminated	86% (carditis) 90% 42-87%	[32] [88] [88]		
	Serum	Neuroborreliosis	90%	[32]	96-100%	[59]
		Late disseminated	100% (arthritis) 97-100%	[32] [88]		
	Serum	Early localized	53% (acute) 58% (acute) 89% (convalescent) 67% (convalescent)	[37] [33] [25] [37] [33] [25]	~99% 96-100%	[36] [86]
		Early disseminated	71-86% (carditis)	[100]		
Modified two-tiered testing	Serum	Neuroborreliosis	98-100%	[22] [37] [100]	96-100%	[22] [37] [38]
		Late disseminated	~100% (arthritis)	[24] [100]		
	Serum and/or skin	Early localized	64-81%	[97]	~100%	[102] ^a [103]
		Serum/Plasma	62%	[101]		
	Serum	Early disseminated	29% (carditis) 25-38%	[32] [102] ^a		[104]
		Neuroborreliosis	73%	[89]		
Polymerase chain reaction	CSF	Neuroborreliosis	73%	[89]		
		Synovial fluid	85% (arthritis) 83% (arthritis)	[102] ^a [89]		

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Kobayashi, Auwaerter. Inf Dis Clinics N Am Sept 2022

Common Clinical Scenarios: Improper Use of Serology

- EIA/ELISA only, no Western blot (WB aka immunoblot)
- Ordering just WB -- w/o EIA/ELISA (total ab)
 - >50% population reactive to 1 or more antigens
- Using the IgM WB alone for symptoms > 1 month
- Serology at time of erythema migrans
- Treating tests that “stay positive [IgM or IgG]”
- Testing samples by WB other than serum
 - CSF or synovial fluid

Other Test Info

- Second-generation Ab assays: both STTT & MTTT
 - Use specific proteins, e.g., C6 or VlsE (variable major protein-like sequence expressed)
 - Offer better sensitivity and specificity than older whole-cell lysate assays
- Beware of “Lyme” specialty labs with unvalidated or poorly validated testing

Clin Infect Dis 2013;57(3):333-343.

Lyme Disease: Initial Regimens

Treatment	Disease Manifestation	Route	Medication ^a	Duration (days) ^b
Lyme disease	Erythema migrans	Oral	Doxycycline	10
			Amoxicillin or Cefuroxime axetil	14
Meningitis/radiculopathy	Oral	IV	Doxycycline	14-21
			Ceftriaxone	14-21
Cranial nerve palsy	Oral	IV	Doxycycline	14-21
			Ceftriaxone	14-21
Encephalomyelitis	Oral	IV	Doxycycline	14-21
			Ceftriaxone	14-21
Carditis	Oral	IV ^c	Doxycycline	14-21
			Amoxicillin or Cefuroxime axetil	14-21
Arthritis	Oral	IV	Doxycycline	28
			Amoxicillin or Cefuroxime axetil	28

^aFurther details regarding adult and pediatric dosing can be found in the 2021 Guideline.
^bRanges are given if available studies are insufficient to determine the optimal duration.
^cCefotaxime and penicillin G are alternative IV options.
^dParenteral therapy is used for hospitalized patients, who, with improvement, may transition to oral antibiotics to complete the treatment course.

Some key points

- 10d doxy ok for early EM
- Neuroborreliosis
 - Oral doxy = IV CTX
 - Ex. Parenchymal CNS dz
- Lyme carditis
 - Once improved → oral

Lantos et al. IDSA/AAO/ACR Lyme Guideline, CID 2021; 72(1):e1-e48

Treatment: Late Lyme Arthritis

- Initial treatment: amoxicillin or doxycycline PO x 28d
 - If lack of response: second course orals or ceftriaxone IV x 14-28d
 - ~10% do not respond to repeated antibiotic therapy
- Post-antibiotic Lyme arthritis
 - No viable organisms (may remain with [+] PCR)
 - Autoimmune phenomenon, associated with certain HLA DR alleles binding to OspA → strong Th1 response
- Treatment: DMARDs, intra-articular corticosteroids, synovectomy

Lyme Disease: Expectations Regarding Resolution

- Subjective problems, post-treatment
 - Prospective studies, treated erythema migrans

Time	Symptomatic
Erythema migrans (d0)	73%
3 months	24%
≥ 6 months	11.5% [0-40.8%]
15 years	Equivalent to general US population

Need to manage expectations

No benefit from additional antibiotics

Post-infectious syndromes not unique to LD

Wormser, et al. Ann Intern Med 2003;138:697; Wormser, et al. Clin Infect Dis 2015;61(2):244
 Cerar, et al. Am J Med 2010;123:79

Randomized, Placebo-controlled Trial Scorecard for Persistent Symptoms Attributed to Lyme Disease after Initial Treatment

Longer-term abx v. placebo Subjective sx OR Encephalopathy after initial treatment	Antibiotics with Durable Effect and Clinically Significant Benefit	Antibiotics Not Effective
7 trials	0	7

Placebo effect: noted in up to 36%

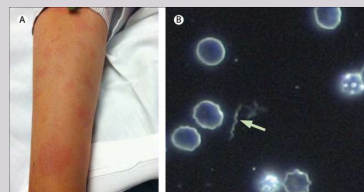
No study yielded evidence of *B. burgdorferi* by culture or PCR in these patients

Klempner M, et al. NEJM 2001; 345:85 (2 studies)
 Krupp LB, et al. Neurology 2003;60:1923
 Oksa J, et al. Eur J Clin Micro 2007;26(8):671
 Fallon BA, et al. Neurology 2008; 70:992
 Sjöwall, BMC Infectious Diseases 2012; 12:186
 Berende A, et al. NEJM 2016;375(13):1209-20 (PLEASE trial)

“Chronic Lyme Disease”

- What is it? Originally, late Lyme disease
 - Now: vague term, often used by some to encompass broad range of symptoms
 - Objective evidence of LD not needed
 - Lack of good clinical history
 - Often no reliable evidence of LD by laboratory testing
 - Offered as explanation for
 - Chronic—fatigue, pain, headaches, brain fog, sleep problems, depression
 - Misattributed to multiple sclerosis, ALS, Alzheimer's, autism, Parkinson's

Borrelia mayonii Considered Part of Lyme Disease



- Ixodes scapularis transmits
- High fever may be present
- May have high spirochetemia
- Lyme serology
 - May be cross-reactive
- Dx:
 - spirochetemia
 - PCR (Mayo, ARUP)

Initial Report: 5 of 6: acute febrile illness with rash (patchy, macular)
1 of 6: 1 month knee pain/swelling
To date: seen in Minnesota, Wisconsin and New York (2025)

Pritt BS, Lancet ID 2016; 16(5):556-564
McGowan MS, OFID 2023;10(11) Oct 24
Nafiz TN, MMWR 6/4/26 75(21)271-272

Question #5

- 42M went camping with his son on Cape Cod, MA
- Didn't use DEET, no tick bites known
- About 4d after returning home, fever, chills, myalgia. Noted rash on thigh
- PMH: none
- PE: Appears ill, non-toxic, 104/60, P96 T101.7°F
- Exam only notable for 3 pink ovoid rashes over trunk, R thigh (largest ~7cm)
- Labs: WBC 2.2 Hg 9.6 plt 110K
- ALT 80 AST 58 Tot Bili 2.4

Doxycycline is prescribed.

What should also be performed as part of the plan?

- A. PCR for *E. chaffeensis*
- B. Serology for spotted fever rickettsia (RMSF)
- C. Blood smear
- D. Serology for *B. burgdorferi*
- E. Nothing additional

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Lyme Disease: Co-infections

- Incidence depends on geographic acquisition
 - *B. microti*: 2-40%
 - HGA: 2-11.7%
 - Uncommon to rare
 - *B. miyamotoi*
 - *B. mayonii*
 - *Ehrlichia ewingii*
 - Powassan virus (Deer Tick virus)
- Disease severity
 - Lyme + HGA:
 - Data mixed on effect
 - Lyme + Babesia:
 - Increases severity of Lyme disease presentation
 - Converse: Lyme doesn't appear to affect Babesia presentations

IDSA/AAO/ACR Lyme disease Guideline 2020

Question #6

- 42M just returned from a hiking trip Colorado, a tick on his arm removed 2d earlier. Now heading out of town for a beach vacation.
- Today, intense itching and redness at the site he thinks may be larger (~1cm) than yesterday. He is otherwise well.



Which would be the best course of action?

- A. Doxycycline 200mg x single dose
- B. Doxycycline x 14d
- C. Doxycycline x 30d
- D. Cefuroxime x 14d
- E. Observation

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- E. **Observation***

I. scapularis Tick Bite Prophylaxis

B. burgdorferi transmittal

Tick attachment time

< 24 h:	0/58 (0%)
< 48 h:	4/50 (8%)
< 72 h:	36/52 (69%)

Infection risk in highly endemic areas

Intervention	Risk	95% CI
No tick found	20%	
Removing tick	2.2%	[1.2-3.9%]
Single 200mg dose doxycycline*	0.4%	[0.02-2.1%]
10d doxy	0%	[0-0.97%]

Prophylaxis: Doxy 200 mg x 1 dose only for high-risk Ixodes bites in an endemic area, ≥ 36 hrs attached, dose within 72 h

JID 2001; 183:773-8; J Antimicrob Chemother 2010;65:1137-1144; N Engl J Med 2001; 345:79-84; 2020 IDSA/AAO/ACR Lyme disease Guideline

Lyme Disease: Some Pearls

- No need for serology for erythema migrans = clinical dx
- *B. burgdorferi* IgM immunoblot most common cause of misdiagnosis for patients w/ symptoms > 1 month
- Late Lyme arthritis: ~100% seropositive (IgG)
 - No evidence that seronegative Lyme exists in patients with long-term symptoms
- Lab evidence of LD essential unless hx of EM exists
- Prolonged antibiotic treatment doesn't improve resolution of subjective symptoms