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 Pharmaceutics

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

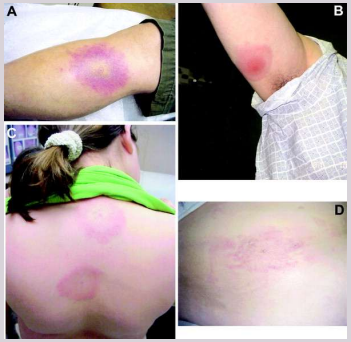
- Annular “bulls-eye” ~6 cm
- (same area that engorged tick was removed earlier in the week)

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

STARI
Southern Tick-associated Rash Illness



CDC

- 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

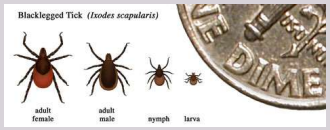
STARI

- 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)

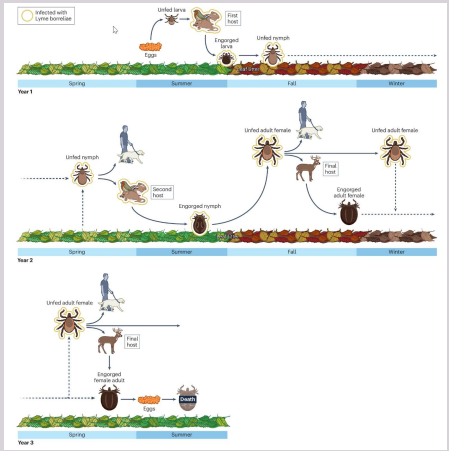
B. Burgdorferi
Vector-borne Infection

- 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



Source: CDC

- 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

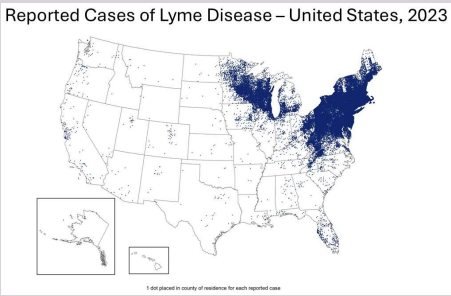
Europe (+ other genospecies)

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

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

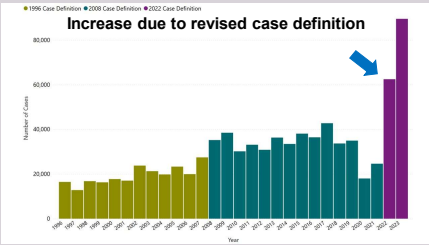
Newer States

Ohio
Michigan
Indiana
Iowa
Virginia
North Carolina



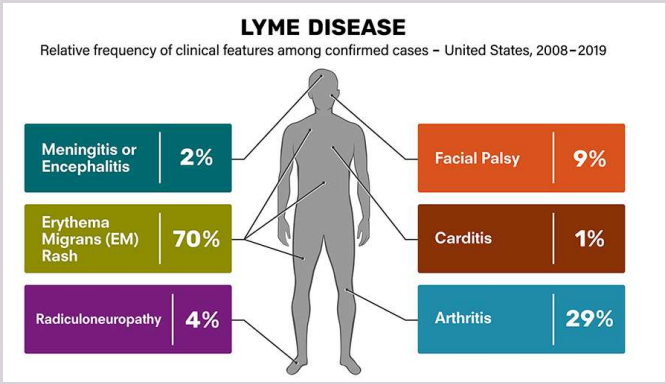
Source: CDC
Accessed 7/18/26

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/chartstables/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?

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

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

19 Lyme Disease
Speaker: Paul Auwaerter, MD

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

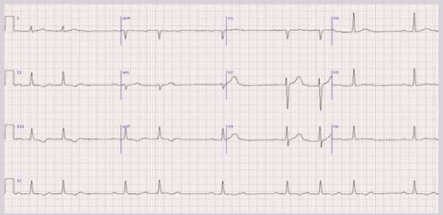
Diagnosis:
Facial Palsy

- 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

[1]Neurology 1992; 41:1268.
[2]Laryngoscope 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

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

19 Lyme Disease
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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 Micro Biol 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

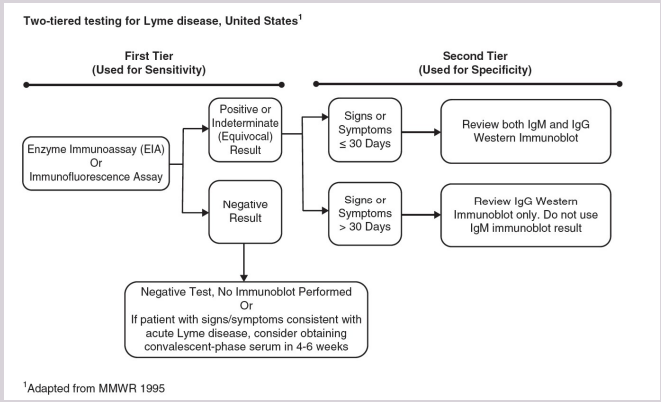
- 49F complains of four years of fatigue, headache, poor sleep and joint aches since trip to London UK
  - PMH: TAH/BSO
  - Medications: hormone replacement
  - SH: Married, accountant. Lives in central Pennsylvania. Two dogs, often sleep in bed.
  - PE: normal
  - Labs: normal CBC, ESR, TSH
    - *B. 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

Standard Two-tier Testing (STTT)



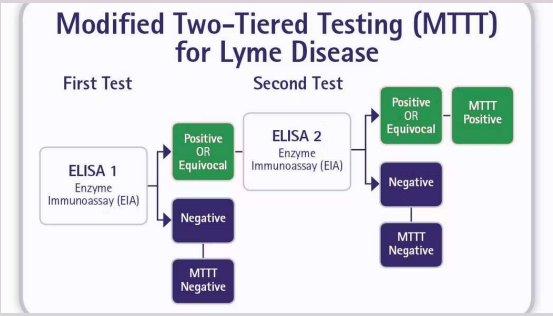
[1]Adapted from MMWR 1995

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 Infec 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

Table1: 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] [97] [33] [32]	~99%	[36]
	Serum	Early disseminated	86% (carditis) 90% 42–87%	[32] [98] [99]	~99%	[98]
	Serum	Neuroborreliosis	90%	[32]	96–100%	[39]
	Serum	Late disseminated	100% (arthritis) 97–100%	[32] [99]	99–100%	[24] [39]
Modified two-tiered testing	Serum	Early localized	53% (acute) 58% (acute) 89% (convalescent) 67% (convalescent)	[37] [33] [25] [37] [33] [25]	~99% 96–100%	[36] [39]
	Serum	Early disseminated	71-86% (carditis)	[100]	96–100%	[39]
	Serum	Neuroborreliosis	98–100%	[22] [37] [100]	96–100%	[22] [37] [39]
	Serum	Late disseminated	~100% (arthritis)	[24] [100]	96–100%	[24] [39]
Polymerase chain reaction	Serum and/or skin Serum/Plasma	Early localized	64–81% 62%	[97] [101]	~100%	[102]* [103] [104]
	Serum	Early disseminated	29% (carditis)	[32]		
	CSF	Neuroborreliosis	25-38% 73%	[102]* [99]		
	Synovial fluid	Late disseminated	85% (arthritis) 83% (arthritis)	[102]* [99]		

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 or Amoxicillin or Cefuroxime axetil	10 14 14
Meningitis/radiculopathy	Oral IV[c]	Doxycycline Ceftriaxone	14-21 14-21
Cranial nerve palsy	Oral	Doxycycline	14-21
Encephalomyelitis	IV[c]	Ceftriaxone	14-28
Carditis	Oral IV[d]	Doxycycline or Amoxicillin or Cefuroxime axetil Ceftriaxone	14-21 14-21
Arthritis	Oral	Doxycycline or Amoxicillin or Cefuroxime axetil	28

[a]Further details regarding adult and pediatric dosing can be found in the 2021 Guideline
[b]Ranges are given if available studies are insufficient to determine the optimal duration.
[c]Cefotaxime and penicillin G are alternative IV options.
[d]Parenteral 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/AAN/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%

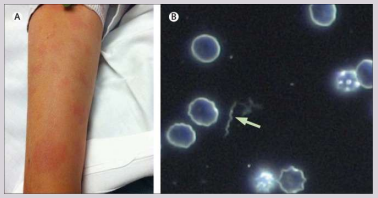
No study yielded evidence of *B. burgdorferi* by culture or PCR in these patients

Klempner M, et al. NEJM 2001; 345:85 (2 studies)
Krupp LB, et al. Neurology 2003;60:1923
Oksi J, et al. Eur J Clin Micro 2007;26(8)571
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: seem 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

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 eauclairensis*
    - 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/AAN/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

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/AAN/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