Lyme Disease
AKA Lyme Borreliosis

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8/5/2025

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Disclosures of Financial Relationships with Relevant Commercial Interests

- **Research:** Pfizer (investigational vaccine)
- **Consulting:** medical-legal

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Question #1

A 56-year-old man from southern Missouri

Onset in July:

- Myalgia and malaise
- Rash x 2d at site of tick bite 1 week ago

Exam: T 37.0°C

Annular "bulls-eye" ~6 cm

(same area that engorged tick was removed earlier in the week)

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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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CDC

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

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No infection yet convincingly documented

- *B. lonestarii* (single case)

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

STARI

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

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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 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

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Borrelia burgdorferi sensu lato

USA

- *Borrelia burgdorferi*
  - Geographically localized
    - 90% cases in 15 states
    - Estimates 300,000-476,000 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: changing to *Borreliella?*

(to distinguish from relapsing fever *Borrelia spp.*)

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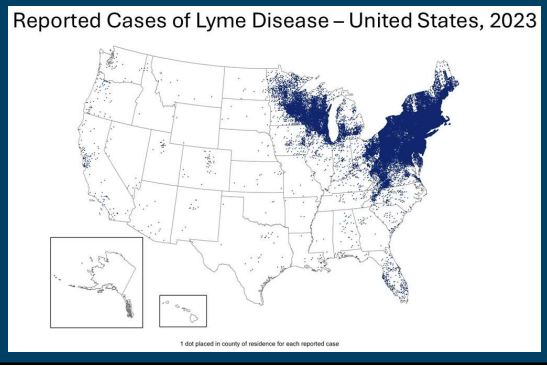
Most Common Vector-borne Infection in US: A Mostly Regional Disease

Source: CDC accessed 5/15/25

Newer States
Ohio
Michigan
Indiana
Iowa
Virginia
North Carolina



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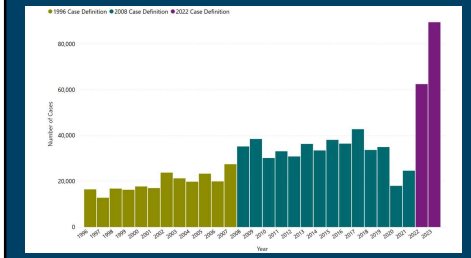
CDC Case Definition (Revised 2020*)



- 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

*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.

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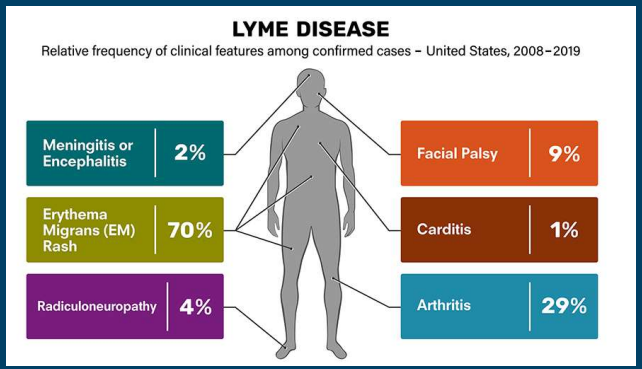

(based on 62% of 311,561 confirmed cases reported--probably favoring later presentations, Source CDC)
http://www.cdc.gov/lyme/stats/chartstables/casesbysymptom.html

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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

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29 Lyme Disease
Speaker: Paul Auwaerter, MD

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

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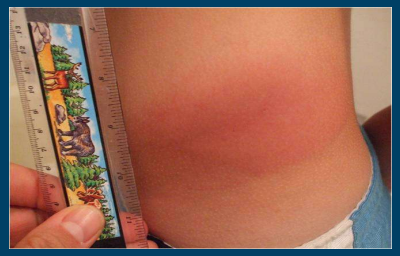
Early, Localized LD: Erythema migrans

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

Most common: homogeneous, pink-red ovoid



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Typical Erythema Migrans

Punctum:
site of bite

Lesions: occur typically below neck and above knees & elbows

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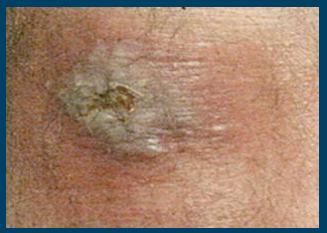
Spider Bite?: Differential Diagnosis May Also be Confused with MRSA, Cellulitis



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

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Erythema Migrans

- Primary lesion: occurs 3-30d [7-14d average] @ site tick bite site
  - > 5cm = 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)

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Early, Disseminated Lyme Disease (1)

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

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Early, Disseminated Lyme Disease (2)

- Neuroborreliosis
  - Aseptic meningitis
    - Lymphocytic predominance
  - Cranial nerve palsy
    - CN VII (facial)
      - Most common
      - Bilateral CN VII may occur
      - Other CN palsies: seen less
        - e.g., III, VI, VIII
  - Radiculoneuritis
  - Mononeuritis multiplex

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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 therapy[2]
  - 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

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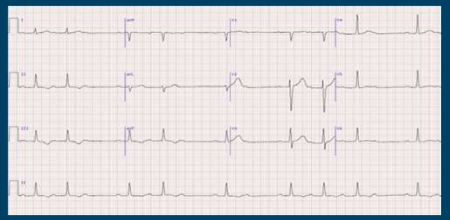
Early, Disseminated Lyme Disease (3)

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



- Lyme carditis
  - 1°, 2° or 3° block
    - May be variable
    - 3° most identified since symptomatic
      - May need temporary pacer
      - Complete heart block usually resolves within several days of antibiotic, lesser block may take weeks

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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

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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

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Late Lyme Disease (3): Dermatologic

Europe only

Acrodermitis chronica atrophicans (Europe)
Distal extremities most commonly seen

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

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Question #4

PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

49-year-old F 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

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Question #4

PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

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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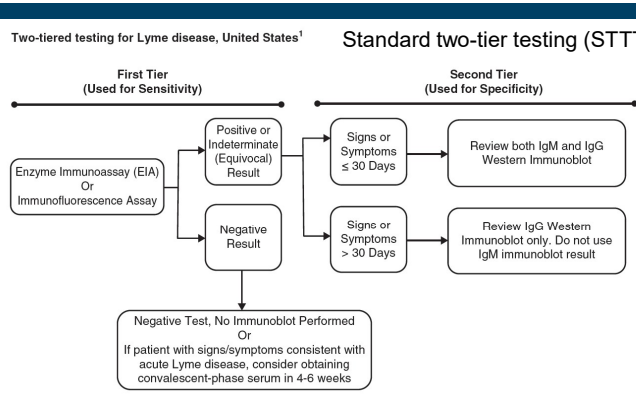
Two-tiered testing for Lyme disease, United States[1]

Standard two-tier testing (STTT)



[1]Adapted from MMWR 1995

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Speaker: Paul Auwaerter, MD

Laboratory Testing

- Two tier 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

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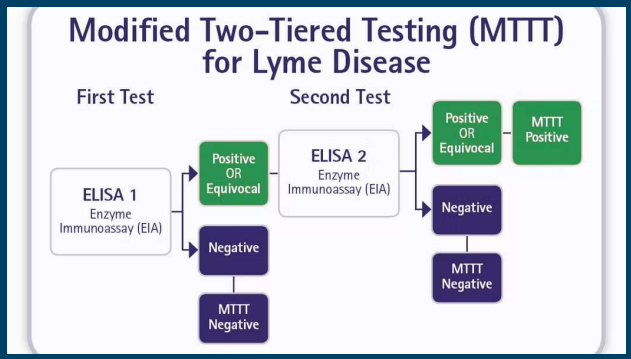
MTTT: Faster, Cheaper, Better (Early LD)



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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

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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

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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]		

Kobayashi, Auwaerter. Inf Dis Clinics N Am Sept 2022

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Common Clinical Scenarios: Improper Use of Serology

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

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Other Tests

- Second generation Ab assays: both STTT & MTTT
  - C6 or VlsE (variable major protein-like sequence expressed)
  - Offers better sensitivity and specificity than whole cell lysate assays
- Beware of "Lyme" specialty labs with unvalidated or poorly validated testing

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

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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
1. 10d doxy ok for early EM
2. Neuroborreliosis
   Oral doxy = IV CTX
   Do not need CTX
3. Lyme carditis
   Once improved → oral

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

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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
    - Bb culture/PCR (-), no viable organisms
    - Autoimmune phenomenon, associated with certain HLA DR alleles binding to OspA → strong Th1 response
  - Treatment: DMARDs, intra-articular corticosteroids, synovectomy

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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

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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

1. Klempner M, et al. NEJM 2001; 345:85 (2 studies)
2. Krupp LB, et al. Neurology 2003;60:1923
3. Oksi J, et al. Eur J Clin Micro 2007;26(8)571
4. Fallon BA, et al. Neurology 2008; 70:992
5. Sjöwall, BMC Infectious Diseases 2012; 12:186
6. Berende A, et al. NEJM 2016;375(13):1209-20 (PLEASE trial)

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"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
    - Legitimate diseases: multiple sclerosis, ALS, Alzheimer's, autism, Parkinson's

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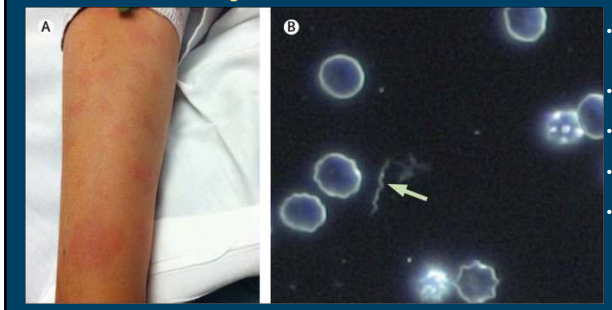
Borrelia mayonii, Considered Part of Lyme Disease



- Acquired from *Ixodes scapularis*
- High fever may be present
- May have high Spirochetemia
- Lyme seroconversion absent
- Dx: spirochetemia, PCR

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

Pritt BS, Lancet ID 2016; 16(5):556-564
McGowan MS. OFID 2023;10(11) Oct 24

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PA2

Question #5

PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

42-year-old M 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

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PA2

Question #5

PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

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 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

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Slide 42

PA2 Correct answer is e

Paul Auwaerter, 7/12/2015

Slide 43

PA2 Correct answer is e

Paul Auwaerter, 7/12/2015

Question #6

42-year-old M 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.

What would the best course of action be?

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

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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%)

JID 2001; 183:773-8

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%]

*200 mg given with 72h of tick bite

J Antimicrob Chemother 2010;65:1137-1144
N Engl J Med 2001; 345:79-84

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Lyme Disease: Some Pearls

- No need for serology if diagnosing erythema migrans
- *B. burgdorferi* IgM immunoblot most common cause of misdiagnosis for patients w/ symptoms > 1 month
- Late Lyme arthritis: always 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

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