

30 – Lyme Disease

Speaker: Paul Auwaerter, MD

IDBR
INFECTIOUS DISEASE BOARD REVIEW
AUGUST 17-21, 2024

Lyme Disease

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- Disclosures of Financial Relationships with Relevant Commercial Interests
 - Consultant: Gilead, Shionogi
 - Research Grant: Pfizer
 - Ownership Interest: Johnson & Johnson

Question # 1 **PREVIEW QUESTION**

A 56 y.o 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)

Question # 1 **PREVIEW QUESTION**

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



- Rash variable
- Usually single lesion
- Multiple described
- Maybe Bull's eye-like

CDC

STARI

No infection yet convincingly documented
B. lonestarii (single case)

Appears to occur after bite of Lone star tick

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 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 6/22/24)

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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

Commonly called the "deer tick"

Small-sized tick, unengorged
Adults: sesame seed
Nymphs: poppy seed

Bacterial reservoir:
Mice, other small mammals
Not: deer, humans

Source: CDC

Borrelia burgdorferi sensu lato

USA

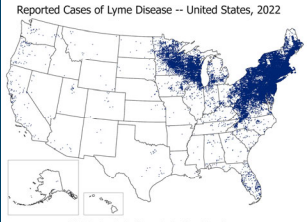
- Borrelia burgdorferi*
 - Geographically localized
 - 90% cases in 15 states
 - Estimates 300,000-476,000 cases/yr
 - Especially coastal, lake and river environs
 - New England
 - Mid-Atlantic
 - Upper Midwest

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.)

Most common vector-borne infection in US: A mostly regional disease

Reported Cases of Lyme Disease -- United States, 2022

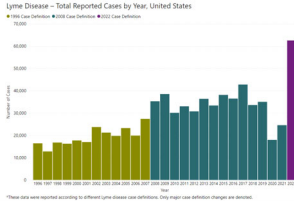


Newer States
Ohio
Michigan
Indiana
Iowa
Virginia
North Carolina

I did place randomly within county of residence for each case

Source: CDC accessed 6/23/24

CDC Case Definition (Revised 2020*)

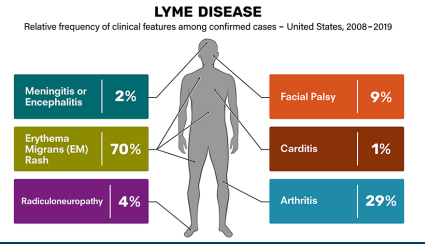


- 2022 ↑ Lyme disease cases = 1.7 x '17-'19
- High incidence states report based on serology only (w/o clinical information)
- Low incidence states require clinical information

*First applied in year 2022 report
As of 2022, high-incidence jurisdictions (15): CT, DE, DC, ME, MD, MA, MN, NH, NJ, NY, PA, RI, VT, VA, WV and WI.

LYME DISEASE

Relative frequency of clinical features among confirmed cases - United States, 2008-2019



Meningitis or Encephalitis	2%	Facial Palsy	9%
Erythema Migrans (EM) Rash	70%	Carditis	1%
Radiculoneuropathy	4%	Arthritis	29%

(based on 62% of 311,561 confirmed cases reported—probably favoring later presentations. Source CDC)
<http://www.cdc.gov/lyme/diagn/char/bb/bb/caseserv/p00m.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

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Question # 2

PREVIEW QUESTION



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

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
 - > 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)

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

Diagnosis – Facial Palsy

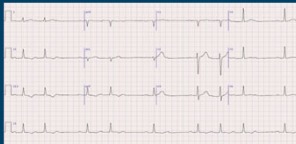
- Facial Palsy: up to 25% due to *B. burgdorferi* (Long Island NY)¹
- Serology may take 4-6 wks turn positive
 - (if untreated, recheck if negative and suspicious)
- Lumbar puncture
 - Not required
- Most would recover without antibiotic therapy²
 - Main role of abx: prevent later disease manifestations

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
 - 3° most identified since symptomatic
 - May need temporary pacer
 - Complete heart block usually resolves within several days of antibiotic, lesser block may take weeks

PA2

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

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

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PA2

Correct answer is e

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Late Lyme disease (3): Dermatologic

Acrodermatitis chronica atrophicans (Europe)
Distal extremities most commonly seen

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

Question # 4

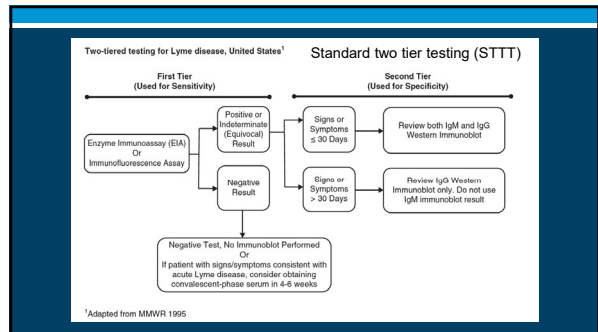
49F complains of four years of fatigue, headache, poor sleep and joint aches since trip to London UK

- 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?

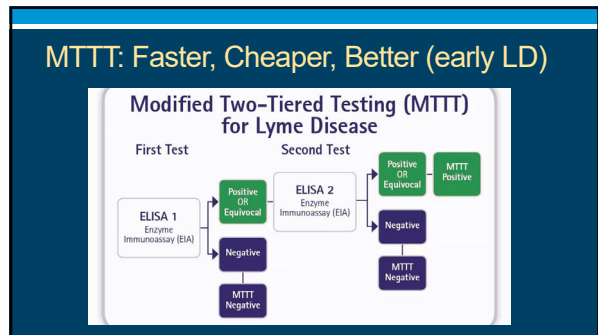
- Doxycycline 100 mg twice daily x 14 days
- Doxycycline 100 mg twice daily x 28 days
- Repeat Lyme serology (two tier: EIA w/ reflex WB)
- Borrelia burgdorferi* PCR (whole blood)
- Neither additional Lyme disease testing nor treatment



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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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 (%)	28-54	38-61	64-68
–Early LD			
–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 (%)	Specificity (%)	Reference	
Standard two-tier testing	Serum	Early localized	~40% (acute)	98-100%	[30]	
		Early disseminated	47% (serum), 67% (CSF)	98-100%	[30]	
	Serum	Late disseminated	80%	98-100%	[30]	
		Neuroborreliosis	80%	96-100%	[30]	
	Modified two-tier testing	Serum	Early localized	60% (acute)	98-100%	[30]
			Early disseminated	60% (acute), 87% (serum), 87% (CSF)	98-100%	[30]
Serum		Late disseminated	73-88% (acute)	96-100%	[30]	
		Neuroborreliosis	86-100%	98-100%	[30]	
Pigmentation		Serum and/or with skin lesions	Early localized	64-87%	100%	[100]
			Early disseminated	82%	100%	[100]
	Serum	Late disseminated	79%	100%	[100]	
		Neuroborreliosis	84-98%	100%	[100]	
	Synovial fluid	Early localized	79%	100%	[100]	
		Late disseminated	80%	100%	[100]	

Kobayashi, Auwaerter. Inf Dis Clinics N Am Sept 2022

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

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.

Lyme disease: Initial Regimens

Disease Manifestation	Route	Medication*	Duration (days)†
Lyme disease	Oral	Doxycycline	10
		Azithromycin or Ceftriaxone axetil	14
Meningitis/radiculopathy	IV‡	Doxycycline	14-21
		Ceftriaxone	14-21
Cranial nerve palsy	Oral	Doxycycline	14-21
		Ceftriaxone	14-28
Carditis	Oral	Doxycycline	14-21
		Azithromycin or Ceftriaxone axetil	14-21
Arthritis	Oral	Doxycycline	21
		Azithromycin or Ceftriaxone axetil	21

*Further details regarding adult and pediatric dosing can be found in the 2021 Guideline.
 †Ranges are given if available studies are insufficient to determine the optimal duration.
 ‡Ceftriaxone and penicillin G are alternative IV options.
 §Parenteral therapy is used for hospitalized patients, who, with improvement, may transition to oral antibiotics to complete the treatment course.

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

- 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

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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
 - Abx-refractory 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

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
Cesar, 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	Antibiotics with Durable Effect and Clinically Significant Benefit	Antibiotics Not Effective
Subjective sx OR Encephalopathy after initial treatment	0	7

Placebo effect: noted in up to 36%
No study yielded evidence of *B. burgdorferi* by culture or PCR in these patients

1. Kampour M, et al. NEJM 2001; 345:85 (2 studies)
2. Krupp LB, et al. Neurology 2003;61:1663
3. Olan J, et al. Eur J Clin Micro 2007;20(6):671
4. Fallon BA, et al. Neurology 2008; 70:289
5. Sowell BMC Infectious Diseases 2012; 12:198
6. 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
 - Legitimate diseases: multiple sclerosis, ALS, Alzheimer’s, autism, Parkinson’s

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 Bill 2.4

Doxycycline is prescribed. What should also be performed as part of the plan?

- PCR for *E. chaffeensis*
- Serology for spotted fever rickettsia (RMSF)
- Blood smear
- Serology for *B. burgdorferi*
- 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

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PA2

Correct answer is e

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Question # 5

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.

The best course of action would be:

- 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 Infection risk in highly endemic areas

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

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

JID 2001; 183:773-8 J Antimicrob Chemother 2010;65:1137-1144
N Engl J Med 2001; 345:79-84

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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Correct answer is e

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