

# 53 – Lyme Disease

Speaker: Paul Auwaerter, MD

**IDBR**  
**INFECTIOUS DISEASE BOARD REVIEW**  
**AUGUST 20-24**  
**2022**

## Lyme Disease

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7/18/2022


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### Disclosures of Financial Relationships with Relevant Commercial Interests

- Consulting –Pfizer, medical-legal
- Research –Pfizer

### Question # 1

A 56 y.o man from southern Missouri  
Onset in July:  
Myalgia and malaise  
Rash of two days duration  
Tick bite 1 week ago



Exam: T 37.0°C  
Annular "bull's-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



- Rash variable
- Usually single lesion
- Multiple described
- Maybe Bull's eye-like
- Expanding range of Lone Star Tick (name may be obsolete?)

### STARI

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


Appears to occur after bite of Lone star tick

*B. burgdorferi* tests including serology negative

\*\*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  
CDC, <https://www.cdc.gov/stari/gpo/index.html>  
(accessed 7/18/22, last updated 11/19/18)

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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*
      - Western black legged tick
- Not known as STD or blood-borne infection



Source: CDC

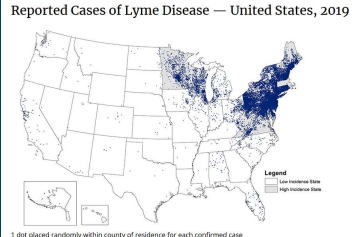
Commonly called the “deer tick”

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

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

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

### Reported Cases of Lyme Disease — United States, 2019



1 dot placed randomly within county of residence for each confirmed case

Legend  
Low incidence state  
High incidence state

Source: CDC accessed 7/18/22

## Lyme Borreliosis

### USA

- Borrelia burgdorferi*
  - Geographically localized
    - ~20-30,000 cases reported annually in US
      - Actual >10x more than reported
    - 95% cases in 14 states
    - Coastal, lake and river environs
      - New England
      - Mid-Atlantic
      - Upper Midwest

### Europe

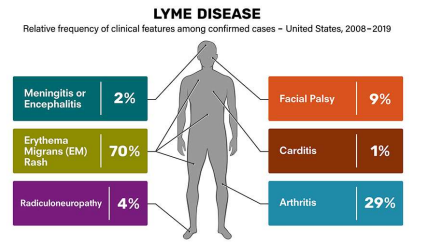
- Borrelia afzelii* & *Borrelia garinii* >> *Borrelia burgdorferi*
- Occasionally others
- Genus name: changing to *Borreliella*?  
(to distinguish from relapsing fever *Borrelia* spp.)

## 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

## LYME DISEASE

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



(based on 62% of 311,561 confirmed cases reported—probably favoring later presentations, Source CDC; accessed 6/21/21)  
<http://www.cdc.gov/lyme/about/characteristics/casesurveyreport.html>

## 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* 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
  - > 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

### 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

# 53 – Lyme Disease

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## Diagnosis – Facial Palsy

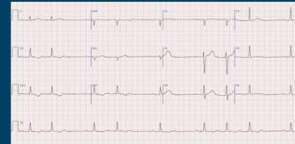
- Facial Palsy: up to 25% due to *B. burgdorferi* (Long Island NY)<sup>1</sup>
- Serology may take 4-6 wks turn positive
  - (if untreated, recheck if negative and suspicious)
- Lumbar puncture
  - Not required
  - Most would recover without antibiotic therapy<sup>2</sup>
  - Main role of abx: prevent later disease manifestations

<sup>1</sup>Neurology 1992; 41:1268.

<sup>2</sup>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
  - 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

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. If untreated, the knee swelling will not remit
- 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



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

- 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

## 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

## Late Lyme disease (3): Dermatologic

Acrodermitis chronica atrophicans (Europe)

Borrelia Lymphocytoma (Europe)



# 53 – Lyme Disease

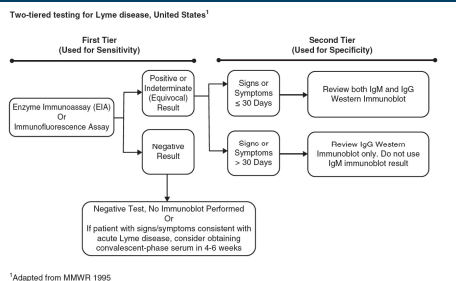
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## Question # 4

- 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)
  - Lyme C6 antibody assay
  - Neither additional Lyme disease testing nor treatment



## Laboratory testing

- Two tier serology: not needed for erythema migrans
- First: total Ab screen – ELISA or EIA
- If positive, second tier reflexes to immunoblots (IB)
  - 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

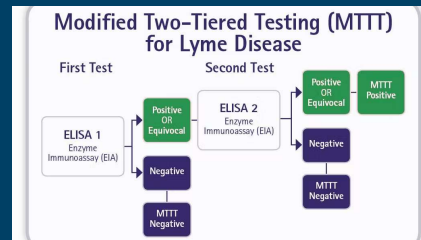
## Modified Two-tier (2-EIA) vs. STTT

- 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
<b>Specificity (%)</b>	98.3-100	98.3-100	96.5-100	96.5-100
<b>Sensitivity (%)</b>				
–Early LD	28-54	38-61	64-68	
–Late LD	96-100	98-100	98-100	98-100

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

## MTTT: Faster, Cheaper, Better?



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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

## 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
Western blot	Serum	Early localized	7-40% (acute)	100%	[16]
		Disseminated	87% (convalescent)	100%	[16]
		Late disseminated	87% (convalescent)	100%	[16]
	Synovial fluid	Early disseminated	80% (acute)	96%	[16]
		Disseminated	80%	96%	[16]
		Late disseminated	80% (convalescent)	96%	[16]
Modified two-tier testing	Serum	Early localized	57% (acute)	100%	[17]
		Disseminated	89% (convalescent)	100%	[17]
		Late disseminated	89% (convalescent)	100%	[17]
	Synovial fluid	Early disseminated	77.8% (acute)	100%	[17]
		Disseminated	86.7%	100%	[17]
		Late disseminated	86.7%	100%	[17]
Polymerase chain reaction	Serum	Early localized	64.4%	100%	[18]
		Disseminated	62%	100%	[18]
		Late disseminated	64.4%	100%	[18]
	Synovial fluid	Early localized	39% (acute)	100%	[18]
		Disseminated	41.2%	100%	[18]
		Late disseminated	41.2%	100%	[18]

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: C6 or VlsE (variable major protein-like sequence expressed)
- C6 Ab: more specific than first tier screen
  - Less specific than full two tier test
  - Positive, earlier in infection
  - Helpful to discriminate false (+) IgM IB
  - Better at detecting *B. garinii*, *B. afzelii* (Europe)
- 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) <sup>b</sup>
Lyme disease	Erythema migrans	Oral	Doxycycline	10
			Amoxicillin or Cefuroxime axetil	14
Meningitis/radiculopathy	Oral	IV <sup>c</sup>	Doxycycline	14-21
			Ceftriaxone	14-21
Cranial nerve palsy	Oral	IV <sup>c</sup>	Doxycycline	14-21
			Ceftriaxone	14-28
Encephalomyelitis	Oral	IV <sup>c</sup>	Doxycycline	14-21
			Amoxicillin or Cefuroxime axetil	14-21
Arthritis	Oral	IV <sup>c</sup>	Ceftriaxone	14-21
			Doxycycline or Amoxicillin or Cefuroxime axetil	28

\*Further details regarding adult and pediatric dosing can be found in the 2021 Guideline.  
<sup>b</sup>Ranges are given if available studies are insufficient to determine the optimal duration.  
<sup>c</sup>Ceftriaxone and penicillin G are alternative IV options.  
<sup>d</sup>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 GL, 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
- 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

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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

## 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

- Kruppner M, et al. NEJM 2001; 345:80 (2 studies)
- Krivy L, et al. Neurology 2003;63:1923
- Chang J, et al. Eur J Clin Microb 2007;26:6271
- Fisher BA, et al. Neurology 2008; 70:922
- Sprell, BMC Infectious Diseases 2012; 12: 188
- Berardo A, et al. NEJM 2016;375:1311-20 (PLEASE read)

## “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

PA2

## 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 Bil 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 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/AAN/ACR Lyme disease Guideline 2020

## *B. miyamotoi*--Ixodes spp. vector

Neither Lyme disease nor Relapsing Fever



- Serosurvey New England: 0.8-4.0%
- Likely underdiagnosed
- Sx: HA, fever, chills, myalgia
- Not like relapsing fever:
  - No rigor, ↓ BP
  - May resemble HGA
    - Leukopenia, thrombocytopenia, LFT abn
  - Opportunistic pathogen?
- Dx: not widely available
  - rGIPQ EIA
  - PCR
  - Spirochetes on fluid H&E
  - Doesn't appear to frequently cross-react with *B. burgdorferi* Ab
  - Treatment: likely identical as for LD

Telford, et al. Clin Lab Med 2015; 35(4):867

# 53 - Lyme Disease

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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
- Late Lyme arthritis: always seropositive
  - 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