

## 48 – Lyme Disease

Speaker: Paul G. Auwaerter, MD

**2020 INFECTIOUS DISEASE BOARD REVIEW**

**Lyme Disease**

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### Disclosures of Financial Relationships with Relevant Commercial Interests

- Scientific Advisory Board – DiaSorin, Adaptive BioTherapeutics
- Grantee – MicroBplex, NIH/SBIR (Lyme disease diagnostics)
- Equity – JNJ

### 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 "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 due to *Borrelia burgdorferi*
- B. Human Monocytic Ehrlichiosis, *Ehrlichia chaffeensis*
- C. *Borrelia mayonii*
- D. Southern tick-associated rash illness (STARI)
- E. B. lonestari 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. lonestari (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
- No sequelae

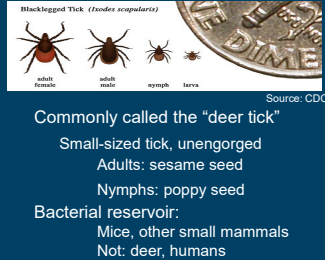
James AM, J Infect Dis 2001;183:1810

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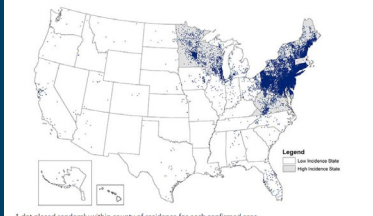
## *B. burgdorferi*: Vector-borne Infection

- 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



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

Reported Cases of Lyme Disease — United States, 2018



## Lyme Borreliosis

### USA

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

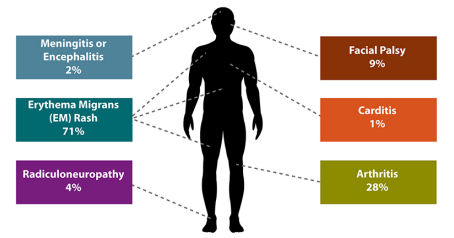
### Europe

- *Borrelia afzelii* & *Borrelia garinii*
  - >> *Borrelia burgdorferi*
- Occasionally others
- Genus name: changing to *Borrelia*?

## Lyme Disease Presentations

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

Lyme disease - Relative frequency of clinical features among confirmed cases - United States, 2008 - 2017



(based on 61% of reported cases 235,037—probably favors later presentations, Source CDC; accessed 7/21/19)  
<http://www.cdc.gov/lyme/stats/chartables/casesbyasymptom.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 Lyme PCR

## 48 – Lyme Disease

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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



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

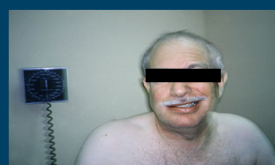
- Primary lesion: occurs 3-30d [7-14d average] @ site tick bite site
  - > 5cm = more secure diagnosis
    - Ddx: includes cellulitis, tinea, erythema marginatum, tick hypersensitivity reaction (smaller)
  - Diagnosis: characteristic rash + epidemiology
    - Serologic testing not recommended, rash sufficient
    - 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: seen less
      - e.g., III, VI, VIII
  - Radiculoneuritis
  - Mononeuritis multiplex

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## Diagnosis – Facial Palsy

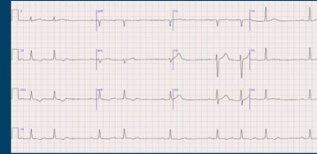
- Facial Palsy: up to 25% due to *B. burgdorferi* (Long Island NY)<sup>1</sup>
- Serology may take 4-6 wks turn positive
  - (if untreated, recheck if negative and suspicious)
- Lumbar puncture
  - Optional
- Most would recover without antibiotic therapy<sup>2</sup>
  - Main role of abx: prevent later disease

<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

## 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



- Recurrent mono- or oligo-arthritis
  - Knee most common
    - Large, cool effusions
    - Baker's cysts may develop
  - Other large joints possible + TMJ
- Affects 50-60% untreated patients
- May remit, recur over period of wks to mos w/o abx rx

Ann Int Med 1987; 107:725

## 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

Acrodermatitis chronica atrophicans (Europe)

Borrelia Lymphocytoma (Europe)



## Slide 21

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**PA2**

Correct answer is e

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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?
  - A. Doxycycline 100 mg x 14 days
  - B. Doxycycline 100 mg x 28 days
  - C. Repeat Lyme serology (two tier: EIA w/ reflex WB)
  - D. Lyme C6 antibody assay
  - E. Neither additional Lyme disease testing or 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:  $\geq 2/3$  bands, use only if  $< 4$  wks of symptoms
      - High rates false (+)
    - IgG:  $\geq 5/10$  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

### 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

### 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.

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## Lyme disease: Antibiotics

- **Oral**
  - Doxycycline
  - Amoxicillin
  - Cefuroxime
- **Parenteral**
  - Ceftriaxone
  - Cefotaxime
  - Penicillin G
- **Duration**
  - 10d EM doxycycline
  - 14d EM amoxicillin
  - 14-21d neurologic-28d days
  - 28d arthritis (oral)
  - 14d arthritis (parenteral, usually as second course)
- **Parenteral therapy**
  - Neuroborreliosis
    - Not necessary, CN VII palsy
    - European data suggests oral doxycycline equivalent
  - Late Lyme arthritis (some usually after oral first course)
  - Carditis (3\*, initially)
- Subjective symptoms may persist after abx
  - More common in women

Sanchez et al. JAMA. 2016;315(16):1767-77

## Treatment: Late Lyme arthritis

- Initial treatment: amoxicillin or doxycycline PO x 28d
  - If lack of response: second course orals or ceftriaxone IV x 14d
- ~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  
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

1. Klemperer M, et al. NEJM 2001; 345:86 (2 studies)
2. Krupp LB, et al. Neurology 2003;60:1923
3. Chera J, et al. Eur J Clin Microb 2007;26:6571
4. Fallon BA, et al. Neurology 2008; 70:992
5. Snyders BMC Infectious Diseases 2012; 12:188
6. Berens 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

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

## Slide 36

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**PA2**

Correct answer is e

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## 48 – Lyme Disease

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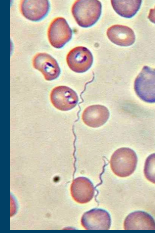
### Lyme disease: co-infections

- Incidence depends on geographic acquisition
  - B. microti*: 2-40%
  - HGA: 2-11.7%
  - Uncommon to rare
    - B. miyamotoi*
    - B. mayonii*
    - Ehrlichia eucairensis*
    - 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 (submitted) 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 abnl
- Opportunistic pathogen?
- Dx: not widely available
  - rGpQ EIA
  - PCR
  - 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

PA2

### Question # 5

42M just returned from a hiking trip Colorado, removing a tick on his arm 2d earlier. He is now heading out of town again on a beach vacation.

There is some 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

## Slide 39

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**PA2**

Correct answer is e

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