# 29 Lyme Disease

*Speaker: Paul Auwaerter, MD*


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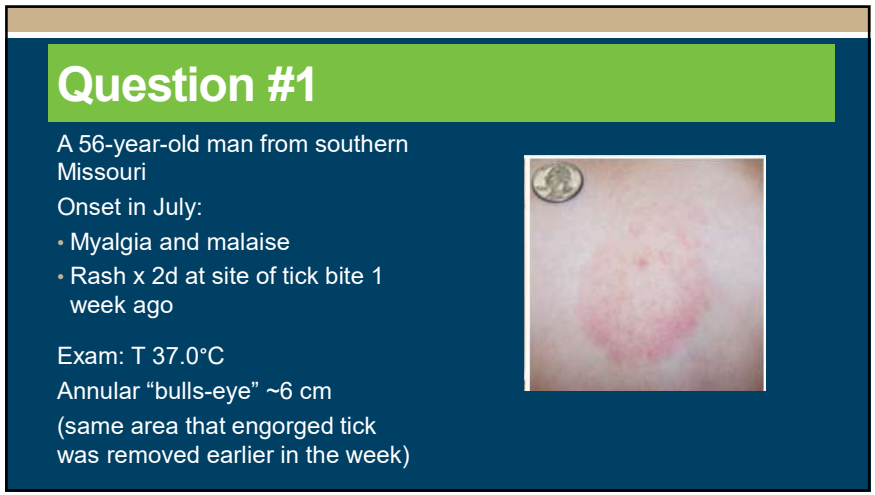


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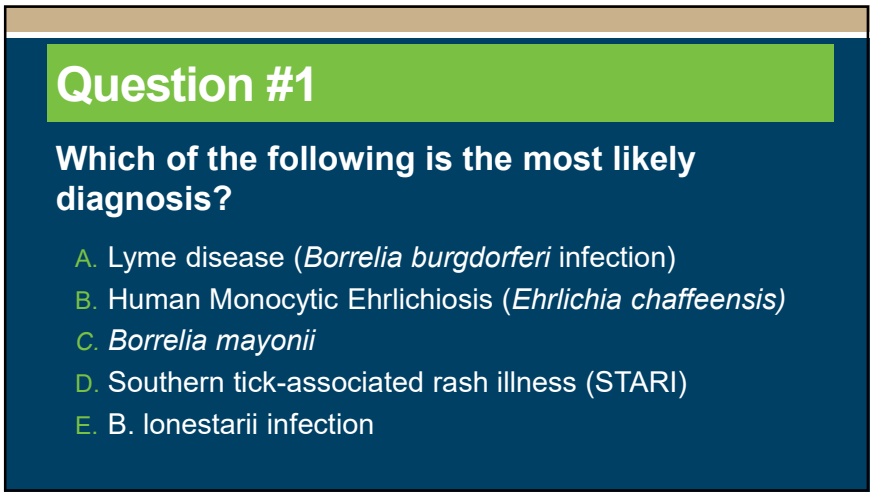



4

# 29 Lyme Disease

*Speaker: Paul Auwaerter, MD*

## 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

5


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

6

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

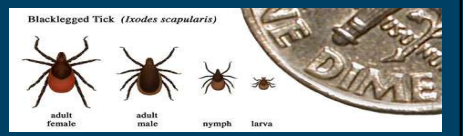
## STARI


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

7

## *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

8

# 29 Lyme Disease

*Speaker: Paul Auwaerter, MD*

## *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)

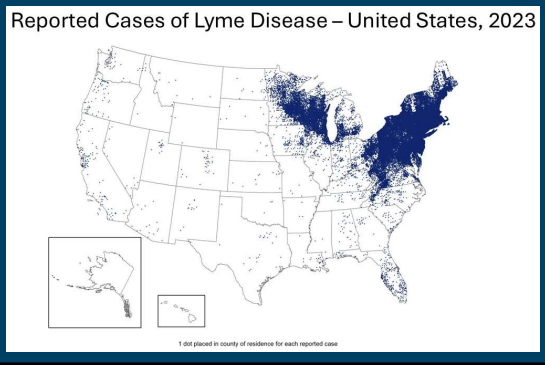
- *Borrelia afzelii > B. garinii >> Borrelia burgdorferi sensu stricto, B. bavariensis*
- Occasionally others
- Genus name: changing to *Borreliella?*
  (to distinguish from relapsing fever *Borrelia spp.)*

9

## 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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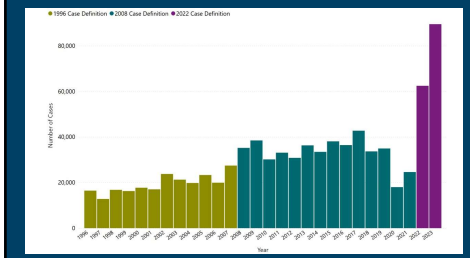
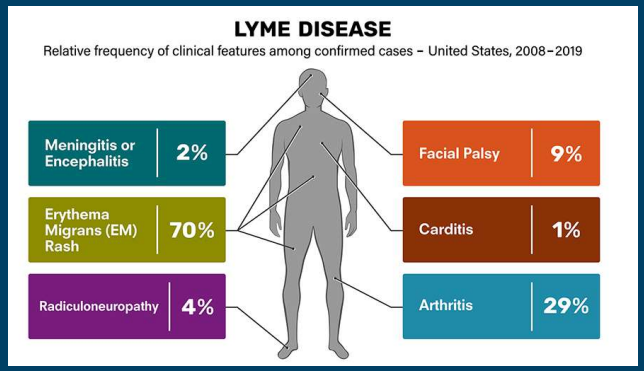
## CDC Case Definition (Revised 2020*)




- 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.

11




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

12

# 29 Lyme Disease

*Speaker: Paul Auwaerter, MD*

## 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

13

## 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

14

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15

## Early, Localized LD: Erythema migrans

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

Most common: homogeneous, pink-red ovoid

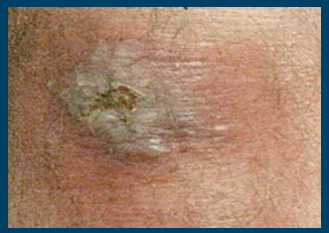
16

## Typical Erythema Migrans


Lesions: occur typically below neck and above knees & elbows

17

## 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)

18

## 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)

19

## Early, Disseminated Lyme Disease (1)

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

20

## 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

21

## Diagnosis – Facial Palsy

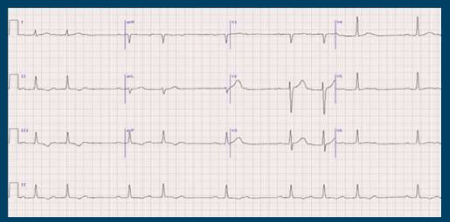
- Facial Palsy: up to 25% due to *B. burgdorferi* (Long Island NY)[1]
- Serology may take 4-6 wks turn positive
  - (if untreated, recheck if negative and suspicious)
- Lumbar puncture
  - Not required
- Most would recover without antibiotic therapy[2]
  - Main role of abx: prevent later disease manifestations

[1]Neurology 1992; 41:1268.
[2]Laryngoscope 1985; 95:1341. Clin Infect Dis. 2006 Nov 1;43(9):1089

22

## 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

23

## 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

24

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D. Synovial fluid *B. burgdorferi* culture ~100% sensitivity
E. **Serum *B. burgdorferi* 2-tier testing ~100% sensitivity**

25

## 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

26

## 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

27

## Late Lyme Disease (3): Dermatologic

Europe only

Acrodermitis chronica atrophicans (Europe)
Distal extremities most commonly seen

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

28

# 29 Lyme Disease

*Speaker: Paul Auwaerter, MD*

## 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

29

## 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

30

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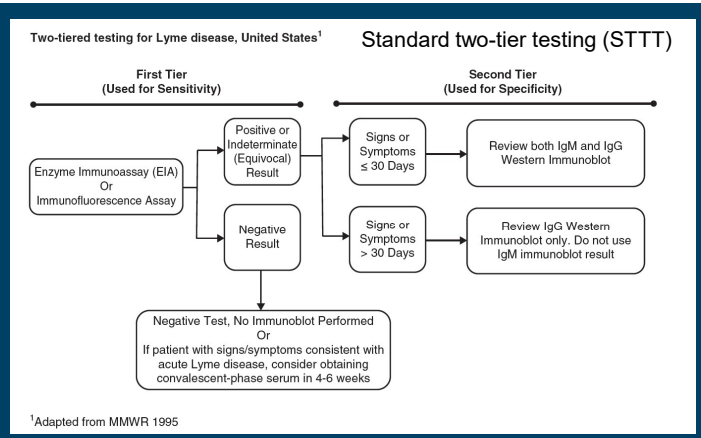
31




32

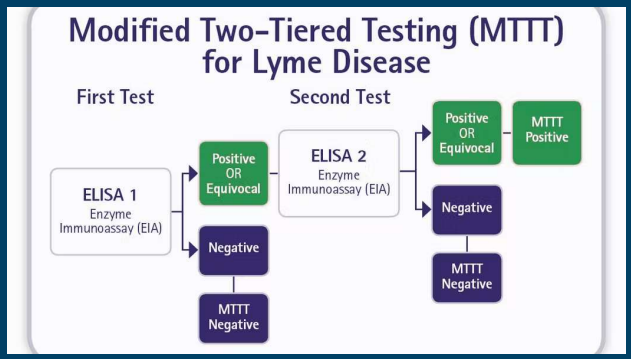
## Laboratory Testing

- 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

33

## MTTT: Faster, Cheaper, Better (Early LD)




34

## 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

35

## 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

36

## 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)<br>27% (convalescent)<br>61% (convalescent) | [32] [33] [97]<br>[33]<br>[32] | ~99% | [36] |
| | Serum | Early disseminated | 86% (carditis)<br>90%<br>42–87% | [32]<br>[98]<br>[99] | ~99% | [98] |
| | Serum | Neuroborreliosis | 90% | [32] | 96–100% | [39] |
| | Serum | Late disseminated | 100% (arthritis)<br>97–100% | [32]<br>[99] | 99–100% | [24] [39] |
| Modified two-tiered testing | Serum | Early localized | 53% (acute)<br>58% (acute)<br>89% (convalescent)<br>67% (convalescent) | [37]<br>[33] [25]<br>[37]<br>[33] [25] | ~99%<br>96–100% | [36]<br>[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<br>Serum/Plasma | Early localized | 64–81%<br>62% | [97]<br>[101] | ~100% | [102]* [103]<br>[104] |
| | Serum | Early disseminated | 29% (carditis) | [32] | | |
| | CSF | Neuroborreliosis | 25-38%<br>73% | [102]*<br>[99] | | |
| | Synovial fluid | Late disseminated | 85% (arthritis)<br>83% (arthritis) | [102]*<br>[99] | | |

Kobayashi, Auwaerter. Inf Dis Clinics N Am Sept 2022

37

## 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

38

## 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.

39

## Lyme Disease: Initial Regimens

| Treatment<br>Disease Manifestation | Route | Medication[a] | Duration (days)[b] |
|---|---|---|---|
| **Lyme disease** | | | |
| Erythema migrans | Oral | Doxycycline<br>or<br>Amoxicillin<br>or<br>Cefuroxime axetil | 10<br><br>14<br><br>14 |
| Meningitis/radiculopathy | Oral<br>IV[c] | Doxycycline<br>Ceftriaxone | 14-21<br>14-21 |
| Cranial nerve palsy | Oral | Doxycycline | 14-21 |
| Encephalomyelitis | IV[c] | Ceftriaxone | 14-28 |
| Carditis | Oral<br><br><br><br>IV[d] | Doxycycline<br>or<br>Amoxicillin<br>or<br>Cefuroxime axetil<br>Ceftriaxone | 14-21<br><br><br><br>14-21 |
| Arthritis | Oral | Doxycycline<br>or<br>Amoxicillin<br>or<br>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

40

## 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

41

## 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

42

## Randomized, placebo-controlled trial scorecard for persistent symptoms attributed to Lyme disease after initial treatment

| Longer-term abx v. placebo<br><br>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)

43

## "Chronic Lyme Disease"

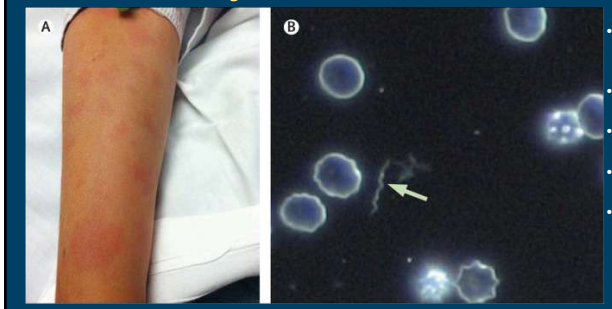
- What is it? Originally, late Lyme disease
  - Now: vague term, often used by some to encompass broad range of symptoms
    - Objective evidence of LD not needed.
      - Lack of good clinical history
      - Often no reliable evidence of LD by laboratory testing
  - Offered as explanation for
    - Chronic—fatigue, pain, headaches, brain fog, sleep problems, depression
    - Legitimate diseases: multiple sclerosis, ALS, Alzheimer's, autism, Parkinson's

44

# 29 Lyme Disease

*Speaker: Paul Auwaerter, MD*

## *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

45

## Question #5

PREVIEW QUESTION

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

46

## Question #5

PREVIEW QUESTION

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

47

## Question #5

PREVIEW QUESTION

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A. PCR for *E. chaffeensis*
B. Serology for spotted fever rickettsia (RMSF)
C. **Blood smear**
D. Serology for *B. burgdorferi*
E. Nothing additional

48

## 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

49

## 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

50

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51

## *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

52

## 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

53