

Lyme Disease: Updates on the management for the general pediatrician

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Learning Objectives

- Describe the etiology and epidemiology of Lyme disease
- Discuss the diagnostic testing and management for Lyme disease
- Elucidate anticipatory guidance regarding prevention methods of tickborne infections
- Dispel myths surrounding Lyme disease including “chronic lyme disease”



Lyme Disease

- *Borrelia burgdorferi*
- Gram negative spirochete

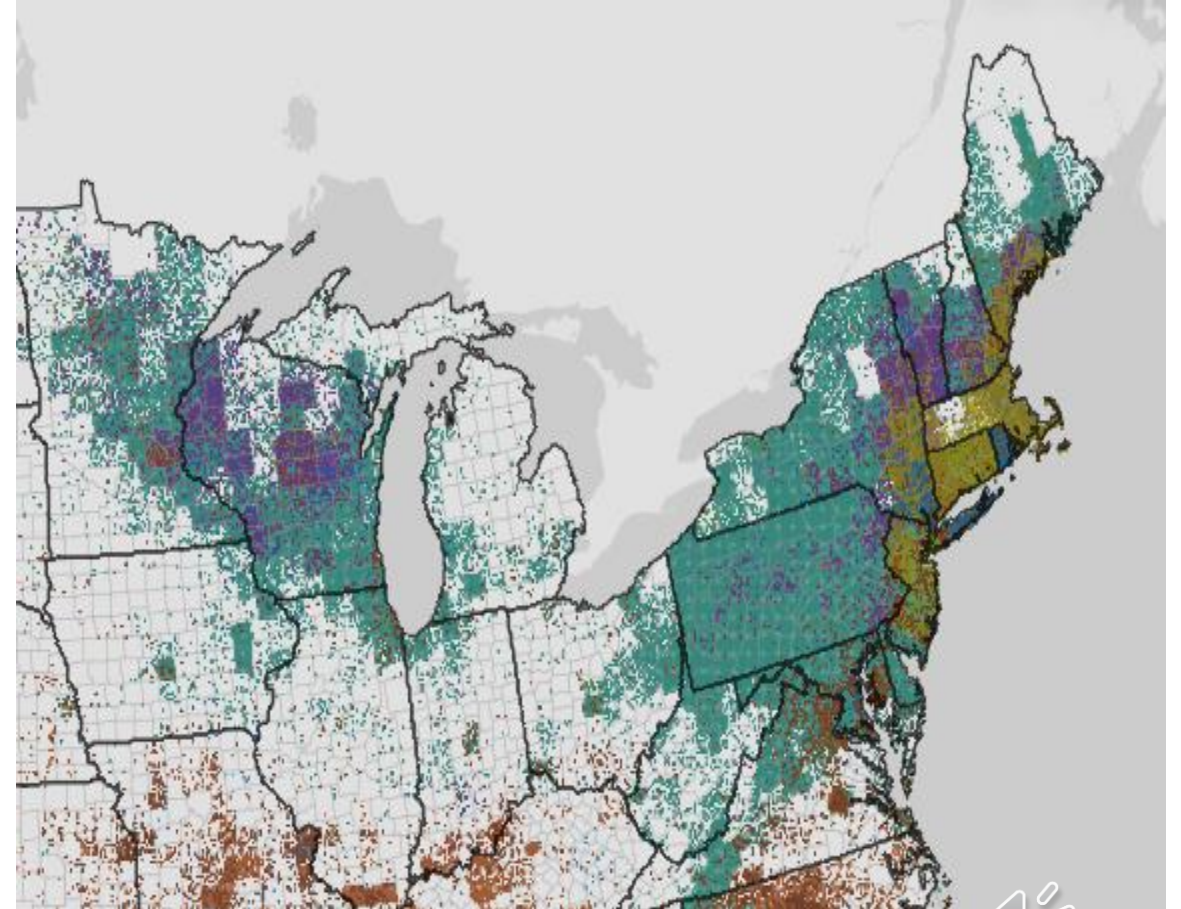
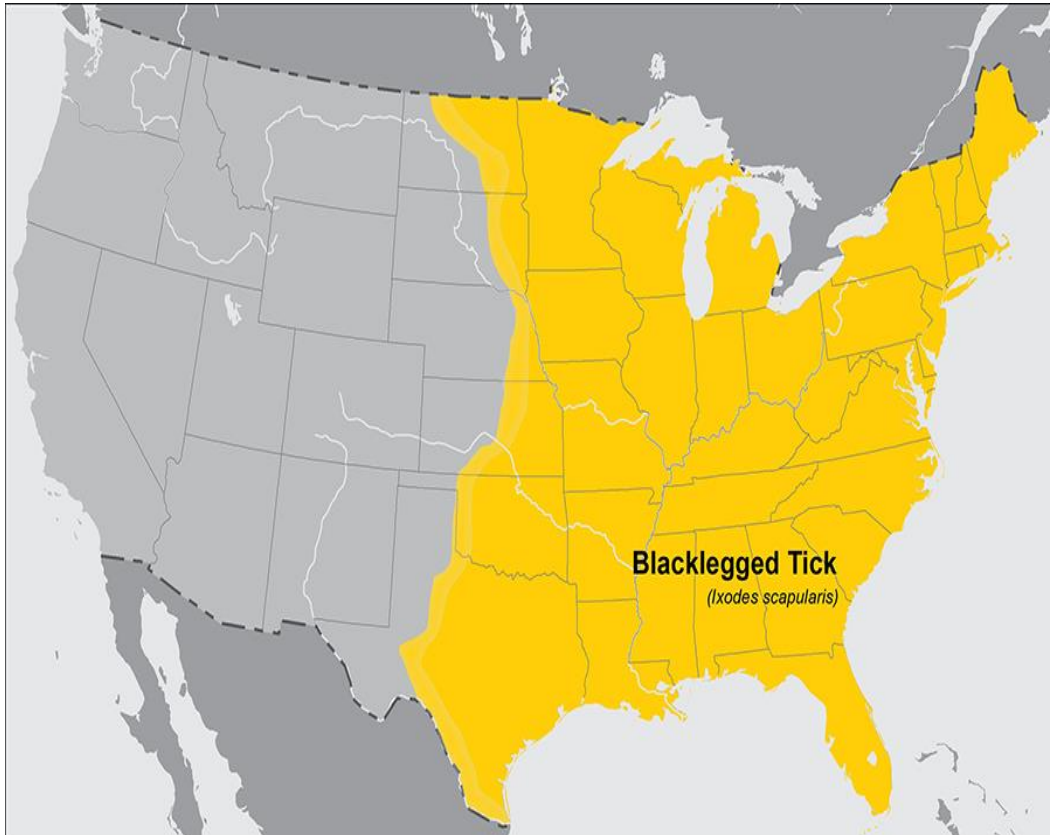
- Vector: Black-legged (deer) tick
 - ***Ixodes scapularis* (NE & Midwest US)**

- Reservoir: white-footed mice & small mammals

- Spring & Summer – most cases occur in June & July
- Most common Vectorborne infection in the US

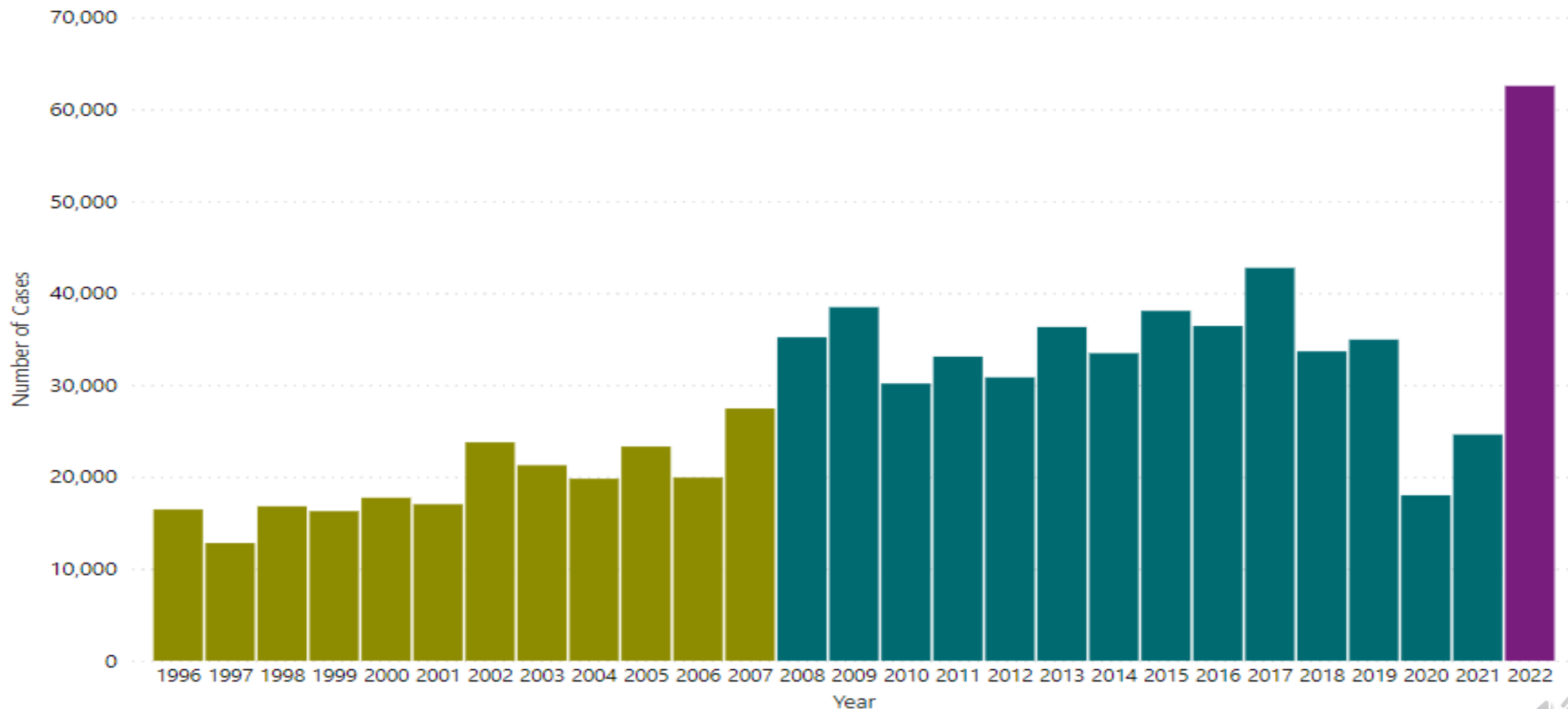


Lyme Disease: Epidemiology



Lyme Disease – Total Reported Cases by Year, United States

● 1996 Case Definition ● 2008 Case Definition ● 2022 Case Definition



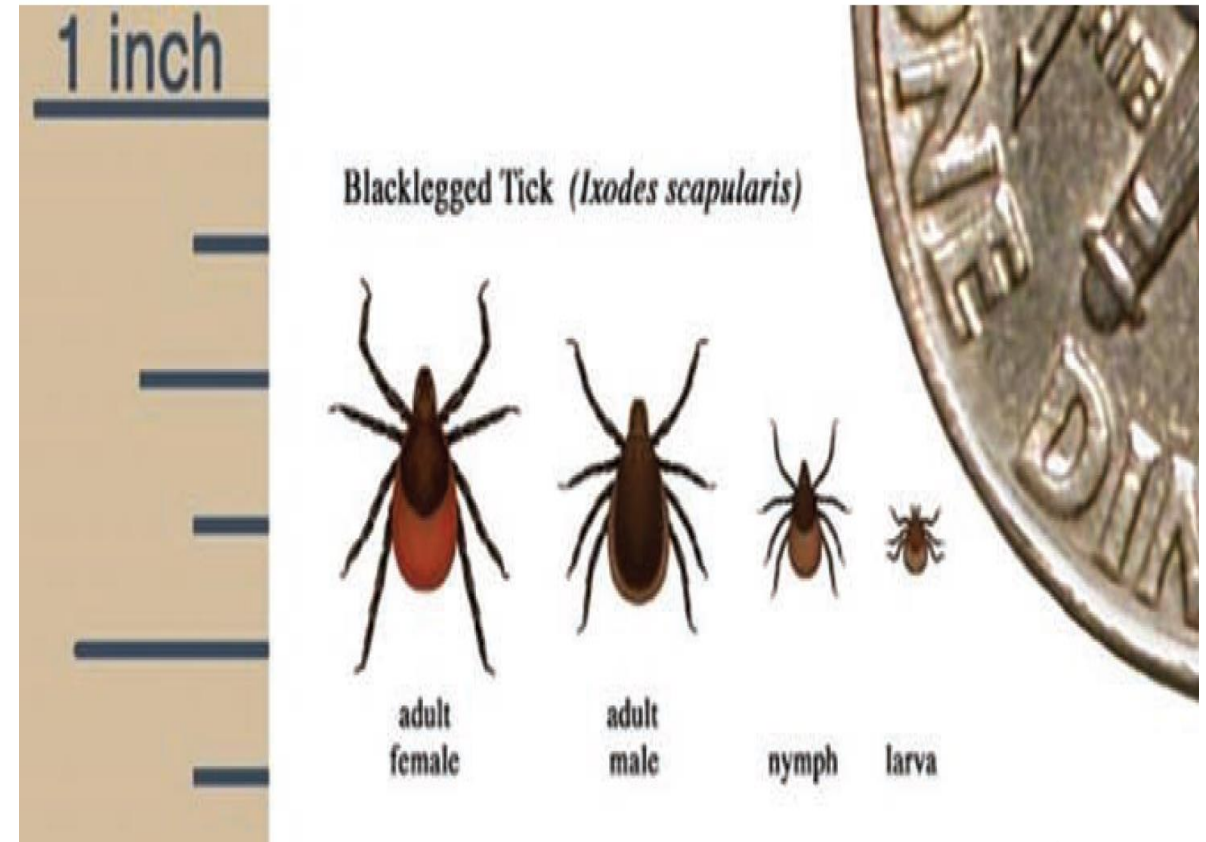
*These data were reported according to different Lyme disease case definitions. Only major case definition changes are denoted.



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Lyme Disease: Epidemiology

- Most cases are transmitted by nymphs
 - Most active during spring/summer & most prevalent
- Adult females are more likely to be detected and don't stay attached for long enough to transmit infection
- Transmission requires tick to be attached for >72 hours



Lyme Disease: Stages

Early

- Onset: < 3 months
- Localized: 1 – 2 weeks
 - Localized EM
- Disseminated: 2 – 12 weeks
 - Multiple EM, Neurologic & Cardiac disease

Late

- Onset: >3 months
- **Arthritis**
- Uncommon in children: acrodermatitis chronicum atrophicans, borrelial lymphocytoma, & late Lyme encephalopathy



Lyme Disease: Systemic Symptoms

- May also have systemic symptoms
 - Fever
 - Headache
 - Myalgia
 - Fatigue
 - Lymphadenopathy
 - Conjunctivitis

- May be present during early stages WITH other Lyme symptoms



Erythema migrans: Localized

- Present in 67% of symptomatic children
- 1-2 weeks after infection (3-32 days)
- Single lesion at the bite site
- Patch with central clearing around bite site (targetoid)
 - Can be incomplete and/or have central necrosis
 - Can also have ecchymosis
- Size \geq 5cm
- Expands over days to weeks, then disappears (1-4 weeks)



Disseminated Erythema migrans

- 25%
- Smaller than 5 cm (most often)
- Multiple patches
- May appear targetoid, annular with central clearing or as red patches that later develop central clearing
- May occur with other early disseminated forms (CNS, Cardiac)





Lyme Carditis

- Chest pain, pre-syncope or syncope, or acute heart failure
- AV-block: 1^o, 2^o or 3^o
 - 3^o AV block is rare, i.e., <1%
- Pericarditis, myocarditis
- **3rd AV-block + EM = Lyme disease ***



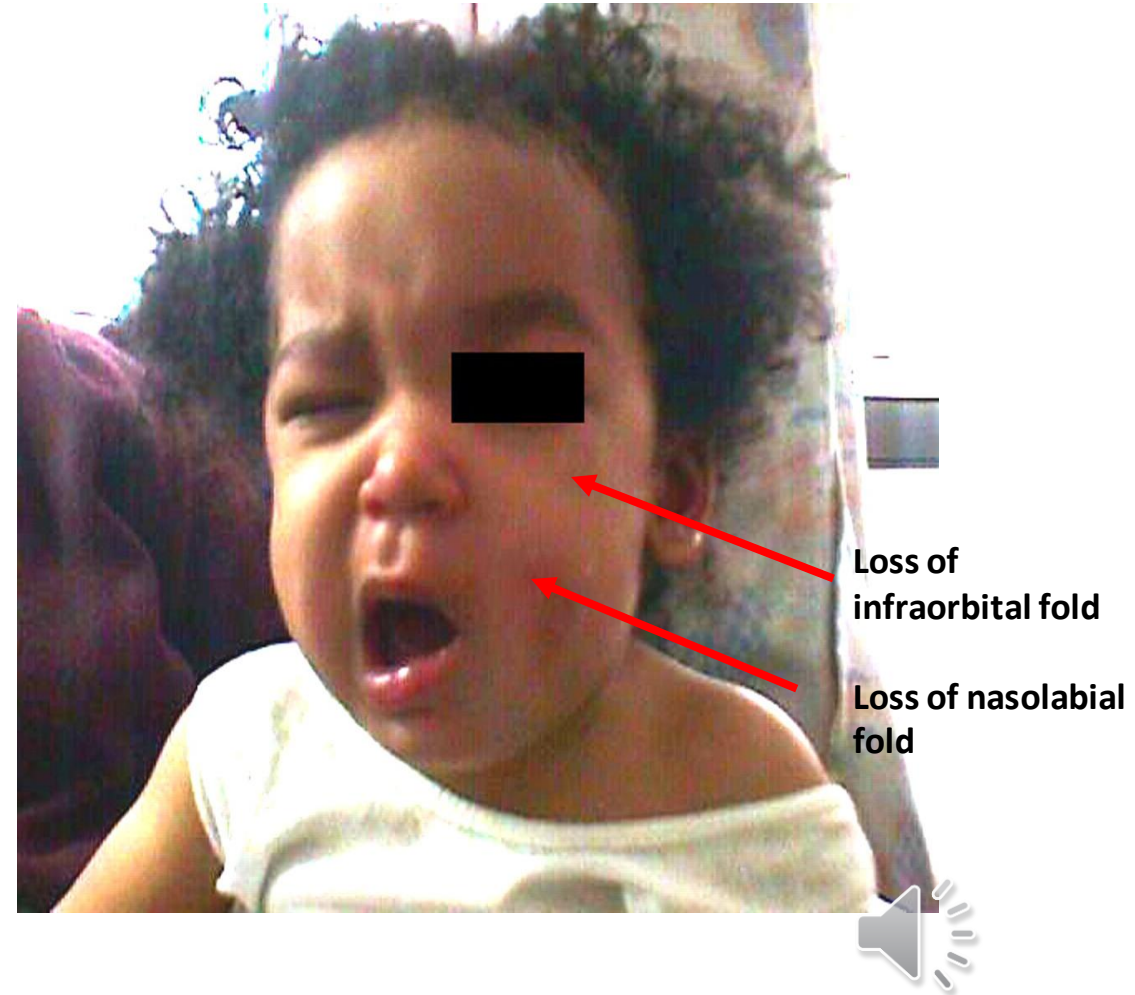
Neuroborreliosis: Early Disseminated

- **Cranial nerve palsies: VII, VIII, III, V, VI, etc...**
- **Lyme-Related Facial nerve palsy**
 - 3 – 5%
 - Unilateral or bilateral (facial diplegia)
 - Hyperacusis
 - ↓ taste sensation in the anterior 2/3 of tongue (chorda tympani)



Lyme-Related Facial nerve palsy

- ↓ ability to wrinkle forehead
- ↓ ability to close eyelid +/-
 - Bell's phenomenon: eye rolls backwards during attempt at eyelid closure
- Asymmetric smile
- Loss of infraorbital & nasolabial folds



Neuroborreliosis: Early Disseminated

- **Radiculoneuritis:** radicular pain with motor and sensory abnormalities of peripheral nerves
- **Lymphocytic meningitis**
 - < 2%
 - Subacute/chronic
 - **Can present with or lead to pseudotumor cerebri**
 - **Pseudotumor due to doxycycline is often delayed by 3 months**
- Peripheral neuropathy, i.e., Mononeuropathy multiplex (at least two different PNs involved)
 - Occurs with meningitis



Lyme arthritis

- 7% of children
- **Large effusion(s)**
 - Pain is usually underwhelming for size of effusion
 - Erythema usually absent
- Oligoarthritis: large joints affected
 - **>90% knee**
 - Hip, ankles, shoulder, elbows
- Initially episode improves over 4-7 days; resolves over 4-6 weeks
 - Waxes and wanes until treated



Lyme arthritis

- Baker cyst is a complication of Lyme arthritis and can occur:
 - Uni- or bilateral
 - Can occur with or without arthritis
 - Before, during or after therapy
- 10 - 20% recurs or persists
 - Small effusions can be monitored or re-treated

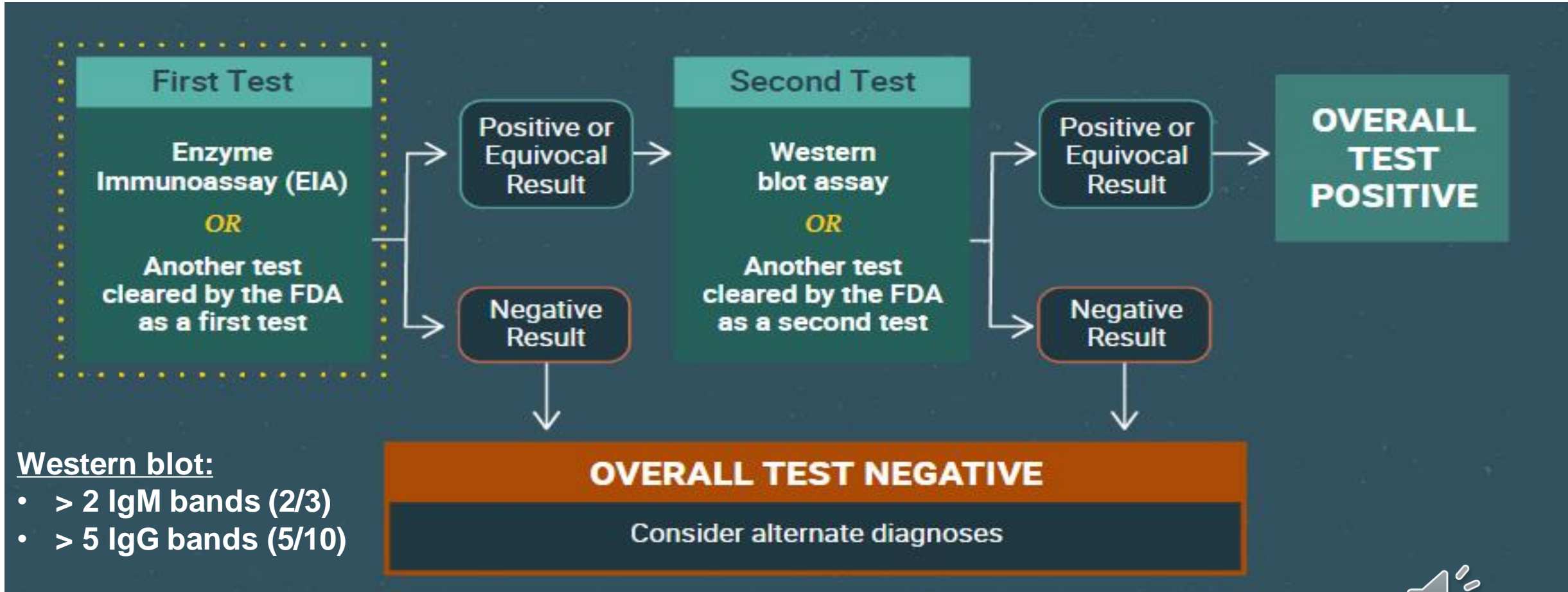


Lyme arthritis

- < 1% developed antibiotic-refractory arthritis (HLA-associated) → requires steroid injections and/or immunosuppression
 - VERY uncommon in children
- Worsening arthritis (pain, effusion) or development of new joint involvement on effective antibiotic therapy is suggestive of an alternative diagnosis (JIA, etc...)



Lyme Disease: Diagnosis



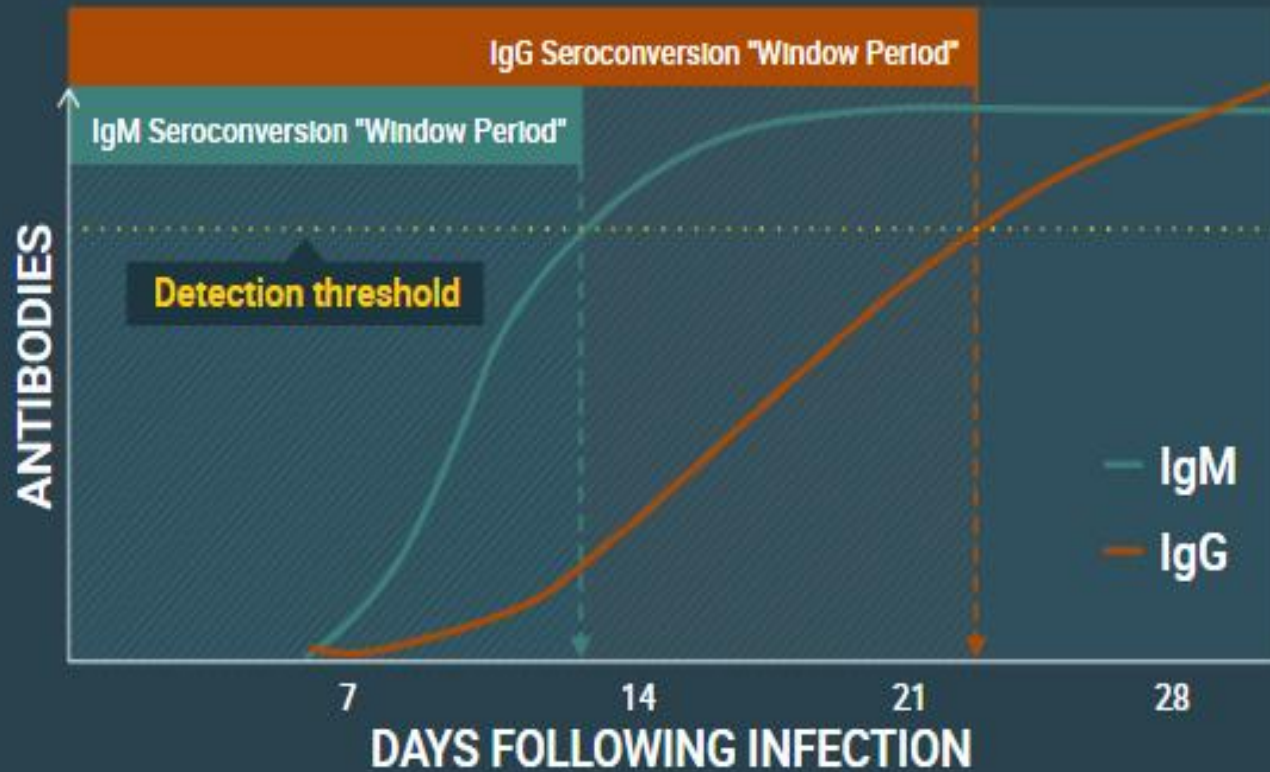
Lyme Disease: Diagnosis - Serology

Stage	Presentations	Sensitivity
Early Localized	Single EM lesion	Poor (50%)
Early Disseminated	Multiple EM rashes, meningitis, bell's palsy, neuritis or carditis	Very Good (>90%)
Late Disseminated	Arthritis	Excellent (~100%)



Lyme Disease: Diagnosis

Antibody response following infection



Understanding the Window Period

- Serologic testing is based on antibody detection.
- Can take several weeks for antibodies to develop after initial infection with Lyme disease.
- Low serologic test sensitivity at early stage Lyme disease is due to lack of antibodies during the *window period*.



Lyme Disease: Diagnosis

- **Early: IgM or IgG**
 - Localized or Disseminated EM patients may not have IgG seroconversion if treated – blunts the immune response
- **Late: IgG only**
- **IgM: Ignore if symptoms present for > 1 month can be considered a false positive**
- **IgG seropositivity persists for many years**
 - Lyme IgG concentrations or WB bands do not correlate with treatment response



Lyme Disease: Diagnosis

- **False positives (screening serology)** are due to cross-reactivity:
 - Oral flora (spirochetes)
 - Infections with other spirochetes: syphilis, yaws, leptospirosis, tickborne-relapsing fever
 - Non-specific antibody production: EBV, VZV or autoimmune disorders (SLE)
- PCR from Synovial fluid reserved for recurrent arthritis
- CSF PCR is rarely helpful



Lyme Disease: When Not to Test

- After attached tick found
- Systemic symptoms (fever, myalgia, fatigue) WITHOUT typical Lyme symptoms
- Localized erythema migrans – except for atypical EM lesions

- Psychiatric symptoms or disorders
- Chronic neurologic disorders – ALS, MS
- Developmental disorders/delays: autism or developmental delay



Lyme Disease: Treatment

<u>Drug</u>	<u>Dosage</u>	<u>Max Dose (mg)</u>	<u>Frequency</u>
Amoxicillin	50mg/kg/ DAY	500	TID
Doxycycline	2.2 mg/kg/DOSE	100	BID
Cefuroxime	10 mg/kg/DOSE	500	BID
Ceftriaxone	50mg/kg/dose	2000	daily
Azithromycin	10 mg/kg/dose	500	daily



Erythema Migrans: Treatment

<u>Antibiotic</u>	<u>Duration (days)</u>
Doxycycline	10
Amoxicillin, Cefuroxime	14
Azithromycin	5 - 10 Avg: 7

- Jarisch-Herxheimer reaction may occur within 48 hours of starting antibiotics
- Fever, chills & myalgia
- Duration: 1 – 3 days
- Treatment: NSAIDs



Lyme Disease: Treatment

<u>Dz Manifestation</u>	<u>Antibiotic</u>	<u>Duration (days)</u>
Meningitis, Radiculopathy, or Lyme-related FNP	Doxycycline Ceftriaxone	14-21
Carditis	Ceftriaxone	Until symptomatic AV block resolves
	Doxycycline, Amox or Cefuroxime	14-21
Amoxicillin & Cefuroxime are NOT indicated for CNS/PNS infection		



Lyme Disease: Treatment

<u>Dz Manifestation</u>	<u>Antibiotic</u>	<u>Duration (days)</u>
Arthritis – 1 st episode	Doxycycline, Amoxicillin or Cefuroxime	28
Recurrent or refractory	Doxycycline, Amoxicillin or Cefuroxime	28
	Ceftriaxone	14



Lyme Disease: Management

- **Lyme-related FNP: PT not usually needed**
- Carditis: 3^o AV block resolves with treatment so permanent pacemakers are not indicated
 - **EKG is NOT indicated they are symptomatic (syncope, palpitations, chest pain)**
- **Arthritis:** Arthrocentesis not indicated unless unable to differentiate between Lyme and pyogenic arthritis; OR recurrent arthritis



Lyme Disease: Finding Tick Attached

- We recommend submitting the removed tick for species identification (*good practice statement*)
- We recommend against testing a removed *Ixodes* tick for *B. burgdorferi* (*strong recommendation, moderate-quality evidence*)
 - The presence or absence of *B. burgdorferi* in an *Ixodes* tick removed from a person does not reliably predict the likelihood of clinical infection
- **Diagnostic testing of patients who are asymptomatic after an attached tick was found is NOT recommended**



Lyme Disease: Post-Exposure Prophylaxis

Determine if tick meets high-risk criteria:

- Identified as *Ixodes scapularis*
- Bite occurred in a highly endemic area
- Attached for ≥ 36 hours

- Consider initiating prophylaxis if a, b, and c are met, **AND** within 72 hours of tick removal

- Doxycycline 4.4 mg/kg/dose x 1
 - Max dose: 200 mg

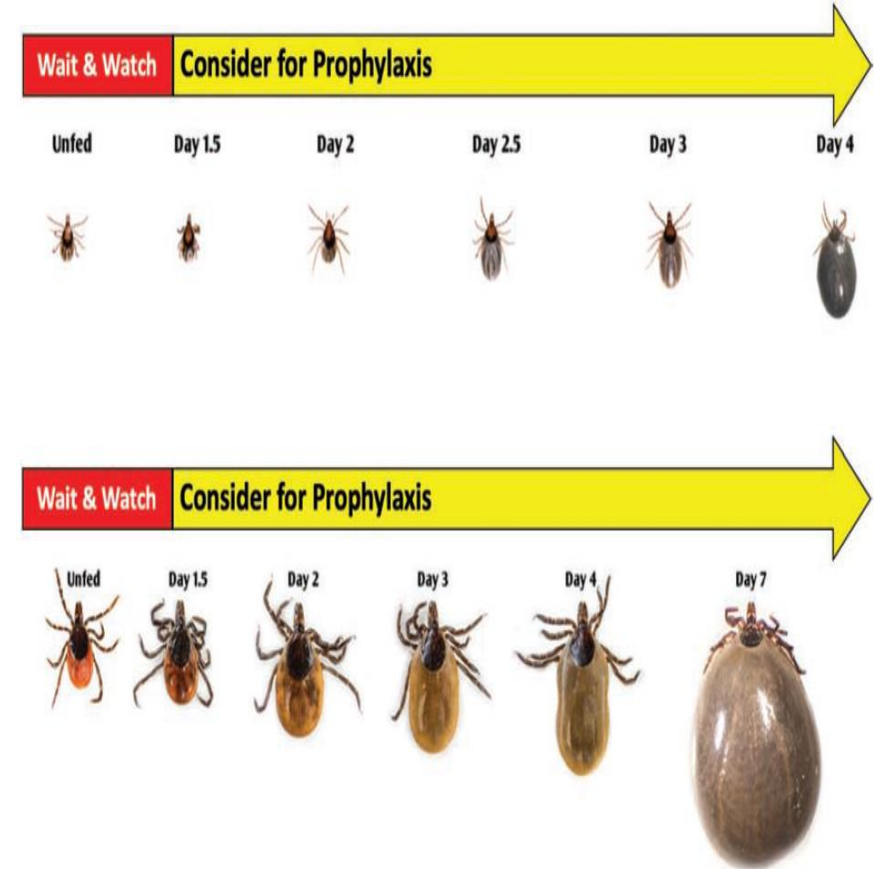


Figure 6. Relative sizes of engorging nymphal and adult female *Ixodes scapularis* (blacklegged = deer tick) as a function of time spent feeding (= attachment time). Transmission of *Borrelia burgdorferi* requires 36–48 hours of feeding [101], and therefore antibiotic prophylaxis is recommended only if the tick was attached for at least 36 hours, or 1.5 days [148]. By itself, duration of feeding is insufficient for recommending antibiotic prophylaxis; see Figure 7 for the complete list of criteria needed to determine whether a tick bite is a high risk tick bite. A, Nymphs (Feeding time: Unfed = 0 hrs; Day 1.5 = 36 hrs; Day 2 = 48 hrs; Day 2.5 = 60 hrs; Day 3 = 72 hrs; Day 4 = 96 hrs). B, Adult females over the same time period. Unfed nymph and adult female are the sizes of poppy and sesame seeds, respectively. Not actual size. (Source: https://tickencounter.org/tick_identification/tick_growth_comparison, accessed 11/22/19.)

Tick Prevention

Table 5. Personal Prevention Measures

Before venturing outside	During and/or after exposure to tick habitat^b
<p>Personal Prevention Measures^a</p> <ul style="list-style-type: none"> Avoid risky habitats Wear light-colored clothing Wear long sleeves and pants Tuck pants into socks or footwear Wear permethrin-treated clothing 	<ul style="list-style-type: none"> Conduct a thorough tick check of extremities, torso, and areas where ticks may be visually obscured (eg, axilla, nape of neck, hairline, in and around ears, umbilicus, groin, popliteal fossa) Bathe or shower within 2 hours Dry clothes on high heat for at least 10 minutes; if not possible, wash clothes in hot water.
<p>Use an EPA-approved repellent or insecticide as per manufacturer's instructions</p> <ul style="list-style-type: none"> DEET Picaridin IR3535 Oil of lemon eucalyptus (OLE) p-methane-3,8-diol (PMD) 2-undecanone Permethrin (for application to clothing and gear only) 	<p><u>If an attached tick is detected</u></p> <ul style="list-style-type: none"> Remove properly (see Figure 5) and clean bite area https://www.cdc.gov/lyme/removal/index.html Tip: store tick (eg, in sealed container / plastic bag; wrapped in clear tape; or taped to a piece of paper). Label with date and likely geographic location of exposure. See clinician and show tick if concerned that it is an <i>Ixodes</i> spp. and has fed at least 36 hours (Figures 2 and 6 and Table 3). Monitor health for symptoms of Lyme disease and other tick-borne diseases

Abbreviations: DEET, N,N-Diethyl-meta-toluamide; EPA, Environmental Protection Agency.

^aTip: Have handy—fine-tipped tweezers, tick storage container, and hand sanitizer.

^bContinue to conduct a tick check whenever possible to detect and remove feeding ticks as soon as possible.

- Feel free to email me for my EPIC SmartPhrase on this topic**



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Post-Treatment Lyme Disease Symptoms

- Onset with 6 months of the diagnosis of Lyme disease & persistence of continuous or relapsing symptoms for at least a 6-month period after completion of antibiotic therapy:
 - Fatigue
 - Widespread musculoskeletal pain
 - Complaints of cognitive difficulties
 - Subjective symptoms are of such severity that, when present, they result in substantial reduction in previous levels of occupational, educational, social or personal activities

- **RCTs have not shown benefit of additional antibiotics**

Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;43(9):1121



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Lyme Disease: Follow up

- Post-lyme disease syndrome: Brain fog, arthralgia & fatigue can take months to resolve
 - Extending antibiotics does not speed up resolution of symptoms
- Repeat serologies are not recommended except for select circumstances:
 - Early disseminated disease (Carditis, Meningitis or FNP) that is initially seronegative or only IgM +
 - Atypical EM-like rash: IgG seroconversion may not occur



Lyme Disease: Follow up

- Repeat infections are rare except for those with localized EM treated early
 - Especially in patients with lyme arthritis



Co-infections

- **Depends on area where infection occurred**
- Bartonella is NOT co-transmitted with *B burgderfori*

- **Testing for these in patients without symptoms is not indicated**



Co-infections: Not endemic to Ohio (yet)

- ***Babesia microti*** – fever, chills & myalgia
 - anemia, thrombocytopenia
 - NE & Midwest

- ***Anaplasma phagocytophilum*** – fever, headache & myalgia;
 - ↓ Na & PLT; ↑ transaminases; neutropenia or lymphopenia
 - Upper Midwest, NE & Northern Cali



Co-infections: Not endemic to Ohio (yet)

- *Powassan virus* – encephalitis
 - Great lakes region
 - One case reported in Ohio (by me 😊)
- *Borrelia miyamotoi* – tickborne relapsing fever
 - Western US



“Chronic Lyme Disease”

- AKA “seronegative” lyme disease
- International Lyme and Associated Diseases Society (ILADS) produced diagnostic criteria & management
- Persistent symptomatology most of which are non-specific or ascribed to an alternative disorder
- There is no data to support that *Borrelia burgderfori* establishes chronic infection



“Chronic Lyme Disease”

- Does not cluster to Lyme-endemic regions
- Many patients who received this diagnosis go on to be diagnosed with a rheumatologic (SLE, Fibromyalgia), neurologic (ALS, MS) or other disorder (Chronic Fatigue syndrome)



“Chronic Lyme Disease”

- Testing should **NEVER** be sent to IGeneX for use of assays that are not approved by CDC
 - These assays (Urine antigen) have been externally validated
 - High false positive rates among patients with no exposure or symptoms ¹²
 - ILADS criteria for positivity includes western blot bands used that are very non-specific
- Do not refer these patients to a “Lyme specialist” or “Lyme-literate” provider



References

1. Steere, A. C., Bartenhagen, N. H., Craft, J. E., Hutchinson, G. J., Newman, J. H., Rahn, D. W., Sigal, L. H., Spieler, P. N., Stenn, K. S., & Malawista, S. E. (1983). The early clinical manifestations of Lyme disease. *Annals of Internal Medicine*, 99(1), 76–82. <https://doi.org/10.7326/0003-4819-99-1-76>
2. Red Book: 2021–2024 Report of the Committee on Infectious Diseases, 2021
3. Lantos, P. M., Rumbaugh, J., Bockenstedt, L. K., Falck-Ytter, Y. T., Agüero-Rosenfeld, M. E., Auwaerter, P. G., Baldwin, K., Bannuru, R. R., Belani, K. K., Bowie, W. R., Branda, J. A., Clifford, D. B., DiMario, F. J., Halperin, J. J., Krause, P. J., Lavergne, V., Liang, M. H., Meissner, H. C., Nigrovic, L. E., ... Zemel, L. S. (2021). Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. *Clinical Infectious Diseases*, 72(1), e1–e48. <https://doi.org/10.1093/cid/ciaa1215> P Lantos. Lantos, P. M. (2015). Chronic Lyme Disease. In *Infectious Disease Clinics of North America* (Vol. 29, Issue 2, pp. 325–340). W.B. Saunders. <https://doi.org/10.1016/j.idc.2015.02.006>
4. Lantos, P. M., & Wormser, G. P. (2014). Chronic coinfections in patients diagnosed with chronic lyme disease: A systematic review. *American Journal of Medicine*, 127(11), 1105–1110. <https://doi.org/10.1016/j.amjmed.2014.05.036>
5. Patrick, D. M., Miller, R. R., Gardy, J. L., Parker, S. M., Morshed, M. G., Steiner, T. S., Singer, J., Shojania, K., Tang, P., Mattman, A., Sirrs, S., Reid, W. D., Phillips, P., Avina-Zubieta, A., Reynolds, J., Wong, H., Bested, A., Hyams, I., Ng, B., ... McCabe, M. (2015). Lyme Disease Diagnosed by Alternative Methods: A Phenotype Similar to That of Chronic Fatigue Syndrome. *Clinical Infectious Diseases*, 61(7), 1084–1091. <https://doi.org/10.1093/cid/civ470>
6. Lantos, P. M., Lipsett, S. C., & Nigrovic, L. E. (2016). False Positive Lyme Disease IgM Immunoblots in Children. *Journal of Pediatrics*, 174, 267–269.e1. <https://doi.org/10.1016/j.jpeds.2016.04.004>
7. Fallon, B. A., Pavlicova, M., Coffino, S. W., & Brenner, C. (2014). A comparison of lyme disease serologic test results from 4 laboratories in patients with persistent symptoms after antibiotic treatment. *Clinical Infectious Diseases*, 59(12), 1705–1710. <https://doi.org/10.1093/cid/ciu703>
8. Wang, P., Glowacki, M. N., Hoet, A. E., Needham, G. R., Smith, K. A., Gary, R. E., & Li, X. (2014). Emergence of *Ixodes scapularis* and *Borrelia burgdorferi*, the Lyme disease vector and agent, in Ohio. *Frontiers in Cellular and Infection Microbiology*, 4(JUN). <https://doi.org/10.3389/fcimb.2014.00070>
9. Luft, B. J., Dattwyler, R. J., Johnson, R. C., Luger, S. W., Bosler, E. M., Rahn, D. W., Masters, E. J., Grunwaldt, E., & Gadgil, S. D. (1996). Azithromycin compared with amoxicillin in the treatment of erythema migrans. A double-blind, randomized, controlled trial. *Annals of Internal Medicine*, 124(9), 785–791. <https://doi.org/10.7326/0003-4819-124-9-199605010-00002>
10. Aberer, E., Kehldorfer, M., Binder, B., & Schauperi, H. (1999). The outcome of Lyme borreliosis in children. *Wiener Klinische Wochenschrift*, 111(22–23), 941–944.
11. Shapiro, E. D. (2015). Repeat or persistent Lyme disease: persistence, recrudescence or reinfection with *Borrelia burgdorferi*? *F1000Prime Reports*, 7. <https://doi.org/10.12703/p7-11>
12. Klempner, M. S., Schmid, C. H., Hu, L., Steere, A. C., Johnson, G., McCloud, B., Noring, R., & Weinstein, A. (2001). Intralaboratory reliability of serologic and urine testing for Lyme disease. *American Journal of Medicine*, 110(3), 217–219. [https://doi.org/10.1016/S0002-9343\(00\)00701-4](https://doi.org/10.1016/S0002-9343(00)00701-4)
13. Patel R, Grogg KL, Edwards WD, Wright AJ, Schwenk NM. Death from inappropriate therapy for Lyme disease. *Clin Infect Dis*. 2000;31(4):1107-1109. doi:10.1086/318138



5-year-old female presents with fever, myalgia and a rash. He lives in Western PA in a suburban neighborhood. No pets. Deer are common in the area. He does spend time in the woods in their backyard. Photo of the rash is shown below. Which of the following would be the best next step in management?

- A. Provide reassurance
- B. Send Lyme serology
- ★ Start doxycycline
- D. Tell the family “its not a tumah”



2-year-old female presents with left facial weakness. Family lives in NE Ohio. No recent travel. No recent URI, AOM or sinusitis. Vaccinations up to date including Varicella. No history of a rash in the past few months. Parents noticed facial asymmetry this morning. In addition, he would spill water when drinking from a cup. Lyme serology was sent. Physical exam significant for the findings shown (Photo). Her grip strength is 5/5; shoulder & elbow strength (flexion & extension) are 5/5. Which of the following would be the best next step in management?

- A. Provide reassurance
- B. Start amoxicillin
- C. Start doxycycline
- ★ Start doxycycline + prednisolone

