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Tick Talk: Digging Deeper into Lyme Disease

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Experts in pediatrics, Advocates for children. 1

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Speaker Disclosure

Clinical Advisor to NAPNAP's Nurse Practitioner Education and Knowledge Assessment for Lyme Disease Initiative, made possible by a cooperative agreement from the Centers for Disease Control and Prevention

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Learning Objectives

- Describe the presentation, diagnosis, and treatment of localized and disseminated Lyme disease in pediatrics
- Improve understanding of diagnostic approach for potential Lyme disease cases, including pre-test probability, evidence-based laboratory testing, and test interpretation
- Examine available evidence regarding prolonged symptoms after Lyme disease treatment
- Explore strategies to care for individuals with prolonged, unexplained symptoms and concern for Lyme disease

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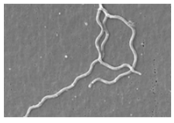
Lyme Disease Pathogens

- Caused by the spirochete (spiral-shaped bacteria) *Borrelia burgdorferi*
  - *B. burgdorferi* sensu stricto is primary species that causes Lyme disease in the US
  - *Borrelia mayonii* recently identified – rare, currently localized to WI and MN
  - Additional *Borrelia* species in Eurasia that may present with distinct features
- Bacteria transmitted through the bite of infected ticks
  - Blacklegged tick (or deer tick, *Ixodes scapularis)* in the Northeast, Mid-Atlantic and North Central states
  - Western blacklegged tick (*Ixodes pacificus)* on the West Coast



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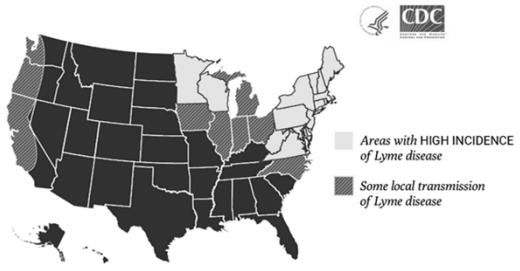
Where is Lyme Disease?



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How big of a problem is Lyme disease?

- ~476,000 individuals are diagnosed and treated each year, based on recent insurance claims data from 2010-2018 [1]
- ~62,000 cases of Lyme disease in 2022 via surveillance systems
  - Revised surveillance case definition in 2022
- Report Lyme disease to local/state health department if you live in an area of emergence or low incidence
  - Cases in high incidence areas are now based on laboratory reporting

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Early Lyme Disease

- Most common manifestation is erythema migrans (EM)
  - Expanding, erythematous, often annular lesion at site of inoculation
- May also have constitutional symptoms such as fatigue, arthralgia, myalgia, headache
- Early Lyme disease is a **clinical** diagnosis [2]
  - Patient has lesion(s) consistent with EM and a potential tick exposure **in a Lyme endemic area**
  - Serology testing may be negative at this early stage even if patient is infected

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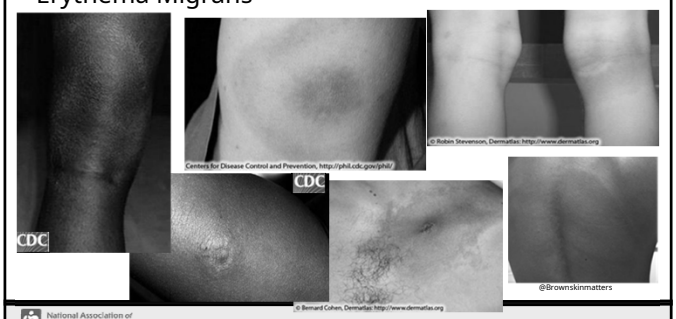
Erythema Migrans



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Disseminated Lyme Disease Presentations

- Early disseminated (avg. 1-2 months after untreated infection) [2]
  - Carditis
    - Typically presents as atrioventricular nodal block, can progress to complete heart block
  - Meningitis
    - Similar to enteroviral and other aseptic meningitis
  - Cranial neuritis
    - Unilateral or bilateral, usually facial nerve but can include other nerves

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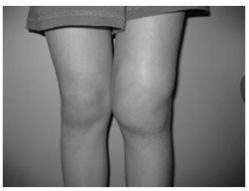
Disseminated Lyme Disease Presentations

- Late disseminated (3+ months after initial untreated infection) [2]
  - Arthritis



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Clinical Testing

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The Basics of Clinical Testing

- Clinicians order clinical tests to either :
  - Screen for a disease before symptoms are present (e.g. cholesterol screens)
  - Diagnose a disease (e.g. EBV serology in a child with infectious mononucleosis)

For diagnosis or confirmation of the presence of disease, the clinician must also consider the child's symptoms, risk history, results of other tests, and clinical experience

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Pretest Probability

- The probability that a patient has the disease before the diagnostic test is performed or the result is known
- Pretest and posttest probabilities take into account test performance (sensitivity and specificity), as well as disease and community context (likelihood ratios, prevalence)
- The probability of the patient having the suspected disease should be known prior to testing

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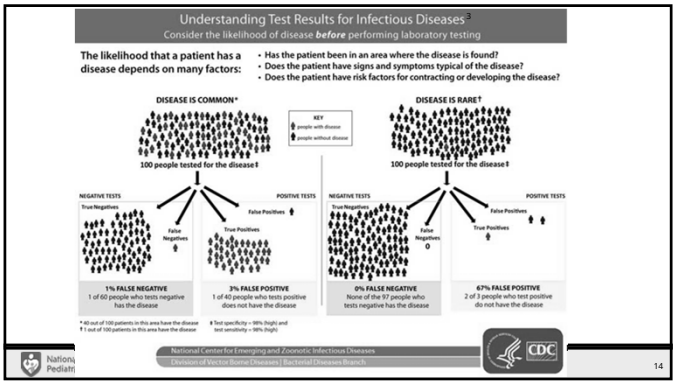

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Sensitivity & Specificity

- Sensitivity - *If patient has disease, what is the likelihood patient will test positive for it?*
  - If a test has high sensitivity, it correctly identifies patients with the disease
    - However, some people who do not have the disease will also test positive
- Specificity - *If patient does not have disease, what is the likelihood patient will test negative for it?"*
  - If a test has high specificity, it correctly identifies patients without the disease

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Predictive Value

- Positive predictive value -*If patient has a positive test, what is the likelihood that patient has the disease?*
  - Proportion of those with a POSITIVE blood test that have the disease
- Negative predictive value - *If patient has a negative test, what is the likelihood that patient does not have the disease?*
  - Proportion of those with a NEGATIVE blood test that do not have the disease
- Positive and negative predictive values are affected by the population prevalence of the disease in question

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Testing for Lyme disease

- Consider serology testing if patients have moderate to high pre-test probability of disseminated Lyme disease:
  - ❑Reside in or have traveled to a geographic area where Lyme disease is common,
  - ❑Have risk factors for a tick bite (outdoor activities, pets who go outside), and
  - ❑Have characteristic symptoms of disseminated Lyme (neurologic or cardiac symptoms, arthritis)
- Serologic testing is highly sensitive in disseminated Lyme disease

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Testing in early localized Lyme disease

- Patients presenting with an erythema migrans rash and an appropriate epidemiologic history consistent with early localized Lyme disease do not require serologic testing
  - Antibodies take several weeks to develop, so clinical diagnosis and treatment is recommended
  - If testing is performed, it may be negative initially- consider retesting in 2-3 weeks

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Lyme Antibody (Serology) Testing

- Two serologic tests are meant to be used in a tiered approach to improve the specificity of the overall result [4]
  - An isolated serologic test has a higher risk of false positivity
- Standard 2-tiered testing protocol
  - Enzyme immunoassay (EIA) or rarely, indirect fluorescent antibody (IFA) test
  - If positive or equivocal, followed by IgM and IgG immunoblots (Western blot)

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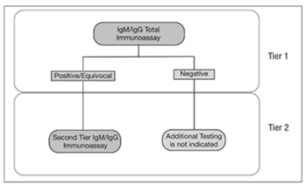
Lyme Antibody (Serology) Testing

- Modified 2-tiered testing protocol [4]
  - Two different FDA- approved EIAs are performed sequentially or concurrently

Figure 2: Modified Two-Tiered Testing (MTTT) 1 – Two Total IgM/IgG immunoassay



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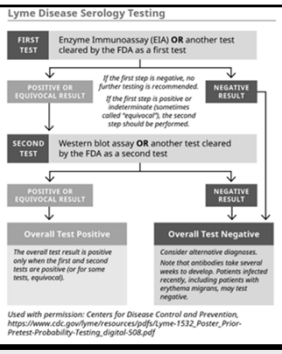
Lyme Serology Algorithm

- Recommend use of tests cleared by the FDA
  - Two step process currently
- Do not recommend the use of alternative or laboratory-specific criteria for interpretation of serologic test results
- Generally caution against tests that have not been cleared by the FDA



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Western Blot

Interpretation of LD Western Blot Results NAPNAP KNOWS LYME

Positive IgM At least 2 of these 3 bands	23/24, 39, 41 kDa
Positive IgG At least 5 of these 10 bands	18, 23/24, 28, 30, 39, 41, 45, 58, 66, 93 kDa

The IgM Western blot is only useful if symptom onset was in the last 30 days. If symptoms have been present for more than 30 days, consider ONLY the IgG Western blot. This is because the IgM result is more prone to false-positive results than the IgG.

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Table 4. Treatment of Specific Manifestations of Lyme Disease

Disease Manifestation	Route	Medication	Duration, days (range)[a]
Erythema migrans[b]	Oral	Doxycycline	10
		Amoxicillin or cefuroxime axetil	14
		Azithromycin[c]	7 (range: 5–10)
Meningitis or radiculopathy	Oral	Doxycycline	14–21
	IV[d]	Ceftriaxone	14–21
Cranial nerve palsy	Oral	Doxycycline	14–21
Carditis	Oral[e]	Doxycycline, amoxicillin, or cefuroxime axetil	14–21
	IV[e]	Ceftriaxone	14–21
Arthritis			
Initial treatment	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	28
Recurrent or refractory arthritis	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	28
	IV	Ceftriaxone	14[f]
Acrodermatitis chronica atrophicans	Oral	Doxycycline, amoxicillin, Or cefuroxime axetil	21–28
Borrelial lymphocytoma	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	14

Abbreviation: IV, intravenous.

[a]Ranges are given where different durations have been studied, and the optimal duration remains uncertain.

[b]This recommendation applies both to solitary and multiple erythema migrans.

[c]Because of concerns for lower efficacy, macrolide antibiotics including azithromycin are considered second line agents, and should be reserved for patients in whom other antibiotic classes are contraindicated. Azithromycin has not been sufficiently studied for manifestations of Lyme disease other than erythema migrans.

[d]The preferred IV agent is ceftriaxone. Cefotaxime and penicillin G are alternatives.

[e]Initial IV therapy is recommended for patients requiring hospital admission. Therapy can be completed orally for the same total 14-day duration. Patients with Lyme carditis who do not require hospital admission can be treated orally.

[f]Repeat IV therapy can be extended to 28 days if inflammation is not resolving.

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Prolonged Symptoms

A study overview

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Postantibiotic Lyme arthritis

- Majority of children have resolution after initial course of antibiotics [5]
- For patients with no or minimal improvement, a second course of treatment with IV ceftriaxone is recommended [2]
  - 14 to 28 days
- Patients with persistent joint inflammation exhibit immune-mediated proliferative synovitis
  - Persistent infection has not been documented in this subgroup
  - Consider scheduled NSAIDS, intraarticular steroid injections or disease-modifying antirheumatic drugs [6]

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Post treatment symptoms

- Longitudinal studies (retrospective and prospective cohorts)
  - Persistent or recurrent fatigue, musculoskeletal pain, neurocognitive and other nonspecific subjective symptoms in 10–20% or more 1 year after treatment [7, 8]
  - Fatigue rarely identified long-term- if present, due to other identified etiologies [9]
  - Mean physical and mental health scores at 11-20 years after presentation of culture confirmed Lyme disease were similar to those of the general population [10]
  - Mean physical and mental health scores after 3 years of follow up increased to just above the national average [11]

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Interestingly…

- Prospective controlled trials
  - Prior to antibiotic treatment, fatigue and pain statistically higher than controls; after treatment, there are no group differences [12]
  - The frequency of non-specific symptoms in patients was similar to that in controls without a history of Lyme borreliosis [13]
  - The frequency of nonspecific symptoms in patients did not exceed that of a control group at > or =6 months after enrollment [14]
- Longitudinal and age matched cohort study
  - Frequencies of reports in symptoms were similar to the frequencies of such reports among age-matched controls without Lyme disease [15]

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Anchoring bias

- A cognitive bias that places excessive weighting of initial information
  - Inability to adjust the initial diagnostic hypothesis
  - Additional information becomes irrelevant
- Even irrelevant or incorrect details can serve as anchors
  - Media literacy and medical literacy become crucial
- Both patients and providers can have anchoring bias
  - Internet based self-diagnosis of Lyme disease leading to death [21]

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TABLE I
Laboratory Results and Clinical Features of Cases Misdiagnosed as Lyme Disease [21]

	Case 1	Case 2	Case 3
Exposure risk	None	Resided in Lyme-endemic area 4 years before symptom onset	None
Lyme test results			
EIA	Positive	Positive	Positive
IgM	Positive	Positive	Negative
IgG	Negative	Negative	Negative
Interpretation in clinical context	Negative	False-positive	Negative
Rationale	Rationale > 30 days of symptoms	Rationale no recent exposure	Rationale negative confirmatory testing
Lyme-directed treatment(s)	Doxycycline, 10 days	Doxycycline, 21 days	Doxycycline, 21 days
	Doxycycline, 30 days		Amoxicillin, 14 days
	Amoxicillin, 10 days		Doxycycline, 45 days
Final diagnosis	Subacute infective endocarditis	Papillary thyroid cancer	Systemic lupus erythematosus
Duration of delay in diagnosis[a]	197 days	21 days	103 days

[a]From the date of Lyme misdiagnosis to the date of final diagnosis.
EIA, enzyme-linked immunoassay.

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"Chronic" Lyme disease

- Undefined diagnosis given to patients with a variety of symptoms
  - Sometimes it is used to describe untreated late disseminated disease
  - More commonly it is used by a small subset of practitioners to describe patients whom they believe have persistent *B. burgdorferi* infection, despite the lack of evidence that this occurs
- Often without clear evidence of prior *B. burgdorferi* infection
  - Or based on private laboratory Lyme disease testing that is not FDA cleared or is used incorrectly
- Risk of harm due to:
  - Treatment plan
  - Missed diagnosis of other treatable conditions

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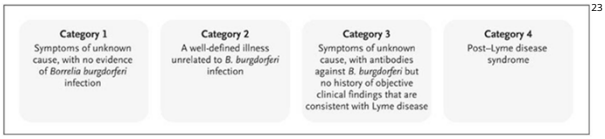
"Chronic" Lyme disease



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Antibiotic retreatment studies

- Previously treated Lyme disease patients with persistent musculoskeletal pain, neurocognitive symptoms, fatigue, or dysesthesias [16, 17]
  - Randomized to receive 30 days of IV ceftriaxone followed by 60 days of oral doxycycline, compared to IV placebo and oral placebo
  - At 30, 60, and 180 days there was no difference in symptom severity and neurocognitive functioning between the treatment and placebo arms
  - 1.6% incidence of life threatening complications

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Antibiotic retreatment studies

- Single-center randomized double-masked placebo-controlled trial on 55 patients with Lyme disease with persistent severe fatigue at least 6 or more months after antibiotic therapy [18]
  - Randomly assigned to receive 28 days of ceftriaxone or placebo
- Ceftriaxone therapy in patients with severe fatigue associated with an improvement in fatigue but not with cognitive function
  - Difference in fatigue scores between those who received antibiotics and those who did not was not statistically significant at 6 months (p = 0.08)
  - Study losses of >20%
- 7.3% incidence of life threatening complications

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Antibiotic retreatment studies

- Randomized double-masked placebo-controlled trial of IV ceftriaxone (23 subjects) to IV placebo (14 subjects) for 10 weeks [19]
- A cognitive index score at 24 weeks did not differ between treatment and placebo groups
- Fatigue at 24 weeks did not differ between treatment and placebo groups
- Secondary outcome measure for pain and physical functioning improved at 24 weeks
  - *Post-hoc* analysis, no information regarding the use of pain medications
- 26.1% incidence of severe adverse events in antibiotic arm

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Antibiotic retreatment studies

- Randomized, double-blind, placebo-controlled trial of 280 patients [20]
  - 89% of whom had previously received antibiotic treatment for the diagnosis of Lyme disease
  - 14 days of IV ceftriaxone then 3 arms of 12 weeks of either: doxycycline, clarithromycin plus hydroxychloroquine, or placebo
- Health-related quality of life scores did not differ significantly among the 3 groups at 52 weeks

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Antibiotic retreatment studies

- In all studies, antibiotic-treated subjects improved- but so did the placebo-treated subjects
- Adverse events reported in all studies
  - Serious antibiotic allergic reaction
  - IV catheter complications
  - Ceftriaxone-associated gallbladder pseudolithiasis requiring cholecystectomy
  - Persistent diarrhea

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Caring for patients

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Listen, really listen

- Utilize active listening
  - The symptoms are real
  - Listen to their concerns
- Patients want answers
  - Many have spent a long time looking for an explanation for their symptoms
  - It is reassuring to have a diagnosis
  - Bacterial infections can be "fixed"

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Inherent bias

- Physicians are taught from a disease-centric model
  - Illness with disease, and disease without illness are given greater authority
  - If there is not a diagnosis, symptoms may be questioned
- Nurse practitioners are taught from a nursing model
  - Focus on the whole person- patient centered model
  - Initial emphasis on diagnosis focuses on how symptoms/conditions will affect the individual
  - Considers how the plan and implementation of care will affect the individual holistically

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It starts with the history

- Take a complete history
  - Understand the chronology of symptoms
  - Alleviating and aggravating factors
  - How are these symptoms affecting their quality of life?
  - What would an improved quality of life look like for them

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Diagnostic evaluation

- Review previous laboratory testing, imaging
- Expand your differential
  - Avoid anchoring bias
  - Systematically go through your differential
    - What is needed to rule in or out a diagnosis
  - Determine what specialist referrals may be helpful for further workup

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Plan of care

- If a diagnosis is unclear, return the focus to care of the patient
  - Utilize shared decision making
- Utilize a multidisciplinary approach
  - Symptom-based referrals
  - Mental health care
  - Support groups
- The end goal may not be recovery but improvement

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"Good news.
Your cholesterol has stayed the same,
but the research findings have changed."

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Questions?

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