**In-person**
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On-demand until July 31, 2022

**Virtual**
April 26-29, 2022
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43rd National Conference
on Pediatric Health Care

# Tick Talk: Lyme Edition

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National Association of Pediatric Nurse Practitioners


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

- Review the etiology and epidemiology of Lyme disease in the United States
- Identify common presentations of Lyme disease, including early localized, early disseminated, and late Lyme disease
- Improve understanding of diagnostic approach for potential Lyme disease cases, including laboratory testing
- Formulate appropriate treatment plans based on clinical presentation of Lyme disease
- Encourage patient education on tick bite prevention strategies

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## Lyme Disease Pathogenesis

- 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
- Other *Borrelia* species in Eurasia that may present differently as well

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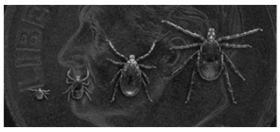
## Vectors

- Transmitted by infected ticks
- The blacklegged tick (or deer tick, *Ixodes scapularis)* spreads the disease in the Northeast, Mid-Atlantic and North Central states
- The Western blacklegged tick (*Ixodes pacificus)* spreads the disease on the West Coast



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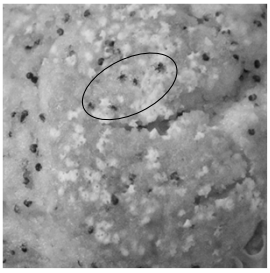
## Nymphal Blacklegged Ticks



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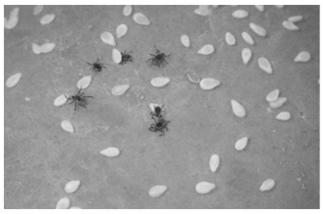
## Adult Blacklegged Ticks



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


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## Case Estimate

- Approximately 476,000 individuals are diagnosed and treated each year, based on recent insurance claims data from spanning 2010-2018 (2, 3)
- Approximately 35,000 cases of Lyme disease are actually reported to the CDC each year

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# General Testing Principles

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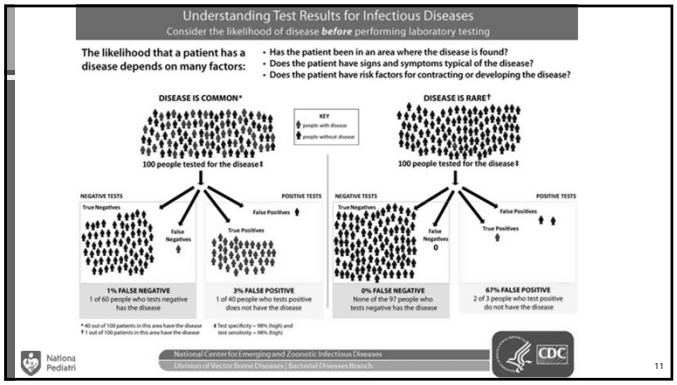


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## Antibody (Serology) Testing

- Conventional 2-tiered testing protocol
  - Enzyme immunoassay (EIA) or indirect fluorescent antibody (IFA) test
  - Followed by IgM and IgG immunoblots (Western Blot)
- Modified 2-tiered testing protocol
  - Two different EIAs are performed sequentially or concurrently
    - Specific EIA that have been approved by the FDA
  - No Western Blot
  - Does have limitation in testing for Lyme arthritis
- Serologic tests are meant to be used with 2-tiers rather than individually to improve specificity

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**Tier 1- EIA/IFA**

| | |
|---|---|
| B. Burgdorferi | ↑ 9.54 * |

⬇

**Tier 2- Western Blot**

| | | |
|---|---|---|
| IgM Western Blot Confi... | Negative * | -- |
| IgM Western Blot Bands | None * | -- |
| B. Burgdorferi | ↑ 9.54 * | -- |
| IgG Western Blot Confi... | ↑ Positive * | -- |
| IgG Western Blot Bands | See Comments * | -- |
| Interpretation Lyme Se... | See Comments * | -- |
| Fluid Type/Source | -- | -- |

| | |
|---|---|
| IgM is considered positive when.... | 2 out of 3 of the following bands are present*: 23/24, 39, 41 kDa |
| IgG is considered positive when... | 5 out of 10 of the following bands are present: 18, 23/24, 28, 30, 39, 41, 45, 60, 66, 93 kDa |

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## Serology Pitfalls

- Falsely negative in the days to weeks following exposure
  - Just like antibody responses to other illnesses, these take time to develop
  - In early localized cases with EM, serology is often negative as EM develops as early as 3 days after exposure
- IgM and IgG responses can persist for years
  - Difficult to determine past infection vs active/current infection
- Reinfections can occur
  - Especially if initial infection was treated promptly
  - May need to rely primarily on clinical presentation rather than testing
- False positives may also occur
  - This increases when pre-test probability is low

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## *B burgdorferi* PCR Testing

- No FDA-cleared molecular assays
- PCR on skin biopsy of erythema migrans lesion
  - ~80% sensitive in one study (5) but highly variable
  - Unlikely to be highly utilized in clinical pediatric practice
- *B burgdorferi* PCR from the blood or CSF
  - Clinical role is unclear due to poor sensitivity
- *B burgdorferi* PCR from the synovial fluid is >70% sensitive in patients with Lyme arthritis

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## CSF : Serum antibody index

- Paired CSF and serum collected within 24 hours of each other
- Should be performed in an experienced laboratory with well-validated methods as an adjunctive test
- Tests for :
  - Anti-*Borrelia* species IgG levels in CSF and serum
  - Total IgG in CSF and serum
  - Albumin in CSF and serum
- Positive (elevated) antibody index can support the diagnosis – highly specific
- Negative antibody index does not rule out the diagnosis

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# General Treatment Principles

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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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**Table 3. Drug Doses**

| Drug | Dosage for Adults | Dosage for Children |
|---|---|---|
| **Oral Regimens** | | |
| **Preferred** | | |
| Amoxicillin[a] | 500 mg 3 times daily | 50 mg/kg divided 3 times daily (maximum 500 mg per dose) |
| Doxycycline[b] | 100 mg twice daily or 200 mg once daily[b] | 4.4 mg/kg divided twice daily (maximum 200 mg daily) |
| Cefuroxime axetil[a,c] | 500 mg twice daily | 30 mg/kg divided twice daily (maximum 500 mg per dose) |
| **Alternative** | | |
| Azithromycin[d] | 500 mg once daily | 10 mg/kg once daily (maximum 500 mg per dose) |
| **Intravenous Therapy** | | |
| **Preferred** | | |
| Ceftriaxone | 2000 mg once daily | 50–75 mg/kg once daily (maximum 2000 mg per dose) |
| **Alternative** | | |
| Cefotaxime[a] | 2000 mg three times daily | 150–200 mg/kg divided 3–4 times daily (maximum 6000 mg daily) |
| Penicillin G[a] | 18–24 million units divided every 4 hours | 200 000–400 000 units/kg divided every 4 hours (maximum 18–24 million units daily) |

Regardless of the treatment regimen, complete response to treatment may be delayed beyond the treatment duration. Relapse may occur with any of these regimens; patients with objective signs of relapse may need a second course of treatment.

[a]Doses of some beta lactam antibiotics (amoxicillin, penicillin, cefuroxime, and cefotaxime) may require adjusted dosing for patients with impaired renal function.

[b]There is increasing favorable information on the safety of short courses of doxycycline in young children, which should impact the risk to benefit ratio of using this antibiotic in patients with various manifestations of Lyme disease; see the General Principles and the individual treatment sections of this guideline for further discussion.

[c]The oral suspension of cefuroxime is currently not available in the USA.

[d]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.

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## Doxycycline in Children

- Doxycycline may be used in any age group
  - If the patient is 7 years old or younger, they may use doxycycline safely for up to 21 days
  - If the patient is 8 years old or older, they may use doxycycline safely for any duration
- Doxycycline is not likely to cause visible teeth staining or enamel hypoplasia in children younger than 8 years
  - Doxycycline binds less readily to calcium compared with other members of the tetracycline class

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# Cases

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## Case 1

- 4 yo healthy female brought to clinic by parents after they noted a tick embedded in her left axilla
- They live in a suburb in NJ with woods surrounding their house, spend a lot of time outdoors
- Parents were unsure how to remove the tick so brought her in this morning

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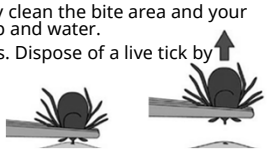
## Removing a tick

- Use clean, fine-tipped tweezers to grasp the tick as close to the skin's surface as possible.
- Pull upward with steady, even pressure. Don't twist or jerk the tick; this can cause the mouth-parts to break off and remain in the skin. If this happens, remove the mouth-parts with tweezers. If you cannot remove the mouth easily with tweezers, leave it alone and let the skin heal.
- After removing the tick, thoroughly clean the bite area and your hands with rubbing alcohol or soap and water.
- Never crush a tick with your fingers. Dispose of a live tick by
  - Putting it in alcohol,
  - Placing it in a sealed bag/container,
  - Wrapping it tightly in tape, or
  - Flushing it down the toilet.



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## Antibiotic Prophylaxis

- Prophylactic antibiotic therapy is recommended for adults and children within 72 hours of removal of identified high risk tick bite
- High risk criteria includes
  - An identified *Ixodes* spp. Vector
  - Occurred in highly endemic area
  - Tick was attached for ≥36 hours
- Wait-and-watch approach is recommended if the tick bite cannot be classified with a high level of certainty as a high risk tick bite
  - Utilize shared decision making with family
- Single dose doxycycline 4.4 mg/kg (max dose 200 mg) for all ages
  - Low risk for single dose of doxycycline

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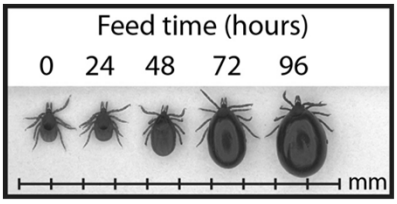
## Estimation of Attachment Time

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## Case 2

- 10 yo male presents in August with the pictured rash.
- He reports that he did go on a trip to the Boundary Waters in northern Minnesota a few weeks ago, which consisted of frequent hiking and portages.
- He does not recall any tick bites and used appropriate preventative measures

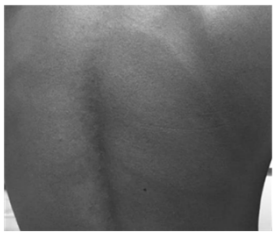

Photo credit to @BrwnSkinMatters

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## Early Lyme Disease

- Most common manifestation is erythema migrans
  - Expanding, erythematous, often annular lesion
  - Occurs at the site of inoculation
- May also have constitutional symptoms such as fatigue, arthralgia, myalgia, headache
- This is a clinical diagnosis
  - Patient has one or multiple lesions consistent with erythema migrans with a potential tick exposure in a Lyme endemic area
- If lesion(s) are atypical for erythema migrans, serology testing may be helpful in the diagnosis
  - Pair with convalescent serology in 2-3 weeks if initial testing is negative

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## Erythema Migrans


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## Multiple EM- Early Disseminated

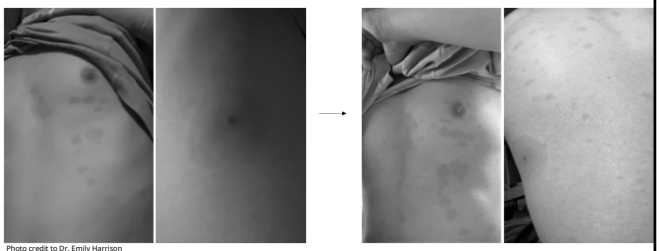

Photo credit to Dr. Emily Harrison

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Lesion of inoculation as well as multiple secondary annular lesions
Serology likely to be positive in early disseminated stage

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## Lyme Carditis

- Early disseminated disease
- Pericarditis and myocarditis can occur
- Most typically presents as atrioventricular nodal block
  - Varying degrees of heart block
  - Can progress to or fluctuate between complete heart block
- Symptoms may include dyspnea, edema, palpitations, syncope, chest pain, exercise intolerance
- ECG does not need to be performed routinely on all patients with early Lyme disease- only if symptoms are present

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## Testing for Lyme Carditis

- Serum antibody testing is preferred
  - Exposure/symptoms <4 weeks, Western Blot IgM only may be positive
  - Exposure/symptoms >4 weeks IgG should also be positive
  - If IgG negative, consider repeat serology in 2-3 weeks to confirm seroconversion
- Consider in children who present with carditis of unknown cause with appropriate epidemiologic history
- Testing is not recommend for children with chronic cardiomyopathy

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## Case 3

- 17yo previously healthy male with 1 week history bilateral frontal headache, primarily around left eye
- Admitted to OSH
  - CSF Pleocytosis with 220 WBC, 83% lymphocytes, 12% monocytes, 5% neutrophils, no growth on culture
  - Discharged with diagnosis of viral meningitis
- Two days later, onset of left facial droop, admitted to our hospital
  - Repeat CSF with 48 WBC, 91% lymphocytes, 9% monocytes. Normal glucose 54, slightly elevated protein at 44 (15-40)
- Trip to Maine 1.5 months ago, at that time a tick bite noted on left thigh, thought to be in place <24 hours. No rash subsequently noted at that site.

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Case credit to Dr. Kiran Belani

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## Case 3

MRI Brain w/wo Contrast

IMPRESSION:

Asymmetric enhancement within the left IAC and along the left facial nerve. Findings are consistent with a left facial neuritis. Findings would be consistent with Bell's palsy but other infectious/inflammatory etiologies including Lyme disease can have this appearance.

The degree of vascular enhancement along the surface of the brain is at the upper range of normal. This may represent a normal finding in a child of this age but may also represent some irritation related to the patient's reported meningitis. No focal areas of abnormal enhancement with no evidence for cerebritis.

Head MRI otherwise negative.

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Case credit to Dr. Kiran Belani

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## *Borrelia burgdorferi* serology in Case 3

- *B. Burgdorferi* EIA Positive

- IgM Western Blot Confirmation 3 bands
- IgM Western Blot Bands 23,39,41 kDa
- IgG Western Blot Confirmation 4 bands
- IgG Western Blot Bands 23,39,41,45 kDa

| | |
|---|---|
| IgM is considered positive when.... | 2 out of 3 of the following bands are present*: 23/24, 39, 41 kDa |
| IgG is considered positive when... | 5 out of 10 of the following bands are present: 18, 23/24, 28, 30, 39, 41, 45, 60, 66, 93 kDa |

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## Lyme Neuroborreliosis

- Early disseminated or (rarely) late finding
- Peripheral nervous system
  - Cranial neuritis
  - Radiculoneuritis (rare in children)
  - Mononeuropathy and mononeuropathy multiplex (rare in children)
- Central nervous system
  - Meningitis
  - Increased ICP (vision compromise, no reports of herniation) (7, 8)
  - Encephalitis – rare in all age groups
  - Myelitis – rare in all age groups

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## Meningitis

- Presentation is similar to enteroviral and other aseptic meningitis
- CSF studies reveal lymphocytic pleocytosis, slightly elevated protein, normal glucose
- The presence of the following increases likelihood of Lyme meningitis (9) :
  - Co-occurrence of facial nerve palsy
  - Symptoms of longer duration (>7 days)
  - Mononuclear cell predominant CSF pleocytosis (10,11,12)

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## Cranial Neuritis

- Usually involves facial nerve (CN VII)
  - Less often trigeminal (CN V), oculomotor and abducens (CN III, VI), and vestibulocochlear (CN VIII)
- Difficult to distinguish from idiopathic facial nerve palsy for which current guidelines recommend corticosteroid initiation within 72 hours
- IDSA Lyme guidelines make no recommendation for or against corticosteroids
  - Often the diagnosis of Lyme neuroborreliosis is not obvious or cannot be confirmed within 72 hours
  - Consider initiating both corticosteroids and antimicrobial therapy if Lyme diagnosis is uncertain

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## Testing for Lyme Neuroborreliosis

- Serum antibody testing is preferred
  - Exposure/symptoms <4 weeks, Western Blot IgM only may be positive
  - Exposure/symptoms >4 weeks IgG should also be positive
  - If IgG negative, consider repeat serology in 2-3 weeks to confirm seroconversion
- CSF : Serum antibody index (if CSF is obtained)
  - Elevated antibody index can support the diagnosis – highly specific
  - Normal antibody index does not rule out the diagnosis
- Not recommended:
  - CSF antibody testing without CSF : Serum antibody index
  - Routine PCR or culture of CSF or serum
    - Poor sensitivity

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## Lyme Neuroborreliosis Treatment (Parenchymal)

- Parenchymal involvement of brain or spinal cord
  - Extremely rare
  - Evident by MRI imaging or focal neurologic exam findings
- Treatment has not been systemically studied
- Recommend parenteral therapy rather than oral
- Typical duration is 2-4 weeks

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## Case 4

- 16yo healthy male with right knee swelling x8 days
  - 7 days into illness, calf became swollen and painful
  - Low grade fevers (Tmax 100.8F)
- Admission to OSH
  - Negative for DVT
  - Large knee effusion with calf fluid collection
  - I&D for septic arthritis, culture negative
  - Improved clinical and laboratory parameters initially, then worsened
  - IV Ancef
- Transferred to our facility for further evaluation

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## Case 4

SH: Patient spends lots of time outdoors. Plays soccer and tennis. Scout camp every summer in Northern Minnesota, no known tick bites in the past year.

ROS: Occasionally, over past year playing soccer, patient's right (dominant) knee would swell and resolve in few days, although he never trouble with walking. No rashes. No other symptoms reported at this time.

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## Case 4

IMPRESSION:

- Large right knee joint effusion including fluid extending into a large popliteal cyst
- Synovial hyper-enhancement
- Multiple enlarged popliteal lymph nodes
- Edema of the adjacent muscle structures

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## *Borrelia burgdorferi* serology in Case 4

- *B. burgdorferi* EIA: Positive

- IgM Western Blot Confirmation: Negative
- IgM Western Blot Bands: None
- IgG Western Blot Confirmation: Positive
- IgG Western Blot Bands: p93,p66,p58,p45,p41,p39,p28,p18

| | |
|---|---|
| IgM is considered positive when.... | 2 out of 3 of the following bands are present*: 23/24, 39, 41 kDa |
| IgG is considered positive when... | 5 out of 10 of the following bands are present: 18, 23/24, 28, 30, 39, 41, 45, 60, 66, 93 kDa |

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## Lyme Arthritis

- Usual manifestation of late disease in children
- Marked swelling of primarily affects large joints (>90% knee)
- Can be difficult to differentiate from septic arthritis
  - Predictors of Lyme arthritis include known history of tick bite, isolated knee involvement, lack of fever
  - Predictors for septic arthritis include absolute neutrophil count >10k, ESR >40, hip involvement, pain with short arc motion
  - Synovial fluid white blood cell counts can overlap, neutrophil predominance
- Baker cyst (popliteal cyst) can occur
  - Ruptures can look very similar to calf deep vein thrombosis

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## Testing for Lyme Arthritis

- Serum antibody testing is preferred
  - Sensitivity is 95-100%
  - IgM can be positive or negative; IgG must be positive
  - Reconsider the diagnosis if IgM only is positive, or IgG has <5/10 bands
- In addition, may consider PCR testing of synovial fluid or tissue
  - Sensitivity >70% (13, 14, 15)
- Not recommended
  - Culture of synovial fluid or tissue
  - Blood PCR or culture

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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.

IDSA-AAN-ACR Lyme Disease Guidelines • CID 2021:72 (1 January) • e11



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## Treatment of Lyme Arthritis

- Initial therapy is an appropriate oral antibiotic x 28 days
  - Children <8y should not use doxycycline for more than 21 days
- Children with partial response (mild residual joint swelling)
  - Consider observation
  - Consider a second course of antibiotic therapy for up to one month (particularly when family prefers a second trial of oral antibiotic over IV)
- Children with no or minimal response, worsening of arthritis, new joint involvement
  - A course of IV ceftriaxone is preferred over a second course of oral abx
  - Duration is 2-4 weeks based on response

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## Refractory Lyme Arthritis

- Children with persistent synovitis or effusion after one course of oral antibiotics and one course of IV antibiotics
  - Exhibit immune-mediated proliferative synovitis that can lead to significant joint damage and dysfunction
  - Antibiotic therapy for more than 8 weeks is not expected to provide additional benefit (as long as this has included a course of IV)
  - Consider referral to rheumatology for additional treatment modalities

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## Persistent Symptoms after Lyme Disease Treatment

- Persistent or recurring fatigue, musculoskeletal pain, neurocognitive, and other nonspecific subjective symptoms 1+ years after treatment
  - Symptoms appear to subside over time
  - Diagnosis anchoring? (16-19)
- Additional antibiotic therapy is not recommended unless there is objective evidence of treatment failure or reinfection (arthritis, meningitis, neuropathy) (20-22)
- IDSA Guidelines, Section XXV for a great review of available evidence
- Term "Chronic Lyme disease" currently lacks accepted definition for clinical use or scientific study

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# Prevention

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## Prevention Strategies

- Permethrin 0.5% for clothing and gear
  - Easily found, including on Amazon, Wal-mart, REI
  - Follow application instructions and do not apply to skin
  - Protects for multiple months/washes after treatment
- EPA-registered insect repellent
  - Deet and many others (EPA website)
  - Deet is safe for children >2m of age, avoid face and hands
  - 10-30% concentration
- Avoid the tall grass, bushy areas when possible
  - Ticks don't fly or jump, they wait for a host to brush up against them

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## Prevention Strategies

- Tick checks!
  - Check clothing, children's skin, pay attention to folds and hairline
  - Shower soon after playing outdoors (wash off unattached ticks, do a tick check)
  - Any gear such as boots, bags, etc.
- Outdoor/indoor pets should be checked for ticks as well
  - Even if they are on a tick medication- many do not kill ticks on contact with skin, so the tick can be transmitted inside and to others
- Mow yards regularly, keep tall grasses and bushes away from busy yard areas

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## Vaccine

- Valneva and Pfizer have developed a Lyme disease vaccine candidate, VLA15, that is currently in Phase 2 human trials
  - Designed to protect people against North American and European strains of the Lyme disease bacterium
- LYMERix®, only previous Lyme vaccine marketed in the US, was discontinued by the manufacturer in 2002, citing insufficient consumer demand

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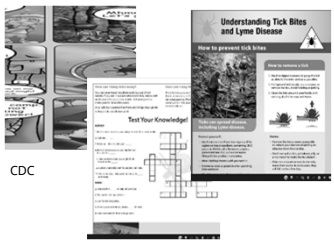
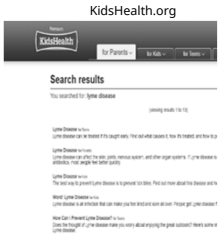
## Prevention Resources for Families




CDC

KidsHealth.org




Coming Soon- NAPNAP sponsored website on Lyme Disease with additional patient and provider resources

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## Survey

Identifying NP Needs for Addressing Lyme Disease in Pediatric Practice Survey

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# Questions?

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