Manifestations and Management of Lyme disease in Children

The 4th Annual J. Owen Hendley
“Hot Topics in Pediatric Infectious Disease”
Memorial Lecture
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Disclosures

• I have no financial conflicts of interest relevant to the content of this presentation

• Unapproved/ off-label use of some antibiotics will be discussed, including:
  • Amoxicillin
  • Doxycycline
  • Cefuroxime
  • Ceftriaxone
Learning Objectives

• Know the agent, vectors, and geography for *B. burgdorferi* infection
• Recognize the presentations of Lyme disease
• Understand the methods available for the diagnosis of Lyme disease
• Plan the therapy for uncomplicated Lyme disease in a child
Agent and vectors of Lyme disease

**Agent:** Borrelia burgdorferi

**Vector:** Ixodes scapularis

All life stages bite humans, but nymphs and adult females transmit pathogens.

http://www.cdc.gov/lyme/transmission/index.html
95% of Lyme occurs in the Upper Midwestern and northeastern US
Lyme Disease Incidence in Virginia, 1990-2012

→ Increase in cases may be related to spatial expansion of *I. scapularis* ticks

1657 cases reported to CDC in VA in 2017

Incidence is about 12.3 per 100,000 cases

VDH, 2013
Reported Cases Lyme Disease, VA, 2016

→ Highest rates are generally seen in counties with moderately high human populations and expanding suburban development
Reported Lyme Disease Cases, Virginia, by month, 2012

<table>
<thead>
<tr>
<th>Month</th>
<th>Cases with Recorded Onset Dates</th>
<th>Cases with Event Dates Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan.</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Feb.</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Mar.</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Apr.</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>May</td>
<td>150</td>
<td>100</td>
</tr>
<tr>
<td>Jun.</td>
<td>180</td>
<td>150</td>
</tr>
<tr>
<td>Jul.</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>Aug.</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>Sep.</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Oct.</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Nov.</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Dec.</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

→ Peak follows the peak in nymph stage blacklegged tick biting activity

VDH, 2013
What is the most common manifestation of Lyme disease in children in the US?

A. Arthritis
B. Erythema migrans
C. Aseptic meningitis
D. Chronic fatigue
E. Lymphocytoma
## Clinical manifestations of Lyme in Children

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single EM</td>
<td>66 %</td>
</tr>
<tr>
<td>Multiple EM</td>
<td>23 %</td>
</tr>
<tr>
<td>Arthritis</td>
<td>7 %</td>
</tr>
<tr>
<td>Facial palsy</td>
<td>3 %</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>1 %</td>
</tr>
<tr>
<td>Carditis</td>
<td>0.5 %</td>
</tr>
</tbody>
</table>

Erythema migrans

• Early localized stage of infection (<4 weeks):
  • Annular, expanding, erythematous
  • Homogenous or central clearing
  • May be accompanied by malaise, headache, fever, myalgia, arthralgia
Differentials of Erythema Migrans

**Tick bite hypersensitivity reaction:**
- Redbumps on the skin arranged in a circle or ring.
- Itchy, raised edge, scaly
- (<48 hours, < 5 cm)

**Tinea corporis:**
- Redbumps on the skin arranged in a ring
- Itchy, raised edge, scaly

**Granuloma annulare**
- Redbumps on the skin arranged in a ring

**Other differentials:**
- Nummular eczema (papules, scale, pruritic)
- Cellulitis (induration)
- STARI
Disseminated Erythema migrans

- Early disseminated disease
- Multiple secondary annular rashes
- May be accompanied by malaise, headache, fever, myalgia, arthralgia
- Lymphadenopathy
Neurologic manifestations

- Early disseminated disease
- Bell’s palsy
- Meningitis (lymphocytic)
- Radiculopathy
- May be accompanied by malaise, headache, fever, myalgia, arthralgia

MRI showing enhancement of tympanic segment of the left facial nerve:

Wong et al, Ped Emerg Care, 2018
Cardiac manifestations

- AV heart block
- Pericarditis
- Myocarditis
- May be accompanied by malaise, headache, fever, myalgia, arthralgia

ECG of 14 yo male with complete heart block (atrial rate 96 bpm, ventricular rate 66 bpm)
Arthritis

• Late disease (> 6 months)
• Synovitis/ effusion
• Mono/ oliogoarticular
• Large weight bearing joints
  • Usually the knee (90%)
• Synovial fluid:
  • >2000-50,000 WBC
• Lasts several weeks before resolving but recurs if untreated
Two-tier serology for non-EM presentations

Positive test:
- 2 of 3 specific IgM bands
- OR
- 5 of 10 specific IgG bands

First test
- Enzyme Immunoassay (EIA)
- OR
- Immunofluorescence Assay (IFA)

Positive or Equivocal Result

Negative Result

Consider alternative diagnosis
- OR
- If patient with signs/symptoms consistent with Lyme disease for ≤ 30 days, consider obtaining a convalescent serum

Second test
- Signs or symptoms ≤ 30 days
- IgM and IgG Western Blot

- Signs or symptoms > 30 days
- IgG Western Blot ONLY

To avoid loss of specificity, do not:
1. Use assays not approved by FDA
2. Omit the first-tier assay
3. Use IgM WB to confirm diagnosis in patient with chronic symptoms and negative IgG WB

Sanchez, Review of Lyme disease, JAMA 2016
5 yo boy with mild HA and lethargy. Treated with doxycycline 3 weeks ago for EM rash. Lyme ELISA positive, reflex Western Blot as shown:

<table>
<thead>
<tr>
<th>Component Results</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B <em>Burgdorferi</em> IgG Western Blot</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Reference range: Negative</td>
<td></td>
</tr>
</tbody>
</table>

| **B *Burgdorferi* IgG Bands Detected**                 | p41            |
| **B *Burgdorferi* IgM Western Blot**                   |                |
| Positive                                               |                |
| Reference Range: Negative                              |                |

| **B *Burgdorferi* IgM Bands Detected**                 | p41, p39, p23  |

What is his diagnosis?

a) Early Lyme, treated
b) Early Lyme, untreated
c) Late Lyme disease
d) No Lyme disease
14 yo female with left knee swelling over the past week without a history of fever or trauma and the following results:

<table>
<thead>
<tr>
<th>NAME</th>
<th>VALUE</th>
<th>NORMAL</th>
<th>UNITS</th>
<th>Flag</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyme Antibodies, ELISA</td>
<td>&gt;0.99</td>
<td>-</td>
<td>-</td>
<td>F</td>
<td></td>
</tr>
</tbody>
</table>

What is her diagnosis?

a) Early Lyme
b) Late Lyme disease
c) Past Lyme disease
d) No Lyme disease
A 16 yo girl with fatigue and mild arthralgias x 6 mo

What is her diagnosis?

a) Early Lyme
b) Late Lyme disease
c) Past Lyme disease
d) No Lyme disease

(Note: Lyme ELISA not ordered)
Other tests

- C6 peptide: variable major protein-like sequence-expressed (VlsE) sixth invariant region (C6)
  - Earlier IgG response, easier to interpret, faster but slightly less specific than WB
- PepC10, an invariant epitope of outer surface protein C
- May see algorithms using these combinations in the future
- CSF: Intrathecal Antibody production and PCR (but low NPV)
- Synovial fluid: PCR

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Steere AC. Clin Infect Dis. 2008
Which of the following would be most appropriate for treatment of early Lyme disease in a 6 year old boy with a severe allergy to penicillin?

A. Amoxicillin
B. Ceftriaxone
C. Cefuroxime axetil
D. Doxycycline
E. Azithromycin

Based on Red Book, AAP 2018
Note the 2006 IDSA guidelines would recommend macrolide
# Treatment of Lyme Disease

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Recommended therapy</th>
<th>Length (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM (single or multiple)</td>
<td>Doxycycline 4.4 mg/kg/day, orally, ÷ BID (max 200 mg/day) OR Amoxicillin 50 mg/kg/day, orally, ÷ TID (max 1.5 g/day) OR Cefuroxime 30 mg/kg/day, orally, ÷ BID (max 1000 mg/day)</td>
<td>10</td>
</tr>
<tr>
<td>CN palsy</td>
<td>Doxycycline 4.4 mg/kg/day, orally, ÷ BID (max 200 mg/day)</td>
<td>14</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Ceftriaxone 50–75 mg/kg, IV, once a day (maximum 2 g/day) OR Doxycycline 4–8 mg/kg per day, orally, ÷ BID (max 200 mg/day)</td>
<td>14</td>
</tr>
<tr>
<td>Carditis</td>
<td>Ceftriaxone 50–75 mg/kg, IV, once a day (maximum 2 g/day) OR As for early localized disease</td>
<td>14-21</td>
</tr>
<tr>
<td>Arthritis</td>
<td>As for early localized disease (Doxy only for kids ≥ 8 yo)</td>
<td>28</td>
</tr>
</tbody>
</table>

Adapted from Red Book, AAP 2018
Antibiotic Refractory Arthritis

- Treatment of Lyme disease is effective at all stages of infection
- Treatment failures are very uncommon
- Occasionally re-treatment may be considered for persistent or recurrent joint swelling after antibiotic therapy
  - 28 d amoxicillin/ doxycycline or 14-28 d ceftriaxone
  - Persistent symptoms beyond this thought to be reactive arthritis
    - Adjunctive non-antimicrobial therapies such as NSAIDs, intra-articular corticosteroids, DMARD, arthoscopic synovectomy
- Prolonged antibiotic therapy inappropriate

2006, IDSA Treatment guidelines
Clinical Outcomes of Pediatric Lyme Arthritis

No patient had continuing symptoms of *B. burgdorferi* infection, chronic debilitating arthritis, or permanent joint deformities at final follow up.

J. Rheumatol 2010; 37 (5): 1049
Clinical Outcomes Pediatric Neuroborreliosis

Mild persistent motor or sensory deficits were detected in about a quarter of children at 5-year follow up.

<p>| TABLE 3 Clinical Outcome in Patients With Confirmed LNB at Follow-up (n = 84) |</p>
<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (range)</td>
<td>13 (7–19)</td>
</tr>
<tr>
<td>Time to follow-up, y, median (range)</td>
<td>5 (3–8)</td>
</tr>
<tr>
<td><strong>Clinical outcome, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Definite sequelae</td>
<td>16 (19)</td>
</tr>
<tr>
<td>Possible sequelae</td>
<td>7 (8)</td>
</tr>
<tr>
<td>No sequelae</td>
<td>61 (73)</td>
</tr>
</tbody>
</table>

| Affected daily activities or school performance, n (%) |
| Definite sequelae | 6 (37) |
| Possible sequelae | 4 (57) |
| No sequelae | 9 (15) |
# Post Lyme Neuroborreliosis symptoms

<table>
<thead>
<tr>
<th>Major Subjective Symptoms</th>
<th>Patients With LNB (n = 84), n (%)</th>
<th>Controls (n = 84), n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>28 (33)</td>
<td>32 (38)</td>
<td>NS</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (23)</td>
<td>29 (34)</td>
<td>NS</td>
</tr>
<tr>
<td>Facial problems</td>
<td>7 (8)</td>
<td>0 (0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neck pain or stiffness</td>
<td>9 (11)</td>
<td>5 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Vertigo</td>
<td>6 (7)</td>
<td>1 (1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pain, numbness, or weakness in limbs</td>
<td>6 (7)</td>
<td>1 (1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Poor appetite or wt loss</td>
<td>4 (5)</td>
<td>5 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Memory or concentration problems</td>
<td>9 (11)</td>
<td>5 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Sleeping disorder</td>
<td>10 (12)</td>
<td>7 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>Affected daily activities</td>
<td>14 (17)</td>
<td>12 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Affected school performance</td>
<td>12 (14)</td>
<td>8 (10)</td>
<td>NS</td>
</tr>
<tr>
<td>No reported symptoms</td>
<td>34 (40)</td>
<td>41 (49)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Persistent post-treatment symptoms

• Some patients with demonstrated Lyme disease have persistent subjective symptoms after appropriate treatment, e.g., fatigue and arthralgia
• Cause unknown, but seen with convalescence from other infections
• Ongoing infection with *B. burgdorferi* not demonstrated
• Long-term antibiotics not beneficial
• Manage symptomatically, will gradually recover
• Antibodies may persist for years after Lyme disease treated and cured; serologic tests cannot be used to measure treatment response

2006, IDSA Treatment guidelines
Prolonged antibiotic therapy following standard treatment is not effective

*68.6% reported ≥ 1 drug related adverse reaction

Potential for serious adverse events from unnecessary long-term IV antibiotic therapy:

- Central-line infections
- Septic shock
- Osteomyelitis
- *Clostridium difficile* colitis
- Paraspinal abscess
- Death

Marzec, MMWR. 2017.
Co-infection: Anaplasmosis

- Caused by *Anaplasma phagocytophilium*
- Occurs in all Lyme–endemic areas
- 1-2 weeks after bite by infected tick
- Acute febrile illness:
  - fever, chills, HA, malaise, myalgia, GI, nausea, emesis, diarrhea, rash (rare)
- Labs:
  - ↓wbc, hgb, plt
  - ↑AST/ALT
- Dx: Blood smear, serology and PCR
- Rx: doxycycline x 10d
  - Do not need to confirm diagnosis
  - Feel better after first dose
  - Re-consider diagnosis if not better>48h

Morulae (microcolonies of anaplasmae) detected in granulocyte on peripheral blood smear

Photos: S. Pritt, Mayo Clinic

CDC, 2015
Co-infection: Babesiosis

- Caused by *Babesia microti*
- Geography narrower than for Lyme
- Incubation period of 1-9 weeks
- Fever, chills, myalgia, arthralgia, dark urine, ↑spleen, jaundice
- Labs:
  - ↓ Hgb (hemolytic anemia), ↓plts
  - ↑ Cr/ BUN; AST/ ALT
- Dx: Smear (‘Maltese cross’), serology, PCR
- Rx: Atovaquone + azithromycin x 7-10 d
  - (Clindamycin + quinine if severe)
  - Persistence or relapse in those with underlying ID, treat longer

Intraerythrocytic parasites seen on blood smear
Borrelia miyamotoi

- Member of the relapsing fever group of *Borrelia*
- Transmitted by *Ixodes scapularis*
- First reported to cause human disease in 2013
- Fever, HA, myalgia, arthralgia, malaise/ fatigue but rash uncommon
  - Fever may be relapsing
  - Chronic meningitis in severely immunocompromised
- ↓ WBC, ↓plt; ↑AST/ALT
- May be misdiagnosed as Lyme disease because causes positive results with serology
- Active infection is most appropriately diagnosed by PCR
- Rx: Doxycycline and amoxicillin
Prevention of Lyme disease

• Control Measures
  • Protective clothing
  • Tick repellents (DEET)
  • Tick checks
  • Bathing within 2 hours
  • Prompt removal of attached ticks

• Vaccine no longer available

• Chemoprophylaxis
  • In areas of high risk, can offer if:
    a) *I. scapularis* tick bite and
    b) Tick attached for ≥ 36 hours and
    c) Prophylaxis can be started within 72 hours of tick removal
  • A single dose of doxycycline 200-mg dose (4.4 mg/kg for people weighing less than 45 kg)

www.cdc.gov/lyme/removal/index.html
Summary

• Lyme disease is a significant infection transmitted by the *Ixodes scapularis* tick
• Endemic in Virginia, with ↑ cases reported in VA since 2007
• Presents with early localized, early disseminated and late manifestations
• Diagnosis of EM is diagnosed by visual inspection
• Diagnosis of later stages is supported by 2 tier serology
  • Limitations: Serology lacks sensitivity in early stage and serology remains + for years
• Carries an excellent prognosis in children with appropriate treatment
  • Amoxicillin, Doxycycline, or Ceftriaxone; duration 10-14 d (28 d for arthritis)
• Suspect co-infection if high fever after *Ixodes* tick bite in area where these infections are endemic or unexplained leukopenia, thrombocytopenia or anemia or resolution of EM rash, but no improvement or worsening of viral infection–like symptoms