SPECIAL PANEL PRESENTATION

Lyme Disease: Big, Bad *Borrelia burgdorferi* & the Tiny Tick

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Infected unfed nymph
23°C, elevated pH

Midgut lumen spirochetes
OspA +
OspB +
OspC -

72 hr feeding nymph
37°C, lower pH

Salivary gland spirochetes
OspA -
OspB -
OspC +
Other group I lipoproteins

Transition stage?
OspA +
OspB +
OspC +
Erythema migrans can present itself in many different forms:

- **Blistering Lesions**
- **Uniformly Red Lesions**
- **Disseminated Lesions**
- **Blue-Red Lesions**
- **Bullseye (Target)/ Central Clearing Lesions**

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Heart block in Lyme disease

- Atrioventricular (AV) node
- Electrical signal from the AV node is "blocked"

ECG Tracings:
- Normal
- First-Degree AV Block
- Second-Degree AV Block (2:1)
- Third-Degree AV Block
The most common and useful lab tests measure a patient's serologic response to Borrelia burgdorferi. IgM responses are first detected within two weeks of infection, peak at three to six weeks, then falls to normal by six months. IgG can usually be detected by four to six weeks; and peak many months after onset of disease. The IgG response lasts for many years.
Anti-Borrelia antibody production during infection
# Treatment of Lyme Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult Dosage</th>
<th>Pediatric Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERYTHEMA MIGRANS</strong>&lt;br&gt;Doxycycline (Vibramycin, and others)&lt;br&gt;OR Amoxicillin (Amoxicil, and others)&lt;br&gt;OR Cefuroxime axetil (Ceftin)</td>
<td>100 mg PO b.i.d. x 21 d&lt;br&gt;500 mg PO t.i.d. x 21 d&lt;br&gt;500 mg PO b.i.d. x 21 d</td>
<td>&gt;8 yrs: 1-2 mg/kg b.i.d&lt;br&gt;50 mg/kg/day divided t.i.d.&lt;br&gt;30 mg/kg/day divided b.i.d</td>
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<tr>
<td><strong>NEUROLOGIC DISEASE</strong>&lt;br&gt;Facial nerve palsy&lt;br&gt;More serious CNS disease&lt;br&gt;OR Amoxicillin&lt;br&gt;OR Ceftriaxone (Rocephin)&lt;br&gt;OR Cefotaxime (Claforan)&lt;br&gt;OR Penicillin G</td>
<td>Doxycycline</td>
<td>100 mg PO b.i.d. x 21-28 d&lt;br&gt;500 mg PO t.i.d. x 21-28 d&lt;br&gt;2 g/day IV x 14-28 d&lt;br&gt;2 g IV q8h x 14-28 d&lt;br&gt;20-24 million units/day IV x 14-28 d</td>
</tr>
<tr>
<td><strong>CARDIAC DISEASE</strong>&lt;br&gt;Mild (first degree AV block)&lt;br&gt;More serious</td>
<td>Doxycycline&lt;br&gt;OR Amoxicillin&lt;br&gt;OR Ceftriaxone&lt;br&gt;OR Penicillin G</td>
<td>100 mg PO b.i.d. x 21-28 d&lt;br&gt;500 mg PO t.i.d. x 21-28 d&lt;br&gt;2 g/day IV x 14-21 d&lt;br&gt;18-24 million units/day IV x 14-21 d</td>
</tr>
<tr>
<td><strong>ARTHRITIS</strong>&lt;br&gt;Oral&lt;br&gt;Parenteral</td>
<td>Doxycycline&lt;br&gt;OR Amoxicillin&lt;br&gt;OR Ceftriaxone&lt;br&gt;OR Penicillin G</td>
<td>100 mg PO b.i.d. x 28 d&lt;br&gt;500 mg PO t.i.d. x 28 d&lt;br&gt;2 g/day IV x 14-28 d&lt;br&gt;18-24 million units/day IV x 14-28 d</td>
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1. The duration of treatment is not well established. Relapse has occurred with all of these regimens; patients who relapse may need a second course of treatment. There is no evidence that either repeated or prolonged treatment benefits subjective symptoms attributed to Lyme disease.
2. Should not exceed adult dosage.
3. Neither doxycycline nor any other tetracycline should be used for children less than eight years old or for pregnant or lactating women.
4. A temporary pacemaker may be necessary.
5. In late disease, the response to treatment may be delayed for several weeks or months.
Lyme Vaccine

LYMErix: In 1998, the FDA approved LYMErix, a Lyme disease vaccine utilizing a recombinant OspA antigen. The approval was based on large clinical studies that demonstrated its safety and effectiveness. Subsequently, some clinicians raised concerns that the vaccine itself might be causing a "reactive" arthritis in some genetically pre-disposed people. The manufacturer SmithKline withdrew the product.

VLA15: FDA just announced plans to expedite approval of a vaccine for Lyme disease. Valneva, the maker of the vaccine candidate, known as VLA15, recently completed an initial evaluation in a small, early stage clinical trial. Now the company has been given a green light by the regulatory agency through a program known as Fast Track to move onto a larger trial at the beginning of 2018. Additionally it will announce findings from the first trial around the same time.
Tickborne Diseases Present in Vermont

1. Lyme disease
2. Anaplasmosis
3. Babesiosis
4. *Borrelia miyamotoi*
5. Ehrlichiosis
6. Spotted fever group rickettsiosis
7. Tularemia
8. Powassan virus disease
9. Heartland virus disease (?)
Causative Agent in Vermont: *Borrelia burgdorferi*

- Upper Midwest: *Borrelia burgdorferi* & *Borrelia mayonni*
- Europe & Asia: *Borrelia afzelii* & *Borrelia garinii*

**Brief History of Lyme Disease**

- Lyme disease was first recognized in late 1970’s\(^{(1)}\)
- Museum specimens from 1890’s contain the bacterium\(^{(2)}\)
- Pathogen was in North America prior to last ice age\(^{(3)}\)
  - ~20,000 years ago
Lyme Disease Vector: Blacklegged Tick

- *Borrelia burgdorferi* is transmitted through tick bite
  - Blacklegged tick (*Ixodes scapularis*)

- Ticks feed on small, warm-blooded animals (host)
  - Ticks pick up *Borrelia burgdorferi* during a feeding
  - Ticks do not hatch with *Borrelia burgdorferi*

- Ticks get onto a host through questing
  - Do not jump (like fleas)
  - Do not fall down from trees above
Blacklegged Tick: Evolved Pathogen Spreader

- Ticks must feed on a host for multiple days
- Components of tick saliva help evade defenses

1. Pain and itch pathway inhibitors
2. Anticoagulants
3. Vasodilators
4. Platelet aggregation inhibitors
5. Wound healing modulators
### Pathogen Prevalence in Vermont Ticks

<table>
<thead>
<tr>
<th>Pathogens Detected</th>
<th>Percentage of Ticks (n = 2,209)*</th>
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</thead>
<tbody>
<tr>
<td>Anaplasma phagophytocilium</td>
<td>7.0%</td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td>52.9%</td>
</tr>
<tr>
<td>Babesia microti</td>
<td>0.8%</td>
</tr>
<tr>
<td>Single Pathogen Carriage Rate</td>
<td>60.7%</td>
</tr>
</tbody>
</table>

- Majority of blacklegged ticks carry one pathogen
- 4.7% of ticks infected with >1 pathogen

* Data contributed by VAAFM & Lyndon State College
Lyme Disease is a Zoonotic Disease

- White-tailed deer are responsible for Lyme disease

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**Deer Culling Discussed Amid Worry Over Tick Diseases**

Alex Elvin  Thursday, July 7, 2016 - 6:11pm

**Deer overpopulation helps spread Lyme**

News-Times, The (Danbury, CT)  Published 1:00 am, Monday, November 24, 2008
Lyme Disease is a Zoonotic Disease

- Competent reservoirs for Lyme disease (Borrelia burgdorferi)\(^\text{(6)}\)
Seasonal Risk for Lyme Disease in Vermont
Lyme Disease Illness

- Symptoms do not begin right away
  - Incubation period: 3 – 30 days

**Early localized infection**
- Erythema migrans
  - Often accompanied by flu-like symptoms in the United States

**Disseminated infection, systemic symptoms**
- Lyme neuroborreliosis
  - Acute neurological involvement, often lymphocytic meningitis, cranial neuritis or radiculoneuritis

**Localized infection, usually without systemic symptoms**
- Lyme arthritis
  - Arthritis in one or a few joints, most commonly the knee, with minimal, if any, systemic symptoms

**Stage 1**
- Days–weeks

**Stage 2**
- Weeks–months

**Stage 3**
- Months–years
Most Commonly Reported Symptoms of Lyme Disease

3% of Vermont Lyme disease cases are hospitalized

36% for anaplasmosis
48% for babesiosis
Who Is At Risk for Lyme Disease in Vermont?
Increasing Cases of Lyme Disease in Vermont

89% increase in cases from 2008 to 2016

*First year that probable cases were counted
Geographic Expansion of Lyme Disease

County-Level Incidence, 2008
(per 100,000 in population)
- ≤16.7
- >16.7 ≤41.6
- >41.6 ≤97.8
- >97.8 ≤168.9
- >168.9 ≤333.6

County-Level Incidence, 2016
(per 100,000 in population)
- ≤16.7
- >16.7 ≤41.6
- >41.6 ≤97.8
- >97.8 ≤168.9
- >168.9 ≤333.6
Human Habitat is Tick Habitat
Lyme Disease Prevention

Reducing exposure to ticks is the best available defense against tickborne diseases

1. Avoid Ticks
   - When outdoors, walk in the center of trails and avoid wooded areas

2. Repel Ticks
   - Use 20-30% DEET on skin/clothing
   - Treat clothing/gear with permethrin

3. Remove Ticks
   1. Bathe or shower within 2 hours after spending time outside in tick prone areas
   2. Conduct a full body tick check using a mirror
   3. Inspect pets and gear for ticks
**Take-home Message:**
- Ticks are really small!
- You are looking for something the size of a poppy or sesame seed
The Problem

- Reported cases of Lyme disease and other tickborne diseases are **INCREASING**
- Prevention recommendations can be difficult to implement
- We needed a new strategy!
Past Recommendations for Washer/Dryer

After spending time outdoors in potential tick habitat:

- Tumble clothes in a dryer on **high heat** for **one hour** to kill remaining ticks

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**The heat is on: Killing blacklegged ticks in residential washers and dryers to prevent tickborne diseases**

Christina A. Nelson, Catherine M. Hayes, Molly A. Markowitz, Jacqueline J. Flynn, Alan C. Graham, Mark J. Delorey, Paul S. Mead, Marc C. Dolan
Current Recommendations for Washer/Dryer

After spending time outdoors in potential tick habitat:

- Tumble **dry clothes** in a dryer on **high heat for 10 minutes** to kill ticks on dry clothing after you come indoors
  - If the clothes are damp, additional time may be needed
- If the clothes are soiled and **require washing first, hot water is recommended**
  - After washing, tumble dry on **low heat for 90 min or high heat for 60 min**. The clothes should be warm and completely dry
How to Create a Tick Safe Yard

- Clear tall grasses and brush around homes and at the edge of lawns.
- Place a 3-ft wide barrier of wood chips or gravel between lawns and wooded areas.
- Mow the lawn frequently and keep leaves raked.
- Stack wood neatly and in a dry area (discourages rodents that ticks feed on).
- Keep playground equipment, decks, and patios away from yard edges and trees and place them in a sunny location, if possible.
- Remove any old furniture, mattresses, or trash from the yard that may give ticks a place to hide.
Take-home Message:
- Ticks like warm moist environments.
- Prevention means minimizing these environments.

**Tick zone**
Avoid areas with forest and brush where deer, rodents, and ticks are common.

**Wood chip barrier**
Use a 3 ft. barrier of wood chips or rock to separate the “tick zone” and rock walls from the lawn.

**Wood pile**
Keep wood piles on the wood chip barrier, away from the home.

**Tick migration zone**
Maintain a 9 ft. barrier of lawn between the wood chips and areas such as patios, gardens, and play sets.

**Tick safe zone**
Enjoy daily living activities such as gardening and outdoor play inside this perimeter.

**Gardens**
Plant deer resistant crops. If desired, an 8-ft. fence can keep deer out of the yard.

**Play sets**
Keep play sets in the “tick safe zone” in sunny areas where ticks have difficulty surviving.

*Based on a diagram by K. Stafford, Connecticut Agricultural Experiment Station*
Preventing Tick Bites for Pets

• Check your pets for ticks daily, especially after they spend time outdoors!
• If you find a tick on your pet, remove it right away
• Reduce tick habitat in your yard
• Consider using tick preventives on your pet, repellent and pesticides products

Take-home Message: Talk with your veterinarian about preventing tick bites on pets
Lyme Disease Vaccine

• It is no longer available.
• Protection provided by this vaccine diminishes over time. Therefore, if you received the Lyme disease vaccine before 2002, you are probably no longer protected against Lyme disease.

Stay tuned!
I have been bitten by a tick....

1. Remove the tick with fine-tipped tweezers.
2. Clean the bite area with rubbing alcohol, an iodine scrub, or soap and water.
3. The chances of getting Lyme disease from a tick bite depend on:
   - The type of tick, **blacklegged ticks**
   - Where the bit happened, mostly Northeastern/Midwest US
   - How long it was attached, for at least **24-36 hours**
When to use Prophylactic Antibiotics

All four criteria should be met:

1. Tick is identified as a blacklegged tick/deer tick, that is estimated to have been attached for $\geq 36 \text{ h}$ on the basis of the degree of engorgement of the tick with blood or of certainty about the time of exposure to the tick

2. Prophylaxis can be started within 72 h of the time that the tick was removed

3. Ecologic information indicates that the local rate of infection of ticks with $B. burgdorferi$ is $\geq 20\%$ (Vermont)

4. Doxycycline treatment is not contraindicated.

Take-home Message: Contact your doctor with questions or concerns
References:

- [https://www.cdc.gov/lyme/index.html](https://www.cdc.gov/lyme/index.html)
- Some slide content courtesy of Dr. Christina Nelson from the CDC
Chronic Lyme Disease

• What do we know we know?
• What do we know that we don’t know?
• What don’t we know that we don’t know?
Antibiotic-Refractory Lyme Arthritis

- Persistent intact *Borrelia*
- Persistent debris of *Borrelia*
- Infection-induced autoimmunity (OspA and LFA-1)
- Genetic predisposition is similar to rheumatoid arthritis (HLA-DR4, GusB deficiency)
- Tissue damage may promote chronic inflammation without *Borrelia*
- Residual effects of previous inflammation
Long-term antibiotics in chronic Lyme arthritis

115 patients randomized to placebo or i.v. ceftriaxone 2 g for 1 mth, then oral doxycycline 200 mg for 2 mth

Value of the Outlier

Mean (Average)

G1

O1

Response of chronic Lyme arthritis to antibiotics
Adaptive Immune Response

- B Cell
- T Cell $\alpha\beta$
- Multiple antigens recognized
- Highly variable receptors
- Low affinity receptors
- Slow response
- Memory

Antigen presenting cell

Innate Immune Response

- Bacterial components
- Viral/bacterial RNA
- DNA
- TLR
- MAVS
- cGAS
- STING
- RIG-I
- NLRP proteins
- Inflamasome
- IFN-I
- IL-1β
- IL-18

- Limited antigens recognized
- Non-variable receptors
- High affinity receptors
- Fast response
- No memory
TLR Ligands
(Pathogen-Associated molecular Patterns, PAMPs)

- dsRNA (virus)
- ssRNA (virus)
- ssRNA (virus)
- CpG DNA (bacteria, virus)
- LPS (bacteria)
- Flagellin (bacteria)
- Triacyl lipopeptides (bacteria)
- Zymosan (fungi)/Triacyl lipopeptides (bacteria)
- Profilin-like molecule (protozoa)

Cytokine production & Co-stimulatory molecules

Borrelia Borrelia Borrelia Borrelia
TLR Ligands
(Pathogen-Associated molecular Patterns, PAMPs)
(Damage-Associated Molecular Patterns, DAMPS)

- LPS (bacteria)
- Flagellin (bacteria)
- Borrelia
- Zymosan (fungi) / Triacyl lipopeptides (bacteria)
- Diacyl lipopeptides (bacteria)
- Borrelia
- Mitochondrial DNA
- Mitochondrial RNA
- ssRNA (virus)
- dsRNA (virus)
- TLR1
- TLR2
- TLR3
- TLR4
- TLR5
- TLR6
- TLR7
- TLR8
- TLR9
- TLR10
- TLR11

Cytokine production & Co-stimulatory molecules

Bacterial DNA

Trauma
Sepsis

Eukaryotic cell
Mitochondrion

Bacterial DNA
Mitochondrial DNA
Formyl peptides
PAMPs

TLR9
FPRL

Acute lung injury

Neutrophil
MAPK
Neutrophil chemotaxis
References


QUESTIONS?