Lyme Disease Update

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Learning Objectives

- Recognize the clinical features of Lyme disease
- Confirm Lyme disease diagnosis by appropriate serologic testing
- Treat acute infection with recommended antimicrobial therapy

Roger: Flu-like symptoms and a rash

- A 54-year-old man complained of several days of fever, chills, headache, photophobia, muscle aches, and joint pains.
- He visited his primary care physician who diagnosed a “viral illness” and recommended symptomatic therapy.
- His symptoms persisted and he noticed a rash on his calf.

Roger: Flu-like symptoms and a rash (cont.)

- He recently returned from visiting his parents along the Maryland shore.
- He was febrile and ill appearing, light sensitive with a mildly stiff neck, and several skin lesions.
Roger: Flu-like symptoms and a rash (cont.)

- *Borrelia burgdorferi* IgM IFA: positive
- *B. burgdorferi* IgG Western Blot: 7 bands (93, 66, 45, 41, 30, 23, 18 kDa)
- Treated with doxycycline for 21 days with complete resolution of all symptoms and signs of disease

### Major Tick-Borne Diseases in the U.S.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Causative Agent</th>
<th>Major Vector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyme disease</td>
<td><em>Borrelia burgdorferi</em></td>
<td><em>Ixodes scapularis,</em> <em>Ixodes pacificus</em></td>
</tr>
<tr>
<td>Ehrlichiosis</td>
<td><em>Ehrlichia chaffeensis</em></td>
<td><em>Amblyomma americanum</em></td>
</tr>
<tr>
<td>Anaplasmosis</td>
<td><em>Anaplasma phagocytophilum</em></td>
<td><em>Ixodes</em></td>
</tr>
<tr>
<td>Rocky Mountain spotted fever</td>
<td><em>Rickettsia rickettsii</em></td>
<td><em>Dermacentor</em></td>
</tr>
<tr>
<td>Babesiosis</td>
<td><em>Babesia microti</em></td>
<td><em>Ixodes</em></td>
</tr>
<tr>
<td>Tickborne relapsing fever</td>
<td><em>Borrelia hermsi</em></td>
<td><em>Ornithodoros</em></td>
</tr>
<tr>
<td>Tularemia</td>
<td><em>Francisella tularensis</em></td>
<td><em>Dermacentor</em></td>
</tr>
</tbody>
</table>

### Fun Facts About Ticks

- 869 species and subspecies of ticks
- 2 major families
  - Ixodidae (hard ticks)
    - Bite is painless
    - Remain firmly attached and feed for several days
    - Feed only once
    - Utilize a great variety of vertebrates that occupy diverse habitats
  - Argasidae (soft ticks)
    - Feed briefly but often
    - Usually feed on a single host species

### More Fun Facts About (Hard) Ticks

- No eyes, sensory organs respond to chemical stimuli, airborne vibrations, and body temperatures associate with warm-blooded animals
- May wander for several hours on the host
- Hypostome: anchors the tick to the host’s skin
- Salivary gland secretions include cement, enzymes, vasodilators, and anesthetic, antihemostatic and antiinflammatory substances
- During first 23-36 hours of attachment: little or no ingestion of blood
- Feed for 2-15 days
- Periods of sucking blood and salivation alternate with frequent regurgitation

### Comparison of *Ixodes scapularis*, *Amblyomma americanum* and *Dermacentor variabilis* by Stage

[Image: Comparison of *Ixodes scapularis*, *Amblyomma americanum* and *Dermacentor variabilis* by Stage]
**Ixodes scapularis** (Blacklegged Tick, Deer Tick)

- L-R: nymph pre-attachment, engorged nymph, adult pre-attachment, engorged adult

**Approximate Distribution of the Blacklegged Tick**

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**Adult Female Ixodes pacificus** (Western Black-legged Tick)

**Approximate Distribution of the Western Blacklegged Tick**

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**Reported Cases of Lyme Disease by Year, United States, 2003-2012**

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**Lyme Disease Testing by Large Commercial Laboratories in the United States, 2008**

- 7 participating laboratories performed ~3.4 million LD tests on ~2.4 million specimens nationwide in 2008
- Estimated frequency of true infection: 12%
- Yielded an estimated 288,000 infected source patients

*Clin Infect Dis. 2014 May 30. pii: ciu397*
Reported Cases of Lyme Disease—United States, 2012

http://www.cdc.gov/lyme/

Reported Lyme Disease Cases by State, 2012

- Connecticut: 2657
- Massachusetts: 5138
- New York: 2998
- New Jersey: 3616
- Pennsylvania: 5033
- Maryland: 1651
- Wisconsin: 1766
- Minnesota: 1515
- Illinois: 204
- Iowa: 165
- Indiana: 74
- Michigan: 98

http://www.cdc.gov/lyme/stats/chartstables/reportedcases_statelocality.html

Global Distribution of Lyme Borreliosis

European Concerted Action on Lyme Borreliosis

Confirmed Lyme Disease Cases by Age and Sex--United States, 2001-2010

CDC

Confirmed Lyme Disease Cases by Month of Disease Onset--United States, 2001-2010

CDC

Lyme Disease-Related Deaths

U.S. National Center for Health Statistics, 1999-2003

96,068 cases of Lyme disease reported to CDC during 1999–2003; coded as an underlying cause of death in 23 cases; only 1 record consistent with Lyme disease

Lyme Disease: Clinical Manifestations

**Early**
- **Erythema migrans (EM)**
  - Develops 3-30 days after a tick bite
- **Early disseminated infection**
  - May occur weeks-months after the tick bite
  - Secondary or multiple EM lesions
  - Central or peripheral nervous system disease (meningitis, cranial neuritis, or peripheral neuropathies)
  - Cardiac abnormalities (varying degrees of AV block, myocarditis)
  - Migratory arthralgias or arthritis

**Late**
- Late or persistent infection may occur weeks-years later
  - Arthritis
  - Neurologic complications

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Clinical Manifestations of Confirmed Lyme Disease Cases--United States, 2001-2010

![Graph showing clinical manifestations of Lyme disease](image)

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Lyme Disease Clinical Diagnosis

- No clinical manifestation except erythema migrans allows diagnosis without laboratory confirmation.

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Choosing Wisely: The American College of Rheumatology’s Top 5 List of Things Physicians and Patients Should Question

- Do not test for Lyme disease as a cause of musculoskeletal symptoms without an exposure history and appropriate examination findings.
  - The musculoskeletal manifestations of Lyme disease include brief attacks of arthralgia or intermittent or persistent episodes of arthritis in 1 or a few large joints at a time, especially the knee.
  - Lyme testing in the absence of these features increases the likelihood of false-positive results and may lead to unnecessary followup and therapy.
  - Diffuse arthralgias, myalgias, or fibromyalgia alone are not criteria for musculoskeletal Lyme disease.

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Lyme Disease Serologic Testing

- Measurable antibody response
  - Requires several weeks to develop
  - Persists after successful treatment
  - Not prevented by noncurative therapy
- IgG rather than IgM Western blots should be used after 1-2 months of illness

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Prospective Study of Serologic Testing for Lyme Disease

<table>
<thead>
<tr>
<th>% positive ELISA</th>
<th>Patients with Lyme Disease + WB (IgM or IgG)</th>
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</thead>
<tbody>
<tr>
<td>EM, localized</td>
<td></td>
</tr>
<tr>
<td>Acute (n = 36)</td>
<td>17</td>
</tr>
<tr>
<td>Convalescent, after antibiotics (n = 36)</td>
<td>53</td>
</tr>
<tr>
<td>EM, disseminated</td>
<td></td>
</tr>
<tr>
<td>Acute (n = 40)</td>
<td>43</td>
</tr>
<tr>
<td>Convalescent, after antibiotics (n = 40)</td>
<td>75</td>
</tr>
<tr>
<td>Disseminated (stage 2)</td>
<td></td>
</tr>
<tr>
<td>Acute neurologic or cardiac disease (n = 13)</td>
<td>100</td>
</tr>
<tr>
<td>Persistent infection (stage 3)</td>
<td></td>
</tr>
<tr>
<td>Arthritis or chronic neurologic disease (n = 13)</td>
<td>100</td>
</tr>
<tr>
<td>Patients with Another Illness</td>
<td></td>
</tr>
<tr>
<td>And previous Lyme disease (n = 14)</td>
<td>79</td>
</tr>
<tr>
<td>Not Lyme disease (n = 75)</td>
<td>0</td>
</tr>
</tbody>
</table>

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*Clin Infect Dis 2008; 47:188–95*
Unvalidated Tests for Lyme Disease

- Urine antigen capture assays
- Culture, immunofluorescence staining, or cell sorting of cell wall-deficient or cystic forms of \textit{B. burgdorferi}
- Lymphocyte transformation tests
- Quantitative CD57 lymphocyte assays

Treatment of Acute Disseminated Lyme Disease

<table>
<thead>
<tr>
<th>Ceftriaxone</th>
<th>Doxycycline</th>
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</thead>
<tbody>
<tr>
<td>2g IV q24 x 14d</td>
<td>100 mg po bd x 21d</td>
</tr>
<tr>
<td>n=68</td>
<td>n=72</td>
</tr>
</tbody>
</table>

Clinical Cure 85% 88%
Persistent Symptoms 27% 14%

Lyme Disease Therapy

- Doxycycline, Amoxicillin, Cefuroxime, Ceftriaxone, Penicillin G
- Azithromycin not so much
- 2 to 4 weeks of oral antibiotics is usually sufficient
- Reserve parenteral antibiotics for severe disease

Lyme Disease Symptoms (ILADS)

- Fatigue
- Low grade fevers, “hot flashes” or chills
- Night sweats
- Sore throat
- Swollen glands
- Stiff neck
- Migrating arthralgias, stiffness and frank arthritis
- Myalgia
- Chest pain and palpitations
- Abdominal pain, nausea
- Diarrhea
- Sleep disturbance
- Poor concentration and memory loss
- Irritability and mood swings
- Depression
- Back pain
- Blurred vision and eye pain
- Jaw pain
- Testicular/pelvic pain
- Tinnitus
- Vertigo
- Cranial nerve disturbance (facial numbness, pain, tingling, palsy or optic neuritis)
- Headaches
- Lightheadedness
- Dizziness

Treatment of Post-Lyme Disease Symptoms

- Randomized, double-blind comparison of antibiotics vs. placebo for seropositive or seronegative plus history of documented EM with persistent symptoms despite usual antibiotic therapy
- Antibiotic regimen: ceftriaxone 2 g IV daily x 30 days then doxycycline 100 mg BID x 60 days
- 107 patients completed 180 days of follow-up
- No significant differences in outcomes (QOL)

Perceived Cognitive Difficulty = Lyme Disease?

- Severe cognitive difficulties reported by about 2% of the US population (2000 cases/100,000)
- Assume
  - Incidence of Lyme disease = 300,000 cases annually
  - Half of all patients with Lyme disease develop severe cognitive difficulty
- Therefore
  - Estimated incidence of Lyme disease-associated severe cognitive difficulty of 150 cases/100,000 population
  - Positive predictive value 8%
- Would never justify treatment in the absence of more specific evidence
Non-antimicrobial Activity of Antibiotics

- Tetracyclines
  - Broad range of anti-inflammatory activities
  - Inhibit matrix metalloproteinases, alter neurophysiological activity, modulate neuronal transmission (including pain perception)
- Ceftriaxone
  - Up regulates glutamate transporter in CNS: decreased glutamate → decreased pain

Julie: Pain and neck swelling

- 35 yo woman presents with 9 months of migratory pain and swelling in her neck, shoulders, elbows and hands; episodic lancinating pain in her extremities; and severe fatigue
- She has seen her primary care physician, a neurologist, rheumatologist, acupuncturist, chiropractor, and massage therapist without relief

Julie: Pain and neck swelling (cont)

- June 7 - Travel to New Hampshire; Hartford, CT; Cape Cod, MA
  - Lots of outdoor activities
- June 27 - Acute onset fever, chills
- June 29 - Azithromycin x 5 days
- July 5 - Bell's palsy
  - Treated with prednisone x 1 week
- July 30 - Conjunctivitis symptoms
- August 4 - Jaw and ear pain
  - Treated with antihistamines
- August 6 - Double vision, CN VI palsy
  - Brain MRI negative
  - WBC 11.6
  - CRP 4.1; ESR 0
  - ANA, pANCA, cANCA - negative
  - Lyme serology - 2 IgG bands (23, 41 kD); 1 IgM band (23 kD)
  - Treated with Prednisone x 3 months

Julie: Pain and neck swelling (cont)

- September - present
  - Migrating joint pain and stiffness
    - jaw, neck, spine, shoulder, finger, both elbows (can't straighten elbow)
  - Palpitations, racing HR
  - Severe fatigue

Rheumatoid factor negative
- ESR 2, CRP 0
- Parvovirus B19 IgG positive, IgM negative
- *Borrelia burgdorferi* IgG immunoblot 18, 28, 30, 39, 41, 45, 58, 66, 93; IgM immunoblot 23, 41
- Diagnosis: Lyme borreliosis
- Treated with doxycycline x 4 weeks
Julie: Pain and neck swelling (cont)

• Reported that she was 95% back to baseline within 4 weeks of treatment

• There really is Lyme Disease out there
• Treatment with azithromycin and prednisone may have delayed her seroconversion and exacerbated her illness

Lyme Disease
Prevention

• Avoid tick bites
  – Apply DEET repellent to exposed skin
  – Wear long pants, tuck pants into socks, apply repellents containing permethrin to clothing
  – Walk on cleared trails away from brushy vegetation

• Check for ticks and promptly remove them
  – *B. burgdorferi* transmission unlikely if the tick is removed within 36 hours of attachment

Delayed Transmission of Borreliosis Following Tick Attachment

• Transmission of Lyme borrelia occurs through injection of tick saliva during feeding
• Lyme borrelia carried in the midgut of unfed *Ixodes* ticks
• When an infected tick takes a blood meal
  – Ingested spirochetes increase in number and undergo phenotypic changes, including expression of OspC, which allows them to travel to the host tick’s salivary glands
• Process takes several days and explains transmission delay

Testing of Individual Ticks?

• If the test shows that the tick contained disease-causing organisms
  – Doesn’t necessarily mean that you’ve been infected

• If you have been infected, you will probably develop symptoms before results of the tick test are available

• Negative results can lead to false assurance
  – You may have been unknowingly bitten by a different tick that was infected

Prevention of Lyme Disease After an *Ixodes scapularis* Tick Bite with Doxycycline

• Randomized, double blind, placebo-controlled trial of single dose doxycycline 200 mg in 482 subjects who had removed attached *I. scapularis* ticks within the previous 72 hours
• Erythema migrans
  – Doxycycline 1/235 (0.4%)
  – Placebo 8/247 (3.2%) P<0.04
• Adverse reactions (primarily nausea and vomiting)
  – Doxycycline 30.1%
  – Placebo 11.1% P<0.001
• No asymptomatic seroconversions

Lyme Disease Vaccine

• Licensed by the FDA 1998
  – 3 doses (0, 1 and 12 months)
  – 76% efficacy
  – No excess adverse events through VAERS
  – Unconfirmed adverse events in media and via internet, class action law suit filed
  – Manufacturer discontinued distribution 2002

N Engl J Med 2001;345:79-84
Why Are Tickborne Diseases Emerging?

- Increase in the zoonotic reservoir
  - 1900: 350,000 deer in the U.S.
  - Today: 30 million
- Growth in the susceptible human population
  - Movement into rural areas
  - Aging population
- Improved diagnostics and surveillance

Lyme Disease Update

Summary

- Incidence probably 10x the number of reported cases
- Still very localized
- Treat (don’t test) EM
- Disseminated or late disease should be seropositive
- Post-Lyme disease syndrome – over diagnosed and not antibiotic responsive