LYME DISEASE

THE DISEASE IN YOUR BACKYARD

Kevin I. Young, MD
Free copy of full slide presentation available on request at kevin@plymouthfamilypractice.com
LYME DISEASE
INSTRUCTIONS TO PATIENTS

Rules:

1. Don’t get it in the first place.
2. If you do get it, treat it early!
3. Know the “red flags” for the disease.
4. If you don’t treat it early, study both national guidelines about diagnosis and treatment. (They don’t agree.)
5. Never trust the lab test (completely).
6. If there is any possibility of Lyme disease, never take a steroid (or immunosuppressant).
LYME DISEASE
TAKE HOME INFORMATION

1. Avoidance and prophylaxis
2. Erythema migrans
3. Secondary disease
   - Lyme arthritis
   - Bells palsy
4. Post Lyme syndrome / Chronic Neurologic Lyme disease
5. Lyme serology
   - ELISA
   - Western blot
6. Treatment protocols
HIGH RISK BEHAVIOR:
BRUSHING AGAINST LEAVES

• Definition of endemic exposure to Lyme disease is any behavior that results in brushing against leafy vegetation in a region of moderate or high tick infection rate.
PROBLEM WITH TICK BITE
PROPHYLAXIS

Tick bite

Only 14-32% of patients with Lyme disease recall a tick bite.

Other methods of transmission:
- Vertical transmission from mother to fetus
- Lactation
- Blood transfusion
- Sexual transmission

1. Nadelman RB; Wormser GP. Erythema migrans and early Lyme disease. American Journal of Medicine, 98(4A):15S-23S.
NEW HAMPSHIRE TICKS

**American dog tick** (Dermacentor viropli), carries Rickettsia and tularemia.

**Deer tick** (Ixodes scapularis), the species of black legged tick native to NH, carry Lyme, Borrelia, Bartonella (cat scratch fever), Babesia (North American “malaria”), Ehrlichia, Mycoplasma fermentans, Mycoplasma pneumoniae.

**Lone star tick** (Amblyomma americanum), is known to transmit ehrlichiosis, tularemia, and southern tick-associated rash illness.
DEER TICK
BLACK LEGGED TICK
IXODES SCAPULARIS

Black is bad — black scutum, black legs

Scutum = hard shield
TICK IDENTIFICATION
SIZE VS. APPEARANCE

Dog tick  Deertick  Lone Startick

(All pictures are of adult ticks.)
TICK SIZE
varies by stage

DEER TICK
BLACK LEGGED TICK
TICK SIZE

IXODES SCAPULARIS
(MALE AND FEMALE)

Deer tick, adult —
Female and male
(July-November)

Dog tick, adult

Dear tick nymph —
Female and male
(March – June)
DEER TICK VECTOR

- **Nymphs transmit 85% of cases.**
  - Nymphs are active in late spring through the summer.
- **Adult deer ticks are most common tick bite in the fall.**

- More than 50% of the ticks from Lee and Durham and more than 70% from the Concord sample infected with Lyme causing bacteria. Alan Eaton, UNH, 2008.

- **Tick exposure rates increase with wet weather,** drop off significantly with dry weather.
  - Ticks hide in fissures in bark during dry weather to avoid dying of dehydration
- **Ticks remain active until the temperature is <28 degrees.**
TAKE HOME MESSAGES:

DON’T FEED THE TICKS!

• New Hampshire has the 2\textsuperscript{nd} highest incidence of Lyme disease per capita in the US (2012).

INCIDENCE OF LYME DISEASE    (NEW HAMPSHIRE)
DEET

- DEET = N,N-diethyl-meta-toluamide
- Most common insect repellent since 1946
- Advantage: effective
  - (Emerging resistance—in mosquito, through genetic mutation of insect receptor, Ir40a receptor in antennae)
- Disadvantages
  - Smell
  - Need to reapply every 30 min (5% soln) to 5 hrs (50% soln)
  - Dissolves synthetic fabrics, types of plastic, painted surfaces
  - Weak anti-cholinesterase inhibitor
    - Extremely rare incidence of seizures in children up to age 6
PERMETHRIN

- Sprayed on clothing. Non-toxic when dry.
- 1 application lasts up to 6 washings when self applied, 75 washings when commercially applied
- Odorless after application.
- 3 oz is proper amount for shirt-pants-socks.
- Perspiration and exposure to water does not decrease efficacy.
- Available at Walmart (seasonally), EMS, Cabelas, etc.
TAKE HOME MESSAGES:
AVOIDANCE

• High risk behavior = any behavior that leads to brushing against leafy vegetation in endemic area
• New Hampshire has the 2nd highest incidence of Lyme disease per capita in the US (2012).
• 50-70% of deer ticks tested in Concord are infected.
• Dog ticks do not transmit infection to humans.
• Deer tick (black legged tick)s, black shield on upper back, small size
  • Nymph = March-July = “poppy seed size” = highest risk of transmitting infection
  • Adult = most common tick on humans in October, bigger, easier to see and remove
• Prevent with DEET (on skin) or permethrin (on clothes).
TICK BITE PROPHYLAXIS

• Indications for prophylaxis:
  • Deer tick bite in endemic area
  • Attachment greater than 36 hours ()
  • Starting antibiotic with 72 hours of finding tick.
• No one with a dog tick bite needs antibiotic prophylaxis for Lyme disease.

Meta-analysis of 4 placebo-controlled clinical trials, 1082 subjects
Placebo risk of Lyme disease 2.2%, compared with 0.2% in antibiotic treated group (p=0.0037)
3 of the 4 studies involved 10 day course of antibiotics (PCN, amox, amox+TCN),
4th study used doxycycline 200 mg dose, study ended at 6 wks, outcome measure EM
1 case of Lyme prevented for every 50 people treated (depending on case definition).

TRANSMISSION RATE

- 14-32% of people with Lyme disease remember a tick bite.
- Transmission usually occurs at the end of the 48 hour meal.

<table>
<thead>
<tr>
<th>Attachment</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hr</td>
<td>5%</td>
</tr>
<tr>
<td>48 hr</td>
<td>38%</td>
</tr>
<tr>
<td>72 hr</td>
<td>92%</td>
</tr>
</tbody>
</table>

Nadelman RB, Wormser GP. Recognition and treatment of erythema migrans: are we off target?
**Borrelia burgdorferi**

- Spirochete, designed to travel
- Easily passes through membranes
- Lives in both intracellular and extracellular environments
- Flagella is built into the spirochete shape
- Prokaryotic
- Has up to 23 plasmids
  - Some plasmids required for virulence
- Has hyper-variable DNA regions that codes for isomers of immunogenic surface proteins
- Can eliminate surface proteins (L-form or cyst form)
- Lives in biofilms
- Uses manganese rather than iron
L-FORM

- **L-form lacks immunogenic surface proteins**
- **Advantage:**
  - Minimal antigenic stimulation
  - Resistant to many cell wall antibiotics.
- **Disadvantage:**
  - Loses its motility
  - Strictly intracellular
CYST FORM

- If the bacteria is stressed by cytokines, high oxygen levels, antibiotics, etc., it will **package its DNA** in a small “cyst”.
- Cysts show **minimal metabolic activity**.
- The cyst form has very **few immunogenic surface proteins**.
- After a period of up to 3 weeks, each cyst can transform itself back into a complete spirochete.
BLEB

- Purpose of bleb: unknown
- Speculation: source of “auto-immunity”?  

**Bleb form**

1. The Lyme bacteria makes thousands or short strips of DNA, packages them, and extrudes them as a “bleb” through exocytosis.
2. This DNA enters human cells, and is copied into the human DNA through reverse DNA transcriptase.

**Speculation:**
- The human cell then makes proteins from this bacterial DNA.
- Then the protein is expressed on the surface of the cell, the immune system will attack the human cell.
- The immune system cannot tell “friend from foe” because both contain foreign bacterial surface proteins.
REASONS FOR PERSISTENT INFECTION

• Borrelia does not develop antibiotic resistance.
• Borrelia does evade the immune system:
  • Hides in intracellular environment as L-form
  • Changes into cyst form
  • Develops reservoirs in less vascular tissues
    • Tendons (collagen = growth factor); bone
  • Develops isomers of surface membrane proteins
  • Lives in biofilms
• Borrelia attacks the immune system:
  • Surface proteins are 500X more antigenic than E. coli and other usual bacteria
  • Result: overstimulation of Th1 system ("cytokine storm"), under-stimulation of Th2 system (minimal antibody response)
LYME DISEASE
STAGES

Primary disease
Skin “Flu like” illness

Secondary disease
Joints
Nerves
Meninges
Heart muscle

Tertiary disease or post infection
Chronic CNS and/or immune problems

Erythema migrans
Arthritis
Bell’s palsy, radiculitis
Meningitis
Carditis
Erythema migrans
Lymphocytoma

Chronic neurologic Lyme disease / Post-Lyme syndrome
PRIMARY DISEASE
IDENTIFYING ERYTHEMA MIGRANS

• Clinical characteristics:
  • Red rash
  • Gradually expanding day to day
    • Central clearing—or not.
    • Flat—or slightly raised.
  • Slightly warmer than surrounding skin.
  • Usually no discomfort—or very occasionally mild stinging or itch
  • Starts 4-27 days after the bite
  • Disappears, even without treatment, after 3-12 days
  • Sometimes associated with flu-like symptoms (body aches, fatigue, headache)
ERYTHEMA MIGRANS – NOT THAT SIMPLE

- Homogeneous red skin 59%
- Darker center 32%
- Central bump present 31%
- Central clearing bullseye 9%
- Blister or ulcer 7%
ERYTHEMA MIGRANS
OTHER RASHES
NOT LYME DISEASE

• **RING WORM**
  • Raised, sometimes warm

• **SPIDER BITE**
  • Painful, sometimes necrotic center
PRIMARY DISEASE

**Erythema migrans** (identified in 30-70% of Lyme cases)

**Flu-like illness** (incidence: “sometimes”):
- **Symptoms:** fever, chills, malaise, headache, stiff neck, arthralgias and myalgias
- **Exam:** lymphadenopathy +/- splenomegally

- 45% of patients with erythema migrans had bacteremia (positive blood PCR for *Borrelia burgdorferi*) at time of diagnosis.
SEROLOGY

- **DO NOT** get labs to decide whether a rash is erythema migrans!
  - Immunoglobulins measured by an ELISA or Western blot do to appear in the serum for 3-12 weeks after exposure.
  - Erythema migrans is a clinical diagnosis!
2ND STAGE OF DISEASE

- Lyme arthritis
- Bell’s palsy, radiculitis
- Meningitis
- Carditis
- Lymphocytoma
- Erythema migrans
LYME ARTHRITIS
MIGRATORY PAUCIARTICULAR ARTHRALLGIAS

• Most common presentation of Lyme disease after erythema migrans.

• Initially arthralgia, later arthritis

• Usually pauciarticular
  • Joints affected:
    • Knees most common
    • Other common areas: ankles, low back, neck, shoulders, elbows, wrists
    • Uncommon: fingers.
    • Least common: hips

• Migratory.
• Off-and-on pain and swelling.
• Gradually progressive
  • Later episodes more prolonged and severe.
• Frequently triggered by minor injury
• First attack usually 3 months after initial bite (range 1-6 months)
FINDINGS (LYME ARTHRITIS)

- **Joint exam:**
  - Normal (common)
  - Red, warm
  - **Effusion without periarticular swelling**

- **Blood tests:**
  - Blood count (CBC) normal
  - ESR normal; normal sensitivity CRP normal or moderately elevated
  - RF negative, ANA normal or moderately positive

- **Joint aspirate tests:**
  - White blood count moderately elevated
  - Culture for bacteria negative, including Borelia culture
  - DNA polymerase positive 50-80% of the time
  - No reason to get a Western blot on joint aspirate

- **Xray:**
  - Usually normal (unless secondary degenerative changes)
Bell’s Palsy

- Sudden weakness or paralysis of one side of the face, due to infection of the 7th cranial nerve.

Bell’s (idiopathic) 38%
Lyme 4% (Beth Israel)
25% (Suffolk Co. NY)
Varicella zoster
Cancer
Surgery, injury


ALWAYS EVENTS
(OPPOSITE OF NEVER EVENTS)

• THINK OF LYME DISEASE:

  **Erythema migrans**
  • Red area enlarges every day, then disappears on its own
  • Not painful, occasionally slightly itchy
  • Do NOT use serology for diagnosis.

  **Arthalgias**
  • Primary care presentation: migratory pauciarticular arthralgias, gradually progressive
  • ER, ortho presentation: joint pain and inflammation that is more persistent or more intense than expected after an injury

  **Bell’s palsy**
CHRONIC LYME DISEASE - POST LYME SYNDROME

2 NATIONAL GUIDELINES

CLINICAL SYNDROME
LYME DISEASE
STAGES

Primary disease

- Skin rash
- "Flu like" illness

Secondary disease

- Joints
- Nerves
- Meninges
- Cardiac muscle

Tertiary disease

- Chronic neurologic Lyme disease (neuroborreliosis)
- Chronic brain and immune problems

Chronic neurologic Lyme disease (neuroborreliosis)

Erythema migrans

Lyme arthritis
- Bell’s palsy, radiculitis
- Meningitis
- Carditis
- Lymphocytoma
- Erythema migrans

Autoimmune disease

Post-Lyme syndrome
## IDSA VS ILADS
### CONTROVERSIES

<table>
<thead>
<tr>
<th>Definitions</th>
<th>IDSA</th>
<th>Both</th>
<th>ILADS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Persistent</td>
<td>Recurrent</td>
<td>Chronic = persistent (&gt;30 days) despite appropriate antibiotics</td>
</tr>
<tr>
<td></td>
<td>Recurrent</td>
<td>Refractory</td>
<td>(Older literature = symptoms duration&gt;1 yr, treated or untreated)</td>
</tr>
<tr>
<td>Diagnoses</td>
<td>Erythema migrans</td>
<td></td>
<td>Chronic neurologic Lyme disease</td>
</tr>
<tr>
<td></td>
<td>Lyme arthritis</td>
<td></td>
<td>(accounts for 18-29% of Lyme diagnosed by ILADS criteria?)</td>
</tr>
<tr>
<td></td>
<td>Bell’s palsy, radiculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meningitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphocytoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Acrodermatitis chronica atrophicans)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical model</td>
<td>Autoimmune disease</td>
<td></td>
<td>Active infection</td>
</tr>
<tr>
<td></td>
<td>(Neurologic sequellae)</td>
<td></td>
<td>(cytokine model)</td>
</tr>
<tr>
<td>Serology</td>
<td>ELISA, then Western blot:</td>
<td></td>
<td>Western blot, including bands 31 and 34, “high risk band” criteria</td>
</tr>
<tr>
<td></td>
<td>CDC surveillance criteria</td>
<td></td>
<td>(ILADS: Sensitivity 85%)</td>
</tr>
<tr>
<td></td>
<td>(IDSA: Specificity 99%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Antibiotics: maximum 6 weeks</td>
<td></td>
<td>Antibiotics: single or in combination until symptoms to “baseline intensity” for 2 months</td>
</tr>
</tbody>
</table>
POST LYME SYNDROME
(IDSA CRITERIA – LEVEL III EVIDENCE)

• 2000 IDSA guidelines:
  • **Autoimmune** problem that persists after active infection
  • **Rare**
    • “Late neurologic lyme disease is a very rare event. Collectively, only one patient over the past five years was diagnosed by panel members.” IDSA guidelines (2000)
  • Rx: **wait it out**
    • “The good news is that patients with Post Treatment Lyme Disease Syndrome almost always get better with time; the bad news is that it can take months to feel completely well.” IDSA guidelines (2000)
POST LYME SYNDROME
(IDSA CRITERIA – LEVEL III EVIDENCE)

- 2006 IDSA guidelines
  - The syndrome probably exists, but has no clearly defined diagnostic criteria.
  - Treatment:
    - No comment, except avoid antibiotics
  - Concentrate on diagnostic issues:
    - Lyme re-exposure (rate ~18%)
    - Misdiagnosis
      - Psychiatric illness (depression, anxiety, bipolar, conversion disorder)
      - Inflammatory arthritis
      - Fibromyalgia, chronic fatigue syndrome
ILADS SUMMARY:
CHRONIC NEUROLOGIC LYME DISEASE
PREDICTIVE MODEL

CLINICAL PRESENTATION

- **History of endemic exposure**
- **Symptom clusters:**
  - Non-restorative fatigue
  - Rheumatoid symptoms
  - Allodynia (hyperalgesia)
  - Cognitive/neurologic deficits
  - Emotional dysregulation
- **Positive serology**
  - Western blot positive for 1-2 high risk bands and/or positive PCR and/or positive urine dot blot
- **Clinical progression** consistent with Lyme disease
- Review of exhaustive differential diagnosis

TREATMENT RESPONSE

- **Flare in original symptoms** (Herxheimer reaction), usually within 4-27 days of initiation
- **Pattern of flare and remission** (classically 1 week on, 3 weeks off) developing by the 4th month
- **Symptom intensity decreasing monthly, but persisting for 4-15+ months.**
NON-RESTORATIVE FATIGUE
“NEVER FULLY AWAKE, NEVER FULLY ASLEEP.”

• **Non-restorative fatigue** (level II evidence)—
  • Moderately or severely disabling, significant duration
  • Non-restorative:
    • Not improved with sleep, despite adequate sleep time and absence of other sleep disorders (i.e., sleep apnea).
    • Consistently aggravated by exercise, severe intensity, duration hours to 2 days following activities.

• **Hypersomnia/insomnia** (level II evidence)—
  • Best measure is total hours of sleep per 24, showing major change from prior baseline.
  • Sleep study: abnormal, nonspecific, frequent arousals without hypopnea, major decrease in stage 3 sleep; variable sleep latency; abnormal onset of REM (confounded by high rate of antidepressant usage)

RHEUMATOID SYMPTOMS

Rheumatoid symptoms—

• Classically migratory polyarthritis, gradually progressive over time.
• Knees most common, also ankles, back, neck, shoulders, elbows, wrists
• Unusual in hips, less common in small joints
ALLODYNA (HYPERALGESIA)

- **Fibromyalgia symptoms**, but both axial and extremity muscle tenderness, more diffuse and (sometimes) less intense than classic trigger points

- “**Flu-like**” **body aches**

- **Headache syndromes**, **standard presentations**

- **Sensory issues** (**photophobia, phonophobia, hyperesthesias**, etc., with irritability)

COGNITIVE/NEUROLOGIC

- **Cognitive** symptoms are widely variable, but characteristic is on-off pattern
  - “Brain fog”
  - Delirium
  - **Word search**, reading comprehension problems, dyscalculia
  - **Very slow processing speeds**, can’t keep up, hyper-focalization
  - Memory problems frequently present but more minor
  - **Executive function** skills frequently prominent
    - Concentration, attention; inability to transfer attention, multitask
    - Organization, planning: major increase in non-purposeful behaviors (“I work and I don’t get anything done.”)

- **Neurologic** — **sensory**, CNS; **motor rarely** (unless long tract or radicular)

- **Radiculitis**—CN and spinal, non-vasculitic mononeuritis multiplex; electrophysiologic testing = sensorimotor axon loss


EMOTIONAL DYSREGULATION

- “Migratory” mood symptoms
  - Anxiety, usually intense and disabling (avoidance behaviors)
  - Irritability
  - Depression
  - Happy
- Disabling intensity, labile with on-off pattern
- Different from prior baseline, transition sometimes abrupt

Logigian EL, Kaplan RF, Steere AC. Chronic neurologic manifestations of Lyme disease. NEMJ, 223(21):1438-44, 1990
CHRONIC LYME INCIDENCE (ILADS)

- Chronic neurologic Lyme disease occurs in 18-29% of patients with Lyme disease.
- Risk of disease is predicted by:
  - Autoimmune markers (HLA b27, HLA Dr4);
  - Delay of more than 2 months between onset of symptoms and start of initial antibiotic;
  - Use of steroids between onset of symptoms and start of initial antibiotic.
THE LONG-TERM CLINICAL OUTCOMES OF LYME DISEASE. A POPULATION-BASED RETROSPECTIVE COHORT STUDY.

SHADICK NA; PHILLIPS CB; LOGIGIAN EL; STEERE AC; KAPLAN RF; BERARDI VP; DURAY PH; LARSON MG; WRIGHT EA; GINSBURG KS; KATZ JN; LIANG MH. DEPARTMENT OF RHEUMATOLOGY-IMMUNOLOGY, BRIGHAM & WOMEN'S HOSPITAL, BOSTON, MA 02115.[ANN INTERN MED] 1994 OCT 15; VOL. 121 (8), PP. 560-7.

- Setting: coastal region endemic for Lyme
- Data collected mean of 6.2 years from disease onset
- 34% of study group had arthritis/recurrent arthralgias, cognitive impairment, or neuropathy/myelopathy.
- Patients with long-term sequelae received treatment later (p < 0.0001).

<table>
<thead>
<tr>
<th></th>
<th>Lyme</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>43</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Arthralgias</td>
<td>61%</td>
<td>16%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sleep difficulty</td>
<td>47%</td>
<td>16%</td>
<td>0.003</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26%</td>
<td>4%</td>
<td>0.04</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>18%</td>
<td>5%</td>
<td>0.05</td>
</tr>
<tr>
<td>Concentration problems</td>
<td>16%</td>
<td>2%</td>
<td>0.03</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>16%</td>
<td>2%</td>
<td>0.03</td>
</tr>
<tr>
<td>Persistent depression</td>
<td>8%</td>
<td>5%</td>
<td>NS</td>
</tr>
</tbody>
</table>
NIH trials validate the severity of the symptoms of chronic Lyme disease  
Fallon NIH trial, Neurology 2008

“Pain was similar to those of post-surgery patients”
“Fatigue was similar to that of patients with multiple sclerosis.”
“Limitations in physical functioning were comparable with those of patients with congestive heart failure.”
COST OF CLD-POST LYME SYNDROME

The cost of CLD calculated by investigators from: CDC, University of Maryland, Eason Health Plan (Maryland)

• $1,310 – Average annual cost for early LD
• $16,199 - Average annual cost for chronic Lyme disease
  • 88% of cost of CLD – indirect, non-medical and productivity losses

Zhang et al. Economic cost of Lyme disease. 2006 Emerg Infec Dis
LYME SEROLOGY
“The most dangerous test result in microbiology is a false negative.”

TRUE OR FALSE?

Answer?:

It depends (on how much the clinician bases his diagnosis upon the test result—and the risk of untreated infection).

6 of the 7 clinical syndromes mentioned in both the IDSA and ILADS guidelines are highly dependent on lyme serology results.
SEROLOGIC TESTING

**IDSA**

- **Two tiered testing:**
  - Lyme ELISA,
  - If ELISA positive, then Lyme Western Blot

- **Interpretation criteria:** use CDC surveillance
  - IgM: check
    - Check 3 bands
    - 2 = positive
    - within 30 d of symptom onset
  - IgG:
    - Check 10 bands
    - 5 = positive

**ILADS**

- **Western blot only**

- **Interpretation criteria:** use CDC surveillance criteria or Modified IGeneX criteria:
  - IgM or IgG
    - Check 6 “high-specificity” bands
    - 1 = possible
    - 2 = positive
Approximately 500 participants
Each participant analyzed 50 samples over a 3 year period
- 28 positive according to CDC case definition
- 22 no evidence of lyme
Specificity: 81%
- Sample appropriate? (Pretest probability affects specificity.)
  - 1 sample Treponema pallidum positive reported positive by 70% of participants
Sensitivity 75-93%
- depending upon the conjugate used by the laboratory
EVIDENCE:

ELISA sensitivity: 62.8% IgM, 47.3% IgG
combined specificity 81-94%, sensitivity 70-93% depending on reagents and lab quality

IDSA: negative Elisa = “You do not have Lyme disease.”

ILADS: (does not recommend Elisa testing)
Studies conducted by the group responsible for Lyme Disease proficiency testing for the College of American Pathologists (CAP) concluded that the currently available ELISA assays for Lyme Disease do not have adequate sensitivity to be part of the two-tiered approach of the CDC/ASHLD, whereby only ELISA-positive samples can be tested by Western blotting.

Inter-laboratory comparison of test results of detecting Lyme disease by 516 participants in the Wisconsin State Laboratory of Hygiene College of American Pathologists proficiency testing Program. J Clin Microbiol. 1997 537-543.
WESTERN BLOT (FDA-approved kits)

**CDC IgM (2 = pos)**
- 23-25 kDa (Osp C)
- 39 kDa
- 41 kDa (Flagella)

**CDC IgG (5 = pos)**
- 18 kDa
- 23-25 kDa (Osp C)
- 28 kDa
- 30 kDa
- 39 kDa
- 41 kDa (Flagella)
- 45 kDa
- 58 kDa
- 66 kDa
- 83-93 kDa

**Interpretation criteria:**
- IgM: 2 positive out of 3 bands,
- IgG: 5 positive out of 10 bands
WESTERN BLOT (ILADS)

IGeneX IgM or IgG
(2 = pos)

• 23-25 kDa (Osp C)
• 31 kDa (Osp A)
• 34 kDa (Osp B)
• 39 kDa
• 41 kDa (Flagella)
• 83 - 93 kDa

ILADS:

• Use only 5 “high specificity bands” + band 41
• IgM: 2 out of 6 = positive
• IgG: 2 out of 6 = positive
• Include bands 31 and 34
QUALITY vs QUANTITY

Bar graph of probability of Lyme bands in Lyme patients and control population

Vol. 30, 1992

FIG. 3. Comparison of the frequency of antibody reactivity to various B. burgdorferi protein bands between 186 patients with Lyme borreliosis and 320 normal controls.

<table>
<thead>
<tr>
<th>kDa</th>
<th>Lyme +</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>87%</td>
<td>43%</td>
</tr>
<tr>
<td>39</td>
<td>83%</td>
<td>1.3%</td>
</tr>
<tr>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SERODIAGNOSIS OF LYME BORRELIOSIS 373
Western Blot Pattern: Special Role of Osp A (31 kDa) in Chronic Disease

Bands 31 and 34 were excluded from FDA approved Western blot kits since the Lymerix vaccination turned these bands positive.

Specificity:
- Band 31 98%
- Band 34 98%

Sensitivity:
- Band 31 13%
- Band 34 15%

Sensitivity: Band 31 shows a higher incidence in patients with chronic neurologic symptoms:
- IGeneX study on sera from 30 well defined late Lyme patients:
  - Sera from 29 of the 30 reacted with 30-31 kDa antigens.
  - All 10 negative samples were negative.
## Lyme Western Blot Assay (n=165)

<table>
<thead>
<tr>
<th>Western Blots</th>
<th>CDC criteria</th>
<th>IGeneX criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>100%</td>
<td>96%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>38%</td>
<td>63.3%</td>
</tr>
<tr>
<td>5/10 bands (18, 23-25, 28, 30, 39, 41, 45, 66 and 83-93 kDA)</td>
<td>2/6 bands (23-25, 31, 34, 39, 41 and 83-93 kDA)</td>
<td></td>
</tr>
<tr>
<td><strong>IgM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>99%</td>
<td>96%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>58.3%</td>
<td>73.3%</td>
</tr>
<tr>
<td>2/3 bands (23-25, 39 and 41 kDA)</td>
<td>2/6 bands (23-25, 31, 34, 39, 41 and 83-93 kDA)</td>
<td></td>
</tr>
<tr>
<td><strong>IgG+ IgM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity*</td>
<td>99%</td>
<td>96%</td>
</tr>
<tr>
<td>Sensitivity*</td>
<td>70%</td>
<td>85%</td>
</tr>
</tbody>
</table>

### Serum Sample Types
- 37 Lyme positive patients (CDC LD Panel)
- 23 Lyme positive patients confirmed by PCR
- 60 Tick-borne disease negative patients
- 45 Lyme negative, other tick-borne disease positive patients

* Actual sensitivity and specificity results will vary (slightly?) based upon Borrelia strain and sample characteristics (i.e., pretest probability of disease within study sample)
CLINICAL JUDGMENT: WHICH IS BETTER?

A 99% specificity and 70% sensitivity (IDSA) or
A 96% specificity and 85% sensitivity (ILADS)

Different bias
- IDSA: minimize risk of unnecessary antibiotics (based on false positives)
- ILADS: minimize risk of untreated infection (based on false negatives)

Additional issue: Higher pickup of post Lyme syndrome / chronic Lyme disease with bands 31 and 34?
TREATMENT — ERYTHEMA MIGRANS

- Primary disease: Erythema migrans
  - Duration of antibiotic: 3 weeks
  - Antibiotic choices:
    - Doxycycline 100 mg 2x/day
    - Amoxicillin 500 mg 3x/day
    - Cefuroxime axetil 500 mg 2x/day
    - NOT macrolides

Drug of choice: **DOXYCLINE**
- NOT in children under age 8, pregnant or lactating women
- Treats coinfection: Anaplasma phagocytophilum
- Best CNS penetration
- Photosensitivity!

Cellulitis vs EM — amoxicillin-clavulinate
TREATMENT – SECONDARY DISEASE

- Secondary disease
  - Treatment duration: 4 weeks
  - Facial palsy: Doxycycline 100 bid
  - Meningitis: Ceftriaxone 2g/d
  - Arthritis: Doxycycline 100 bid or Amoxicillin 500 tid
TREATMENT – TERTIARY DISEASE

- Tertiary disease
  - IDSA: symptom treatment only
  - ILADS: 4 treatment options
    - Tetracyclines
    - Clarithromycin + hydroxychloroquin
    - Beta lactams (amoxicillin or cefuroxime axetil)
    - Miscellaneous (usually as “add-ons”)
- Duration: until symptom level to patient baseline x 2 months
THANK YOU

kevin@plymouthfamilypractice.com