Controversies in Lyme Disease Diagnosis & Treatment

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San Francisco, CA
Lyme Disease
State of the Art

"We also know that there are known unknowns; that is to say, we know that there are some things we do not know. But there are also unknown unknowns - the ones that we don't know we don't know."

-Donald Rumsfeld
Lyme Disease: “Hard to Catch, Easy to Cure”

• Lyme disease is rare and occurs in limited locations.
• Lyme disease is easy to diagnose.
• Testing for Lyme disease is very reliable.
• Treatment of Lyme disease rarely fails.
• Chronic Lyme disease does not exist.
Epidemiology of Lyme Disease
From left to right: Larvae, Nymph, Female, Male Tick
Tick in Nymph stage is the size of a poppy seed.
US Distribution of Tick Vectors for Lyme Disease

Tonks, A. BMJ 2007;335:910-912
Figure 2: The geographical distribution of Ixodes spp, with the western distribution for Iricinus and the eastern distribution for I persulcatus

The distribution for these two vectors overlaps in the green area. The dotted line defines the border for the tick-borne encephalitis endemic area. Note that the disease is very focally distributed within its endemic zone. Ixodes distribution in China is uncertain.
Mouse

Shrew
## Reservoir Competence & Potential of Animal Hosts for *Borrelia burgdorferi*

<table>
<thead>
<tr>
<th>Species</th>
<th>Reservoir Competence (%)</th>
<th>Reservoir Potential (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>&gt;85</td>
<td>25</td>
</tr>
<tr>
<td>Shrews</td>
<td>42-57</td>
<td>55</td>
</tr>
<tr>
<td>Chipmunks</td>
<td>55</td>
<td>11</td>
</tr>
<tr>
<td>Other*</td>
<td>1-19</td>
<td>9</td>
</tr>
</tbody>
</table>

* *Squirrels, birds, skunks, deer, opossums, raccoons*

Deer Population in the United States

1900: 500,000

2000: 35-40 Million
Figure 1 The redwing thrush (*Turdus iliacus*), a common migratory bird that is often infested with ticks, can carry Lyme disease as a latent infection for several months. These infections can be subsequently reactivated by migratory restlessness and spread great distances during the bird’s migratory travels.
TOTAL LYME CASES REPORTED BY CDC 1990–2006


Note: CDC says Lyme disease is underreported and that only about 10% of cases that meet CDC surveillance criteria are actually reported to CDC. (For example, Oklahoma’s 362 reported cases = 3,620 probable cases meeting CDC criteria.)

Source: Data compiled from CDC pub data (MMWR) ©2007 Lyme Disease Association, Inc.
Dog vs. Human Cases: 2000-2006
Dog Lyme cases from one test lab*
Human Lyme cases reported to CDC

Are we undercounting human cases?

Bernese Mountain Dogs

Figure 1
Map of Switzerland with the geographical distribution of tested dogs. Origin of Bernese Mountain Dogs (red dots) and control dogs (blue dots).

Figure 2
B. burgdorferi ELISA results (optical density 405 nm) from Bernese Mountain Dogs and control dogs. OD = optical density, BMD = Bernese Mountain Dogs, B.b. = Borrelia burgdorferi
Clinical Features of Lyme Disease
"And I want that guy tested for Lyme Disease!"
Erythema Migrans ("Bullseye") Rash
Classic Features of Lyme Disease

1. **Tickbite**
   - Only 50-60% of Lyme patients recall a tickbite.

2. **Erythema migrans ("bullseye") rash**
   - Only 35-60% of Lyme patients ever see a rash.
   - Variable appearance and location.

3. **Arthritis**
   - Only 20-30% of Lyme patients get joint swelling.
   - May be masked by anti-inflammatory meds.

Table 3. Symptoms in Patients with and Those without Previous Lyme Disease ($P < 0.10$)*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Controls</th>
<th>Case-Patients</th>
<th>$P$ Value $\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>26 (15)</td>
<td>68 (37)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Palpitations</td>
<td>15 (9)</td>
<td>34 (18)</td>
<td>0.058</td>
</tr>
<tr>
<td>Poor coordination</td>
<td>4 (3)</td>
<td>21 (11)</td>
<td>0.0080</td>
</tr>
<tr>
<td>Headaches</td>
<td>27 (16)</td>
<td>59 (32)</td>
<td>0.0040</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>30 (18)</td>
<td>77 (41)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>36 (21)</td>
<td>67 (36)</td>
<td>0.013</td>
</tr>
<tr>
<td>Difficulty with word finding</td>
<td>29 (17)</td>
<td>69 (37)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>24 (14)</td>
<td>61 (33)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Joint pain</td>
<td>46 (27)</td>
<td>114 (61)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>12 (7)</td>
<td>42 (23)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>33 (19)</td>
<td>64 (34)</td>
<td>0.0090</td>
</tr>
<tr>
<td>Weakness)</td>
<td>13 (8)</td>
<td>33 (18)</td>
<td>0.032</td>
</tr>
<tr>
<td>Numbness</td>
<td>22 (13)</td>
<td>57 (31)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>25 (15)</td>
<td>57 (31)</td>
<td>0.0020</td>
</tr>
<tr>
<td>Mean total symptoms $\pm$ SD, $n$</td>
<td>3.2 ± 3.4</td>
<td>5.7 ± 4.3</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

* Data are adjusted for multiple comparisons.
† Obtained by using the $t$-test.
Question

Is it “post-Lyme syndrome” or persistent infection?
Pathophysiology of Lyme Disease
Borrelia burgdorferi
Characteristics of *Borrelia burgdorferi*

- Over 1500 gene sequences
- At least 132 functioning genes (in contrast, *T. pallidum* has 22 functioning genes)
- 21 plasmids (three times more than any known bacteria)
- “Stealth” pathology: evades the immune response

Genome Variation of *B. burgdorferi* Strains

Columns: Bb Strains  
Rows: Gene ORFs  

Black/Green: Conserved sequence  
Red: Divergent sequence  

RST1: Blood culture > skin culture  
RST2: Blood culture = skin culture  
RST3: Blood culture < skin culture  

Wang et al, JID 2002;186:782
Borrelia burgdorferi
“Stealth” Pathology

1. **Immune Suppression**
2. **Phase & Antigenic Variation**
3. **Physical Seclusion**
   - Intracellular Sites
   - Extracellular Sites
4. **Secreted Factors**

Stealth Pathology of *Borrelia burgdorferi*

Borrelia burgdorferi
“Stealth” Pathology

1. **Immune Suppression**
   – Tick Saliva Components
   – Complement Inhibition
   – Inhibitory Cytokine Induction (IL-10)
   – Lymphocyte/Monocyte Tolerization
   – Antibody Sequestration in Immune Complexes

Tick Saliva Components

Effect of Tick Salivary Gland Extract on Levels of *Borrelia burgdorferi* Day 1 Post-Infection in C3H/HeN Mice

Machackova et al, *Folia Parasitol* 2006;53:153
Effect of Tick Salivary Gland Extract on Levels of *Borrelia burgdorferi* Day 3 Post-Infection in C3H/HeN Mice

Machackova et al, *Folia Parasitol* 2006;53:153
Borrelia burgdorferi
“Stealth” Pathology

2. Phase & Antigenic Variation
– Gene switching (Trypanosomes)
– Mutation/Recombination (HIV)
– Variable Antigen Expression (Neisseria)
– Dormant State, Autoinduction (Mycobacteria)
– Fibronectin binding (Staph, Strep)

Borrelia burgdorferi
“Stealth” Pathology

3. **Physical Seclusion**

   – Intracellular Sites

   • Multiple Cell Types
     – Synovial Cells, Endothelial Cells, Fibroblasts, Neurons
     – Macrophages, Kupffer Cells, Glial Cells

   • Persistent Infection *In Vitro* (8 Weeks)

   • Dormant State: Cyst Formation, Neutrophil Calprotectin

Montgomery et al. *Infect Immun* 2006;74:2468-72
Livengood et al. *Microbes Infect* 2006;8:2832-40
Borrelia burgdorferi
“Stealth” Pathology

3. **Physical Seclusion**
   – Extracellular Sites
     • Privileged Sites (Joints, Eyes, CNS)
     • Cloaking Mechanisms (Binding to Proteoglycan, Collagen, Plasminogen, Integrin, Fibronectin)
     • Biofilm Formation

Borrelia burgdorferi
“Stealth” Pathology

4. **Secreted Factors**
   - Hemolysin (BlyB)
   - Porin (Oms 28)
   - Adhesin (Bgp)
   - Pheromones (DPD/AI-2)
   - Aggrecanase (ADAMTS-4)

Behera et al. *Arth Rheum* 2006;54:3319-29
Nasty Bug!
Laboratory Testing for Lyme Disease
Mandatory Laboratory Reporting of Lyme Disease in California

Inception: September 2005

CDC-Reportable Cases*

2007: 193 cases
2006: 174 cases
2005: 50 cases
2004: 32 cases

*May be 10-40 fold less than the number diagnosed by clinicians.

“For surveillance purposes, a reportable case of Lyme disease is defined as 1) physician-diagnosed erythema migrans ≥5 cm in diameter or 2) at least one objective late manifestation (i.e., musculoskeletal, cardiovascular, or neurologic) with laboratory evidence of infection with \textit{B. burgdorferi} in a person with possible exposure to infected ticks. This surveillance case definition was developed for national reporting of Lyme disease; it is not intended to be used in clinical diagnosis.”
New Laboratory Guidelines for Serologic Diagnosis of Lyme Disease: Evaluation of the Two-Test Protocol

THOMAS B. LEDUE,* MARILYN F. COLLINS, AND WENDY Y. CRAIG
Rheumatic Disease Laboratory, Foundation for Blood Research, Scarborough, Maine 04074

<table>
<thead>
<tr>
<th>Group no.</th>
<th>Sample origin</th>
<th>No. of subjects</th>
<th>Clinical sensitivity (%)$^a$</th>
<th>Clinical specificity (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Healthy laboratory workers</td>
<td>29</td>
<td>NA$^b$</td>
<td>100</td>
</tr>
<tr>
<td>2 (CDC panel)</td>
<td>Uninfected</td>
<td>5</td>
<td>NA</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Early Lyme disease</td>
<td>6</td>
<td>50.0</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Late Lyme disease</td>
<td>35</td>
<td>42.9</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>All Lyme disease</td>
<td>41</td>
<td>43.9</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>All subjects</td>
<td>46</td>
<td>43.9</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Cross-reactive</td>
<td>24</td>
<td>NA</td>
<td>100</td>
</tr>
<tr>
<td>4 (CAP panel)</td>
<td>Early Lyme disease</td>
<td>7</td>
<td>85.7</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Late Lyme disease</td>
<td>6</td>
<td>50.0</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>All Lyme disease</td>
<td>13</td>
<td>69.2</td>
<td>NA</td>
</tr>
<tr>
<td>1 to 4</td>
<td>All subjects</td>
<td>112</td>
<td>50.0</td>
<td>100</td>
</tr>
</tbody>
</table>

$^a$ Clinical sensitivity and specificity of the two-test protocol was determined by comparing the laboratory test results with the patient’s clinical history.

$^b$ NA, not applicable.
### Sensitivity/Specificity of Commercial Two-Tier Testing for Lyme Disease

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmitz et al, 1993</td>
<td>66%</td>
<td>100%</td>
</tr>
<tr>
<td>Engstrom et al, 1995</td>
<td>55%</td>
<td>96%</td>
</tr>
<tr>
<td>Ledue et al, 1996</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Trevejo et al, 1999</td>
<td>29%</td>
<td>100%</td>
</tr>
<tr>
<td>Nowakowski et al, 2001</td>
<td>66%</td>
<td>99%</td>
</tr>
<tr>
<td>Bacon et al, 2003</td>
<td>68%</td>
<td>99%</td>
</tr>
<tr>
<td><strong>MEAN TOTAL</strong></td>
<td><strong>56%</strong></td>
<td><strong>99%</strong></td>
</tr>
</tbody>
</table>

Stricker & Johnson, *BMJ* 2007;335:1008
AIDS testing has a sensitivity of 99.5%.

Would an AIDS test with 56% sensitivity be satisfactory?
Protein Microarrays

Applications of Protein and Antibody Arrays

UNI clone set
Protein expression
Generation of specific binders or antibodies by library display or hybridoma technology
Antibody microarrays

- Profiling of antibody binding, specificity and cross-reactivity
- Profiling of sera and bodily fluids to discover diagnostic and prognostic markers
- Potential application in protein-protein interactions studies
- Organ and disease specific protein microarrays
Protein Microarrays of Bb Probed with Patient Sera

L = Sera from patients with late-stage Lyme disease (13)

N = Sera from normal controls (4)

Red = Reactive
Green/Black = Non-reactive

Table 1
*Borrelia burgdorferi* cell envelope proteins showing highest reactivity to sera from patients with late disseminated Lyme disease as revealed by protein microarray

<table>
<thead>
<tr>
<th>Locus</th>
<th>Gene symbol</th>
<th>Protein name</th>
<th>C5/C3 ratio</th>
<th>Number of positive sera</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBP28</td>
<td><em>mlpA</em></td>
<td>Lipoprotein</td>
<td>1.8</td>
<td>13</td>
</tr>
<tr>
<td>BBN39</td>
<td><em>erpB2</em></td>
<td>ErpB2 protein</td>
<td>4.6</td>
<td>12</td>
</tr>
<tr>
<td>BBO40</td>
<td><em>erpM</em></td>
<td>ErpM protein</td>
<td>1.7</td>
<td>12</td>
</tr>
<tr>
<td>BBK50</td>
<td>–</td>
<td>Immunogenic protein P37, putative</td>
<td>2.1</td>
<td>12</td>
</tr>
<tr>
<td>BBA24</td>
<td><em>dbpA</em></td>
<td>Decorin binding protein A</td>
<td>26.0</td>
<td>11</td>
</tr>
<tr>
<td>BBJ09</td>
<td><em>ospD</em></td>
<td>Outer surface protein D</td>
<td>2.3</td>
<td>11</td>
</tr>
<tr>
<td>BBL28</td>
<td><em>mlpH</em></td>
<td>Lipoprotein</td>
<td>1.0</td>
<td>11</td>
</tr>
<tr>
<td>BBI42</td>
<td>–</td>
<td>Outer membrane protein, putative</td>
<td>7.6</td>
<td>10</td>
</tr>
<tr>
<td>BBQ47</td>
<td><em>erpX</em></td>
<td>ErpX protein</td>
<td>1.9</td>
<td>10</td>
</tr>
<tr>
<td>BBO39</td>
<td><em>erpL</em></td>
<td>ErpL protein</td>
<td>1.2</td>
<td>10</td>
</tr>
<tr>
<td>BBO28</td>
<td><em>mlpG</em></td>
<td>Lipoprotein</td>
<td>1.4</td>
<td>10</td>
</tr>
<tr>
<td>BBC06</td>
<td><em>eppA</em></td>
<td>Exported protein A</td>
<td>16.2</td>
<td>9</td>
</tr>
<tr>
<td>BBS41</td>
<td><em>erpG</em></td>
<td>Outer surface protein G</td>
<td>8.2</td>
<td>9</td>
</tr>
<tr>
<td>BBR42</td>
<td><em>erpY</em></td>
<td>Outer surface protein F</td>
<td>5.5</td>
<td>9</td>
</tr>
<tr>
<td>BBQ03</td>
<td>–</td>
<td>Outer membrane protein, putative</td>
<td>4.6</td>
<td>9</td>
</tr>
<tr>
<td>BBJ41</td>
<td>–</td>
<td>Antigen, P35, putative</td>
<td>4.0</td>
<td>9</td>
</tr>
<tr>
<td>BBA15</td>
<td><em>ospA</em></td>
<td>Outer surface protein A</td>
<td>3.7</td>
<td>9</td>
</tr>
<tr>
<td>BBB19</td>
<td><em>ospC</em></td>
<td>Outer surface protein C</td>
<td>3.9</td>
<td>9</td>
</tr>
<tr>
<td>BBS30</td>
<td><em>mlpC</em></td>
<td>Lipoprotein</td>
<td>2.5</td>
<td>9</td>
</tr>
<tr>
<td>BBM28</td>
<td><em>mlpF</em></td>
<td>Lipoprotein</td>
<td>1.9</td>
<td>8</td>
</tr>
<tr>
<td>BBG23</td>
<td></td>
<td>Hypothetical protein</td>
<td>1.4</td>
<td>8</td>
</tr>
<tr>
<td>BBN28</td>
<td><em>mlpl</em></td>
<td>Lipoprotein</td>
<td>1.1</td>
<td>8</td>
</tr>
<tr>
<td>BB0108</td>
<td></td>
<td>Lipoprotein</td>
<td>3.1</td>
<td>7</td>
</tr>
<tr>
<td>BB0442</td>
<td></td>
<td>Inner membrane protein</td>
<td>4.8</td>
<td>7</td>
</tr>
<tr>
<td>BBA14</td>
<td></td>
<td>Lipoprotein</td>
<td>2.1</td>
<td>7</td>
</tr>
</tbody>
</table>

* Mean C5/C3 signal intensity ratio of all positive samples.
Treatment of Lyme Disease
Treatment Failure in Lyme Disease

Culture-confirmed failure of antibiotic treatment was first reported in 1989:

“Antibiotic therapy may abrogate the antibody response to the infection as shown in our patients. *B. burgdorferi* may persist as shown by positive culture in MKP-medium; patients may have subclinical or clinical disease without diagnostic antibody titers to *B. burgdorferi*.”

“There is no credible scientific evidence for the persistence of symptomatic *Borrelia burgdorferi* infection after antibiotic treatment.”

Gary P. Wormser, M.D.
Raymond J. Dattwyler, M.D.
*New York Times*, June 9, 2006
“Credible Scientific Evidence”

Medline lists 21,215 articles about tick-borne diseases as of 11/08
1. Rodents


  “Isolation of *B. burgdorferi* from different organs in gerbils six months post infection demonstrates that borreliae persist in these animals for a long period.”


  “Despite the ability of hamsters to develop a substantial amount of borreliacidal antibody, *B. burgdorferi* can still be isolated from hamsters 16 months after infection.”
Animal Models of Persistent Lyme Disease

1. **Rodents**


- Bockenstedt LK, Mao J, Hodzic E, Barthold SW, Fish D. Detection of attenuated, noninfectious spirochetes in *Borrelia burgdorferi*-infected *mice* after antibiotic treatment. *J Infect Dis* 2002;186:1430-7. “Nine months after treatment, low levels of spirochete DNA could be detected by real-time PCR in a subset of antibiotic-treated mice.”
Animal Models of Persistent Lyme Disease

1. **Rodents**


  “This report shows that, after ceftriaxone treatment for 5 days, a portion of *B. burgdorferi*-infected mice still have live spirochetes in their body, which are activated by anti-TNF-alpha treatment.”


  “Results indicated that following antibiotic treatment, mice remained infected with non-dividing but infectious spirochetes, particularly when antibiotic treatment was commenced during the chronic stage of infection.”
Animal Models of Persistent Lyme Disease

2. Dogs

• Straubinger RK; Summers BA; Chang YF; Appel MJ. Persistence of *Borrelia burgdorferi* in experimentally infected dogs after antibiotic treatment. *J Clin Microbiol* 1997;35:111-6.

  “In dogs experimentally infected with *Borrelia burgdorferi* by tick exposure, treatment with high doses of amoxicillin or doxycycline for 30 days diminished but failed to eliminate persistent infection.”


  “At the end of the experiment, *B. burgdorferi* DNA was detectable at low levels in multiple tissue samples regardless of treatment.”
Animal Models of Persistent Lyme Disease

3. Monkeys

  “These data demonstrate that Lyme neuroborreliosis is a persistent infection, that spirochetal presence is a necessary but not sufficient condition for inflammation, and that antibody measured in serum may not predict the severity of infection.”

  “We conclude that carditis in NHPs infected with *B. burgdorferi* is frequent and can persist for years but is mild unless they are immunosuppressed.”

  “The majority of erp genes were detectably transcribed after more than 3 months of mammalian infection.”
**Animal Models of Persistent Lyme Disease**

4. **Horses**


  “Five months after antibiotic treatment, tissues aseptically collected at necropsy from ponies with increased antibody levels after antibiotic treatment also showed culture positive to *B. burgdorferi* in various post-mortem tissues.”
## Treatment Relapses and Failures

### Persistent Symptoms after Short Term Therapy

<table>
<thead>
<tr>
<th>Study (Failure %)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dvorakova (2004) (50%) [1]</td>
<td>Chronic Lyme disease: Antibiotics are only successful in 50% of cases.</td>
</tr>
<tr>
<td>Kaiser (2004) (80%) [2]</td>
<td>Twelve months after treatment, 93% of patients with acute, but only 20% with chronic neuroborreliosis were cured.</td>
</tr>
<tr>
<td>Treib (1998) (&gt;50%) [5]</td>
<td>After 4.2 years, &gt;50% of 44 treated neuroborreliosis patients with specific intrathecal antibodies were symptomatic.</td>
</tr>
</tbody>
</table>

## Treatment Relapses and Failures

### Persistent Symptoms after Short Term Therapy

<table>
<thead>
<tr>
<th>Study (Failure %)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valesova (1996) (38%) [1]</td>
<td>At 36 months, 10 of 26 patients (38%) had relapsed or progressed (relapse in 6, and new symptoms in 4).</td>
</tr>
<tr>
<td>Asch (1994) (28%) [3]</td>
<td>At a mean of 3.2 years after treatment, 28% of 215 patients had relapsed. Persistent symptoms (fatigue, arthralgia) in 114 patients (53%).</td>
</tr>
<tr>
<td>Pfister (1991) (37%) [4]</td>
<td>After a mean of 8.1 months, 10 of 27 neuroborreliosis patients (37%) were symptomatic &amp; Bb persisted in the CSF of one.</td>
</tr>
<tr>
<td>Logigian (1990) (37%) [5]</td>
<td>After 6 months, 10 of 27 patients (37%) relapsed or failed treatment.</td>
</tr>
</tbody>
</table>

## Persistence Despite Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Culture and/or PCR Evidence of Persistent Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oksi (1999)</td>
<td>Thirteen of 32 patients (40%) had PCR- or culture-confirmed relapses after treatment.</td>
</tr>
<tr>
<td>Bayer (1996)</td>
<td>97 previously treated chronic Lyme patients were PCR- positive in urine samples.</td>
</tr>
<tr>
<td>Preac Mursic (1996)</td>
<td>Isolation of <em>Bb</em> by culture in 5 patients, 4 of whom were seronegative on previous occasions.</td>
</tr>
<tr>
<td>Preac-Mursic (1993)</td>
<td><em>Bb</em> cultured from iris biopsy of treated patient with blurred vision &amp; persistent symptoms lasting several years.</td>
</tr>
</tbody>
</table>

## Treatment May Suppress But Not Eradicate Bb

<table>
<thead>
<tr>
<th>Author</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petrovic (1998)</td>
<td>Despite repeated treatment, symptoms improved only temporarily after treatment, but re-emerged within weeks or months.</td>
</tr>
<tr>
<td>Bayer (1996)</td>
<td>97 patients with chronic Lyme disease confirmed by PCR: ‘It seems to be characteristic for most of the patients in our study that, after antibiotic-free periods of a few months, they had again become increasingly ill with neurological and arthritic symptoms, so that treatment had to be resumed.’</td>
</tr>
<tr>
<td>Ferris (1996)</td>
<td>Despite repeated treatment over a 2-year period, the patient’s condition deteriorated. Twelve months of IV antibiotics followed by 11 months of oral antibiotics significantly improved the quality of life.</td>
</tr>
</tbody>
</table>

Does longer antibiotic treatment help in persistent Lyme disease?
Non-Controlled Studies Supporting Longer Treatment of Persistent Lyme Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oksi (1999)</td>
<td>9/13 patients (69%) with disseminated Lyme disease initially treated for 3 months with oral or IV antibiotics subsequently relapsed. <strong>Good response to retreatment with IV ceftriaxone for 4-6 weeks.</strong></td>
</tr>
<tr>
<td>Donta (1997)</td>
<td>277 patients with chronic Lyme treated for 1-11 months (mean, 4 months): 20% were cured, 70% improved and 10% had treatment failure.</td>
</tr>
<tr>
<td>Oksi (1998)</td>
<td>30 patients with disseminated Lyme treated for 100 days. 90% had good or excellent responses.</td>
</tr>
</tbody>
</table>

Donta Study

<table>
<thead>
<tr>
<th>Tetracycline Treatment Duration</th>
<th>Symptom Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Months</td>
<td>33%</td>
</tr>
<tr>
<td>3 Months</td>
<td>61%</td>
</tr>
</tbody>
</table>

### Non-Controlled Studies Supporting Longer Treatment of Persistent Lyme Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wahlberg (1994)</td>
<td><strong>Success rates for 100 patients with late Lyme disease:</strong> 31% (4/13) with 14 days of ceftriaxone; 89% (50/56) with ceftriaxone, then 100 days of amoxicillin and probenecid; and 83% (19/23) with ceftriaxone, then 100 days of cefadroxil.</td>
</tr>
<tr>
<td>Fallon (1999)</td>
<td>18 patients retreated with intravenous, intramuscular or oral antibiotics scored better on measures of cognition. Those retreated with IV therapy showed greatest improvement.</td>
</tr>
</tbody>
</table>

## Controlled Studies of Persistent Lyme Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krupp et al. (2003)</td>
<td>Ceftriaxone IV for 4 weeks vs. placebo</td>
<td>64% showed improvement in fatigue; no improvement in cognition.</td>
<td>Exact duration of illness not stated (at least 6 months). Previously untreated patients did significantly better than controls in terms of fatigue improvement (69% vs. 0%, p&lt;0.01).</td>
</tr>
<tr>
<td>Klempner et al. (2001)</td>
<td>Ceftriaxone IV for 4 weeks, then oral doxycycline for 2 months vs. placebo</td>
<td>No improvement in fatigue or quality of life.</td>
<td>Study criticized because subjects had been sick an average of 4.7 years and had already failed similar treatment. Treatment regimen inadequate for degree of functional impairment. See ILADS critique (<a href="http://www.ilads.org">www.ilads.org</a>).</td>
</tr>
</tbody>
</table>

# Controlled Studies of Persistent Lyme Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameron (2008)</td>
<td>Oral amoxicillin for 3 months vs. placebo</td>
<td>Retreatment was successful in 2/3 of patients with best initial quality of life.</td>
<td>Average duration of illness 7.1 months. Quality of life worse than diabetes or heart disease.</td>
</tr>
<tr>
<td>Fallon et al. (2008)</td>
<td>Ceftriaxone IV for 10 weeks vs. placebo</td>
<td>Significant cognitive and physical improvement at 12 weeks.</td>
<td>Patients had been sick for an average of nine years and failed prior treatment. Cognitive relapse when treatment withdrawn.</td>
</tr>
</tbody>
</table>

## Precedents for Prolonged Antibiotic Therapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Organism</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis (Drug-sensitive)</td>
<td><em>M. tuberculosis</em></td>
<td>2-4 antibiotics</td>
<td>6-9 months</td>
</tr>
<tr>
<td>Tuberculosis (MDR)</td>
<td><em>M. tuberculosis</em></td>
<td>3-5 antibiotics</td>
<td>18-24 months</td>
</tr>
<tr>
<td>Leprosy</td>
<td><em>M. leprae</em></td>
<td>3 antibiotics</td>
<td>24 months</td>
</tr>
<tr>
<td>Atypical Tuberculosis</td>
<td><em>M. chelonae</em></td>
<td>Oral + IV antibiotics</td>
<td>6-12 months</td>
</tr>
<tr>
<td>Complicated Actinomycosis</td>
<td><em>Actinomyces spp.</em></td>
<td>IV + oral antibiotics</td>
<td>6-18 months</td>
</tr>
<tr>
<td>Q Fever Endocarditis</td>
<td><em>C. burnetii</em></td>
<td>2 antibiotics</td>
<td>36 months</td>
</tr>
</tbody>
</table>

Antibiotic Prophylaxis for Asplenia in Children

<table>
<thead>
<tr>
<th>Country</th>
<th>Minimum Duration</th>
<th>Maximum Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA¹</td>
<td>5 years</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Canada²</td>
<td>5 years</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Germany³</td>
<td>3 years</td>
<td>Lifelong</td>
</tr>
<tr>
<td>France⁴</td>
<td>5 years</td>
<td>15 years</td>
</tr>
</tbody>
</table>

Safety of Intravenous Antibiotic Therapy in Chronic Lyme Disease

• In 199 patients with neurologic Lyme disease, the mean length of intravenous antibiotic treatment was 118 days (range, 7-750 days) representing 23,654 intravascular device (IVD)-days.
• IVD complications occurred in 15 patients (7.5%) representing an incidence of 0.63 per 1,000 IVD-days.
• None of the IVD complications were fatal.

Tickborne Coinfections

- Babesia (Piroplasma)
- Anaplasma
- Ehrlichia
- Bartonella
- Rickettsia/Coxiella
- Tularemia
- Spiroplasma?
- Agrobacterium?
“If somebody comes back in follow-up and has symptoms that have persisted or symptoms that have gotten worse, it may be because they are coinfected and you have treated *Borrelia*, but you haven't treated *Babesia* or *Ehrlichia*.”

Raymond J. Dattwyler, M.D.
FDA Advisory Committee Meeting
July 30, 1998
Ehrlichia Coinfection Exacerbates Lyme Disease


Babesia Coinfection Exacerbates Lyme Disease


Evidence for Persistent Coinfections


Pathogenesis of Babesiosis

### Prevalence of Coinfections in *Ixodes* Ticks, New Jersey 2004

<table>
<thead>
<tr>
<th>Organism</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Borrelia burgdorferi</em></td>
<td>33.6</td>
</tr>
<tr>
<td><em>Babesia microti</em></td>
<td>8.4</td>
</tr>
<tr>
<td><em>Anaplasma phagocytophilum</em></td>
<td>1.9</td>
</tr>
<tr>
<td><em>Bartonella spp.</em></td>
<td>34.5</td>
</tr>
</tbody>
</table>

Lyme Disease Awareness

Santa Cruz County Recreation Areas -
Adult tick infection rates*
Lyme & co-infections

Henry Cowell
Lyme 3.3%
HGE 4.1%
HME 2.1%

DeLaveaga
Lyme 3.3%
HGE 4.1%
HME 0%

Big Basin
Lyme 4.7%
HGE 4.7%
HME 0%

Nisene Marks
Lyme 13.2%
HGE 7.9%
HME 2.6%

UCSC

Wilder Ranch
Lyme 4.5%
HGE 5.2%
HME 0.8%

Seguad

Sunset
Lyme 0%
HGE 0%
HME 0%

Pogonip
Lyme 7%
HGE 7%
HME 20%

New Brighton
Lyme 4.7%
HGE 9.4%
HME 0%

* Nymphal stage ticks are believed to have much higher infection rates

References

Abbreviations
Lyme - Borrelia burgdorferi, Lyme disease agent
HGE - Anaplasma phagocytophilum, human granulocytic ehrlichiosis agent
HME - Ehrlichia chaffeensis, human monocytic ehrlichiosis agent
Tip of the Lyme Iceberg?

Symptomatic Diagnosed Treated

Symptomatic Undiagnosed Untreated

Asymptomatic Undiagnosed Untreated
Borreliosis Link to Alzheimer’s Disease?

MacDonald, *Med Hypotheses* 2006;67:592-600
Conclusions

- Lyme disease and coinfections are spreading.
- *Borrelia burgdorferi* is difficult to eradicate.
- Lyme testing is not as sensitive as we are told.
- Lyme treatment failure is more common than we think.
- Prolonged antibiotic therapy appears to be useful and appropriate in persistent Lyme disease.
Differing recommendations regarding treatment for Lyme disease between two major infectious disease organizations — the Infectious Diseases Society of America (IDSA) and the International Lyme and Associated Diseases Society — have prompted an investigation into whether the IDSA guidelines constitute possible antitrust violations.
I WAS BORN WITH LYME!
DON'T MAKE ME SUFFER!

I WAS BORN WITH LYME
(New Jersey)
Information about Tick-Borne Diseases

ILADS Website
www.ilads.org