Lyme Disease: An Overview and the Struggle with Chronic Symptoms

Kristopher M. Paolino, MD, MTM&H

28 Jan 2019
Conflicts

I currently have no conflicts of interest to include any financial ties to any products discussed.
Outline

• Brief Overview
• Diagnostics
• Chronic Symptoms
• Treatment
• Prevention
• Dangers
Lyme Disease

• Disease
  – *Borrelia burgdorferi* sensu stricto
  – Tick borne infection
  – Primary sites of transmission include the Northeast, Upper Midwest, and Northern California
  – Clinical presentation varies in patients later in disease
Reported Lyme Disease Cases in 1996 and 2014


For more information, visit U.S. EPA’s “Climate Change Indicators in the United States” at www.epa.gov/climate-indicators.
Lyme Disease
Lyme Disease

• Syndromes
  – Early localized (Erythema migrans)
  – Early disseminated
  – Late disseminated
  – Chronic post-treatment symptoms

Lyme Disease

Lyme meningitis  Lyme arthritis  Lyme carditis

https://www.cdc.gov/lyme/resources/TickborneDiseases.pdf
Lyme Disease
Lyme Disease

• Vector

NIH

CDC

UPSTATE Medical University Center for Global Health and Translational Science
Lyme Disease
Lyme Disease

• Treatment
  – Doxycycline
  – Amoxicillin
  – Cefuroxime
  – Ceftriaxone
  – Cefotaxime
  – Penicillin G
Diagnostics

• Standard
  – Clinical (EM rash)
  – Two Step testing
    • ELISA
    • Immunoblot
      – Combination of 23 and 41kDa bands may be false positive for IgM testing
      – Half the population has 41kDa IgG reactivity
Two Step Testing Approach

### First Test
- **Enzyme Immunoassay (EIA)**
  - OR
  - Immunofluorescence Assay (IFA)
- Positive or Equivocal Result
- Negative Result

### Second Test
- Signs or symptoms ≤ 30 days
  - IgM and IgG Western Blot
- Signs or symptoms > 30 days
  - IgG Western Blot ONLY

If patient with signs/symptoms consistent with Lyme disease for ≤ 30 days, consider obtaining a convalescent serum.

### Bands to Consider

<table>
<thead>
<tr>
<th>Onset of Symptoms</th>
<th>Antibody/EIA</th>
<th>Bands to Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>First few weeks</td>
<td>IgM</td>
<td>2 of the following: 24, 39, 41</td>
</tr>
<tr>
<td>After first few weeks</td>
<td>IgG</td>
<td>5 of the following: 18, 23, 28, 30, 39, 41, 45, 58, 66, 93</td>
</tr>
</tbody>
</table>
Patients with Lyme disease

Antibody response to B. burgdorferi

IgM

12,800
6400
3200
1600
800
400
200
100

10

Patient with other diseases

Influenza

MS/ALS

RA/SLE

Chronic fatigue Syphilis

ECM

Acute

Conv

Acute neuro

Arthritis

Chronic neuro

Number of patients

25

25

25

25

Months from disease onset

0-1

0.5-2

3-48

12-144

JID 1993; 16: 392.
Diagnostics

• PCR
  – Only recommended for use in synovial fluid
  – Burden of organism not found to be in sufficient quantities for blood or CSF
Diagnostics

• C6 peptide ELISA
  – Comparable to two tiered testing
  – IgG antibodies develop early
  – May have higher sensitivity in patients infected with other genotypes
  – Titers may indicate response to treatment

CID. 2008; 47(2): 188
Eur J Clin Microbiol Infect Dis 23: 615-8
j Clin Microbiol. 41; 4955-4960
Clin Diagn Lab Immunol. 12: 1069-74
## Diagnostics

<table>
<thead>
<tr>
<th>Variable</th>
<th>IgM</th>
<th></th>
<th>IgG</th>
<th></th>
<th>IgM or IgG</th>
<th></th>
<th>IgG VisE C6 peptide ELISA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Erythema migrans</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute phase</td>
<td>25</td>
<td>99</td>
<td>11</td>
<td>99</td>
<td>29</td>
<td>99</td>
<td>29</td>
</tr>
<tr>
<td>Convalescent phase</td>
<td>55</td>
<td>99</td>
<td>18</td>
<td>99</td>
<td>64</td>
<td>99</td>
<td>56</td>
</tr>
<tr>
<td>Acute neurologic or cardiac abnormalities</td>
<td>85</td>
<td>99</td>
<td>85</td>
<td>99</td>
<td>100</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>Arthritis or chronic neurologic abnormalities</td>
<td>NA</td>
<td>...</td>
<td>100</td>
<td>99</td>
<td>100</td>
<td>99</td>
<td>100</td>
</tr>
</tbody>
</table>

**NOTE.** Sensitivity was determined on the basis of serum samples from 76 patients with erythema migrans, 13 patients with acute neurologic or cardiac abnormalities, and 31 patients with arthritis or chronic neurologic abnormalities. Specificity was determined on the basis of serum samples from 86 healthy subjects from an area in which Lyme disease was endemic and serum samples from 50 subjects from an area in which Lyme disease was not endemic. NA, not applicable.
Diagnostics

Diagnostics

Clin Diagn Lab Immunol. 12: 1069-74
Diagnostics

• Shortcomings of Current Diagnostics
  – Insensitive early in the course of illness
  – Sensitivity may be lower if infected with a different genotype
  – Indirect tests
  – False positives
  – ”Bad” reference laboratories
Diagnostics

Many tests to diagnose Lyme, but no proof they work

Unregulated procedures can be costly, sow confusion

The Boston Globe
## Diagnostics

### Table 2. Number and Percentage of False-Positive Serologic Test Results and Discordant Pairs for 40 Medically Healthy Controls (University Reference Laboratory Versus Commercial and Lyme Specialty Laboratories)

<table>
<thead>
<tr>
<th>Test</th>
<th>University Reference Laboratory</th>
<th>Commercial Laboratory</th>
<th>Specialty Laboratory A</th>
<th>Specialty Laboratory B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Positive&lt;sup&gt;a&lt;/sup&gt; (%)</td>
<td>No. Positive&lt;sup&gt;a&lt;/sup&gt; (%)</td>
<td>P Value</td>
<td>Disc Pairs</td>
</tr>
<tr>
<td>?/+ ELISA</td>
<td>5 (12.5)</td>
<td>3 (7.5)</td>
<td>.683</td>
<td>6</td>
</tr>
<tr>
<td>C6 ELISA</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>WB IgM (CDC)</td>
<td>5 (12.5)</td>
<td>0</td>
<td>.074</td>
<td>5</td>
</tr>
<tr>
<td>WB IgM (laboratory)</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>WB IgG (CDC)</td>
<td>1 (2.5)</td>
<td>0</td>
<td>1.00</td>
<td>1</td>
</tr>
<tr>
<td>WB IgG (laboratory)</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>2-tier: ?/+ ELISA &amp; WB IgG</td>
<td>0</td>
<td>0</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>2-tier: C6 ELISA &amp; WB IgG</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>2-tier: ?/+ ELISA &amp; C6 ELISA</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>+ WB IgM or IgG (CDC)</td>
<td>5 (12.5)</td>
<td>0</td>
<td>.074</td>
<td>5</td>
</tr>
<tr>
<td>+WB IgM or IgG (laboratory)</td>
<td>1 (2.5)</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
</tr>
</tbody>
</table>

CID 2014. 59(12): 1705-10.
PRESS RELEASE

New York State Grants Approval of IGeneX’s Newly Developed Lyme ImmunoBlot Tests

Published: Aug 7, 2018 12:00 p.m. ET

Lyme ImmunoBlots (IgM and IgG) represents quantum leap in test performance over the traditional B. burgdorferi Western blots.
Diagnostics

What about the patients with chronic symptoms and repeatedly negative tests?
Chronic Symptoms

• Symptoms
  – General malaise (i.e. feeling unwell)
  – Arthritis, arthralgias, or myalgias
  – Headaches
  – Brain fog
  – Fatigue
  – Pain and paresthesias
Chronic Symptoms

• Antibiotic-refractory Lyme arthritis
  – Synovial cell hyperplasia
  – Vascular proliferation
  – Infiltration of mononuclear cells (T cells)
  – Upregulation of adhesion molecules
  – May be more likely with RST1 strains
  – Vast majority of these patients are negative on culture and PCR
Chronic Symptoms

• Antibiotic-refractory Lyme arthritis
  – Some mouse models with high pathogen load have shown that spirochetal antigens are retained near cartilage surfaces after antibiotic therapy
  – Patients often homozygous for TLR1 polymorphism (1805GG)
  – HLA-DR specific alleles (DRB1 0101 and 0401)

• Endothelial cell growth factor autoantibodies

Arthritis Rheum. 2008.; 58:3892-3901
<table>
<thead>
<tr>
<th>Study</th>
<th>Biomarker class</th>
<th>Biomarker(s)</th>
<th>Assay</th>
<th>Summary of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lochhead et al. 2017</td>
<td>miRNA</td>
<td>miR-146a, miR142, miR17, miR-155, miR-223, miR20a, let-7a, let-7c</td>
<td>PCR</td>
<td>miR-146a, miR142, miR17, miR-155, miR-223 and miR20a were higher in post- vs. pre-antibiotic treated A-RLA</td>
</tr>
<tr>
<td>Lochhead et al. 2015</td>
<td>miRNA (extracellular)</td>
<td>miR-146a, miR-155 (inflammatory signature), miR-30fam (vascularization signature), miR223, miR142</td>
<td>qPCR</td>
<td>miR-146a, miR-155, miR-223 and miR-142 were higher in A-RLA compared with antibiotic-responsive LA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>miR-146a, miR-155, miR-30fam, miR223 and miR-142 were upregulated in A-RLA compared with osteoarthritis patients</td>
</tr>
</tbody>
</table>
Chronic Symptoms

- Chronic Neurologic Manifestations
  - Chronic axonal polyneuropathy with radicular pain or distal paresthesias
  - Lyme encephalopathy
    - Subtle cognitive disturbances

Chronic Symptoms

• **Persistent Infection?**
  - Some animal studies indicating persistence
  - Several RCTs have not provided evidence that retreatment with prolonged courses of antibiotics significantly help
    • One study indicated improvement in fatigue
    • One small study indicated a temporary cognitive improvement

Am J Path. 2018; 188(3): 672-82.
NEJM. 2001; 345(2): 85.
Neurology. 2003; 60(12): 1923
Neurology. 2008; 70(13):992
Chronic Symptoms

• Wrong diagnosis
  – Other infections
  – Co-infections
  – Autoimmune disorders
Chronic Symptoms

Table 3. Factors associated with incomplete response according to age (middle-aged versus young and elderly versus young).

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI) ^a</th>
<th>p Value ^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle-aged vs. young</td>
<td>1.57 (1.04–2.37)</td>
<td>0.031</td>
</tr>
<tr>
<td>Elderly vs. young</td>
<td>1.94 (1.12–3.37)</td>
<td>0.018</td>
</tr>
<tr>
<td>Time from enrolment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 months vs. 14 days</td>
<td>0.48 (0.37–0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 vs. 2 months</td>
<td>0.50 (0.36–0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 vs. 6 months</td>
<td>0.47 (0.32–0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (female vs. male)</td>
<td>1.43 (1.01–2.02)</td>
<td>0.041</td>
</tr>
<tr>
<td>Presence of comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple EM vs. solitary EM</td>
<td>0.85 (0.59–1.24)</td>
<td>0.399</td>
</tr>
<tr>
<td>Presence of LB-associated constitutional symptoms at enrolment (yes vs. no)</td>
<td>1.67 (1.08–2.58)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

1220 European adults

Treatment

What is there to do?
Figure 3

Clinical Characteristics of Central Pain

- Pain in many different body regions
- Higher personal lifetime history of chronic pain
- Multiple somatic symptoms (e.g., fatigue, memory difficulties, sleep problems, mood disturbance)
- Sensory stimuli sensitivity (e.g., bright light, loud noises, odors, other sensations in internal organs enhanced)
- More common in women
- Strong family history of chronic pain
- Pain triggered or exacerbated by stressors
- Generally normal physical examination except for diffuse tenderness and nonspecific neurological signs

Characteristics of patients with rheumatologic diseases that may have contributions from central pain mechanisms.
Treatment

• Gabapentin
  – Pilot study performed
  – Pain improved in 9/10 patients

• DMARDs such as methotrexate or infliximab have been used for antibiotic refractory arthritis

Dermatology. 2005;211(2):123-7
Arth & Rheum 2006;54(1):3079-86.
Treatment

I hate Google
Dangers

- Misdiagnosis

*Case 2.* A man in his late 30s presented with a 4-year history of fatigue, abdominal pain, and loose stools. Previous evaluations demonstrated stable mesenteric lymphadenopathy. Although he lived in an area where Lyme disease is rare, reported no history of erythema migrans, and had negative Lyme serologic test results, he was diagnosed with chronic Lyme disease by a physician and treated with antibiotics (Table). Subsequently, the patient discontinued treatment and was re-evaluated by a gastroenterologist and an oncologist. Findings from a gastric biopsy demonstrated stage IV mucosa-associated lymphoid tissue lymphoma; successive Lyme serologic test results were negative. Findings from a mesenteric lymph node biopsy and positron emission tomographic scan demonstrated stage IV classic Hodgkin lymphoma, for which the patient underwent chemotherapy. He died 2 years later of complications of advanced lymphoma.
Dangers

• Line infections

Death from Inappropriate Therapy for Lyme Disease

A 30-year-old woman died as a result of a large *Candida parapsilosis* septic thrombus located on the tip of a Groshong catheter. The catheter had been in place for 28 months for administration of a 27 month course of intravenous cefotaxime for an unsubstantiated diagnosis of chronic Lyme disease.

Morbidity and Mortality Weekly Report

Serious Bacterial Infections Acquired During Treatment of Patients Given a Diagnosis of Chronic Lyme Disease — United States

Natalie S. Marzec, MD1; Christina Nelson, MD2; Paul Ravi Waldron, MD3; Brian G. Blackburn, MD4; Syed Hosain, MD5; Tara Greenhow, MD6; Gary M. Green, MD6; Catherine Lomen-Hoerth, MD, PhD7; Marjorie Golden, MD8; Paul S. Mead, MD2

CID. 2000;31(4):1107-9
Dangers

Death Due to Community-Associated *Clostridium difficile* in a Woman Receiving Prolonged Antibiotic Therapy for Suspected Lyme Disease

To the Editor—*Clostridium difficile* infections can occur outside the hospital in association with antibiotic use and can result in fulminant colitis and death. In December 2009, the Minnesota Department of Health investigated a death due to *C. difficile* of a 52-year-old woman with no recent hospitalizations.

Dangers

Antibiotic adverse effects

Antibiotic Treatment for Chronic Lyme Disease—Say No to the DRESS

Clifford M. Marks, AB1; John E. Nawn, MD2; Julie A. Caplow, MD2

Author Affiliations | Article Information


Case Report
Ceftriaxone-induced immune hemolytic anemia as a life-threatening complication of antibiotic treatment of ‘chronic Lyme disease’

Maarten De Wilde, Marijn Speeckaert, Rutger Callens & Wim Van Biesen

Pages 133-137 | Published online: 12 May 2016
Dangers

- Retrospective cohort analysis of medical and pharmacy claims of patients with PLDS
  - Infections increased by 22% and 17% in the IV and Oral treatment groups respectively
  - Emergency room visits were 11.3% vs 0.9% in IV treated compared to untreated patients respectively

CID 2018. In press
Dangers

![Bar chart showing percentages of adverse events (AEs) for different conditions and treatments.](chart.png)

- Any AE: 18.7% (IV Therapy), 16.8% (Oral Therapy), 13.4% (No IV/ABX Therapy)
- Electrolyte Imbalance: 4.0% (IV Therapy), 1.5% (Oral Therapy), 0.7% (No IV/ABX Therapy)
- Infection: 14.0% (IV Therapy), 12.7% (Oral Therapy), 9.3% (No IV/ABX Therapy)
- Hospitalization: 7.3% (IV Therapy), 2.2% (Oral Therapy), 0.9% (No IV/ABX Therapy)
- ED Visit: 11.3% (IV Therapy), 3.4% (Oral Therapy), 1.9% (No IV/ABX Therapy)

*P-values:*
- Any AE: P = 0.019
- Electrolyte Imbalance: P = 0.001
- Infection: P = 0.006
- Hospitalization: P < 0.001
- ED Visit: P < 0.001

CID 2018. In press
Dangers

Clinical Infectious Diseases

ACCEPTED MANUSCRIPT

Holistic approach in patients with presumed Lyme borreliosis leads to less than 10% of confirmation and more than 80% of antibiotics failure

Elie Haddad, Kahina Chabane, Stéphane Jaureguiberry, Gentiane Monsel, Valérie Pourcher, Eric Caumes

Clinical Infectious Diseases, ciy799, https://doi.org/10.1093/cid/ciy799
Published: 18 September 2018 Article history ▼

In about 300 patients consulting for a presumed Lyme Borreliosis, this diagnosis was confirmed in less than 10% of patients whereas 80% were found with another disease. Overall the presumptive treatment administered before or after referral failed in about 80%.

CID 2018 Nov 21 (Epub ahead of print)
Controversy

• Need for additional research
• Subpar diagnostics
• Suffering patients

Who is right?
Prevention

• PPE
  – DEET (~25%)
  – Picaridin
  – Permethrin (not for skin)

• Doxycycline 200 mg PO x 1 if given within 72 hours of engorged tick

NEJM. 2001; 345(2): 79
Prevention

• Lymerix
  – OspA vaccine approved in late 90s
  – Immunogenic and efficacious
  – Controversy over Lyme arthritis type symptoms in vaccine recipients
    • Specific epitopes of concern (hLFA-1)
Prevention

Table 1. Immunogenicity and Safety Results of the SmithKline Beecham Phase III Clinical Trial [3]

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vaccine group</th>
<th>Placebo group</th>
<th>Efficacy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite Lyme disease, no. of cases</td>
<td>22</td>
<td>41</td>
<td>49%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Year 1</td>
<td>16</td>
<td>66</td>
<td>76%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Asymptomatic Lyme disease, no of cases</td>
<td>2</td>
<td>13</td>
<td>83%</td>
<td>.001</td>
</tr>
<tr>
<td>Year 1</td>
<td>0</td>
<td>15</td>
<td>100%</td>
<td>.001</td>
</tr>
<tr>
<td>Adverse events after vaccine, % of subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3.9</td>
<td>3.5</td>
<td></td>
<td>.34</td>
</tr>
<tr>
<td>Myalgias</td>
<td>3.2</td>
<td>1.8</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Achiness</td>
<td>2.0</td>
<td>1.4</td>
<td></td>
<td>.01</td>
</tr>
<tr>
<td>Late arthralgia (&gt;30 days after receipt of dose)</td>
<td>1.3</td>
<td>1.2</td>
<td></td>
<td>.54</td>
</tr>
</tbody>
</table>

Prevention

• Valneva vaccine candidate VLA15
  – Targets OspA
  – Phase 1 study completed
    • No safety concerns in any treatment groups
    • Immunogenic with good OspA IgG responses against OspA serotypes
    • Phase 2 study (2 sites in US in U.S.) started recruiting in December 2018

Data not yet published
Prevention

A

Antibody Delivery  Tick challenge  Euthanize mice  Tissue collection  Culture observation

Day -5  Day 0  Day 21  Day 42

Serum Collection  Serum Collection  Serum Collection

B

<table>
<thead>
<tr>
<th>Antibody Group</th>
<th>Average Concentration (µg/mL)</th>
<th>Protection (Mice)</th>
</tr>
</thead>
<tbody>
<tr>
<td>319-44 WT DMAb</td>
<td>12.86 ± 1.51*</td>
<td>10/13</td>
</tr>
<tr>
<td>319-44 Mod1 DMAb</td>
<td>12.68 ± 1.36*</td>
<td>12/13</td>
</tr>
<tr>
<td>319-44 WT HuMAb</td>
<td>9.29 ± 1.71</td>
<td>3/4</td>
</tr>
<tr>
<td>Irrelevant IgG DMAb Control</td>
<td>NA</td>
<td>0/9</td>
</tr>
</tbody>
</table>
And now for something completely different...
Borrelia miyamotoi

- Spread by *Ixodes* species ticks
- Genetically related to relapsing fever species
- First human cases reported in Russia 2011; U.S. 2013
- Presents with “viral like illness”
  - Neurologic symptoms may be more common in immunocompromised

- Generally treated with 2-4 weeks of doxycycline
  - Jarisch-Herxheimer reaction has been described

- PCR testing and serology is available
  - Blood smear also possible
Transstadial transmission

Lyme
B. miyamotoi
Local unpublished reports indicate a 4-5% tick infection rate
Borrelia miyamotoi

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Meningoencephalitis from Borrelia miyamotoi in an Immunocompromised Patient

**Table 1. Clinical Features of the 51 Case Patients With BMD**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>55 (12-82)</td>
</tr>
<tr>
<td>Male</td>
<td>29 (57)</td>
</tr>
<tr>
<td>Fever/chills</td>
<td>49 (96)</td>
</tr>
<tr>
<td>Headache†</td>
<td>49 (96)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>42 (84)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>39 (76)</td>
</tr>
<tr>
<td>Malaise/fatigue</td>
<td>42 (82)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms‡</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Cardiac/respiratory symptoms§</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Neurologic symptoms‖</td>
<td>4 (8)</td>
</tr>
</tbody>
</table>

BMD = *Borrelia miyamotoi* disease.
* Number (percentage) unless otherwise indicated.
† Severe in most patients.
‡ Nausea, abdominal pain, diarrhea, and anorexia.
§ Dyspnea.
‖ Dizziness, confusion, and vertigo.
<table>
<thead>
<tr>
<th>Group No.</th>
<th>ELISA</th>
<th>Western Blot</th>
<th>Serum Phase</th>
<th>Coinfection</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Positive at 1:320 dilution</td>
<td>Positive</td>
<td>Positive</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Patient 1</td>
<td>Positive at 1:320 dilution</td>
<td>Positive</td>
<td>Negative</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Patient 2</td>
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</tr>
<tr>
<td>Patient 3</td>
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</tr>
<tr>
<td>Patient 4</td>
<td>Positive at ≥1:320 dilution</td>
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</tr>
<tr>
<td>Patient 5</td>
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<td>Not done</td>
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<td>None</td>
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</tr>
<tr>
<td>Patient 6</td>
<td>Positive at 1:320 dilution</td>
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<td>None</td>
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</tr>
<tr>
<td>Group 2</td>
<td>Positive at ≥1:320 dilution</td>
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<td>None</td>
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<tr>
<td>Patient 7</td>
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<td>9</td>
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<td>Patient 8</td>
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<td>Negative</td>
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<td>None</td>
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<td>Patient 9</td>
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<td>6</td>
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<tr>
<td>Patient 10</td>
<td>Positive at ≥1:320 dilution</td>
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<td>None</td>
<td>3</td>
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<tr>
<td>Patient 11</td>
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<td>Not done</td>
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<td>None</td>
<td>4</td>
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<tr>
<td>Patient 12</td>
<td>Positive at 1:1280 dilution</td>
<td>Negative</td>
<td>Positive</td>
<td>Lyme disease</td>
<td>12</td>
</tr>
<tr>
<td>Patient 13</td>
<td>Positive at 1:320 dilution</td>
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<td>Positive</td>
<td>Lyme disease</td>
<td>Uncertain</td>
</tr>
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<td>Patient 14</td>
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<td>Positive</td>
<td>Lyme disease</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Patient 15</td>
<td>Negative at 1:160 dilution</td>
<td>Negative</td>
<td>Negative</td>
<td>Babesiosis</td>
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</tr>
<tr>
<td>Group 3</td>
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<td>None</td>
<td>5</td>
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<tr>
<td>Patient 16</td>
<td>Positive at 1:1280 dilution</td>
<td>Positive</td>
<td>Negative</td>
<td>None</td>
<td>10</td>
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<tr>
<td>Patient 17</td>
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<td>Positive</td>
<td>Negative</td>
<td>None</td>
<td>12</td>
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<tr>
<td>Patient 18</td>
<td>Positive at 1:320 dilution</td>
<td>Positive</td>
<td>Positive</td>
<td>None</td>
<td>12</td>
</tr>
</tbody>
</table>

**SEROPREVALENCE**

- Group 1: 1%
- Group 2: 3.2%
- Group 3: 21%

*NEJM 2013; 368: 291-3.*
Seroreactivity to the C6 Peptide in *Borrelia miyamotoi* Infections Occurring in the Northeastern United States

Phillip J. Molloy, Karen E. Weeks, Brittany Todd, and Gary P. Wormser

**Background.** There are no US Food and Drug Administration (FDA)–approved diagnostic tests for *Borrelia miyamotoi* infection, an emerging tick-borne illness in the United States. The purpose of this study was to evaluate whether the FDA-approved C6 peptide enzyme-linked immunosorbent assay (ELISA) currently used to diagnose Lyme disease may potentially serve as a diagnostic test for *B. miyamotoi* infections.

**Methods.** Serum specimens from 30 patients from the northeastern United States with *B. miyamotoi* infection established by a polymerase chain reaction assay of a blood specimen were tested using the C6 ELISA. To reduce confounding with *Borrelia burgdorferi* coinfection, 6 sera were excluded: 3 from patients with a positive Western immunoblot for antibodies to *B. burgdorferi* and 3 from patients for whom immunoblot testing had not been performed.

**Results.** Twenty-two of 24 (91.7% [95% confidence interval, 73.0%–98.8%]) evaluable *B. miyamotoi* patients were C6 ELISA reactive, principally on a convalescent-phase serum specimen. C6 ELISA index values were often well above the positive cutoff value of 1.1, exceeding 4 in 11 of the 22 (50.0%) C6 ELISA-reactive patients.

**Conclusions.** Although previously regarded as a highly specific test for Lyme disease, the C6 ELISA is also regularly reactive on convalescent-phase serum samples of patients from the northeastern United States with *B. miyamotoi* infection.

**Keywords.** Lyme disease; Lyme serology; C6 Lyme test; Borrelia; *Borrelia miyamotoi*. 
One more thing...
Multistate Infestation with the Exotic Disease–Vector Tick
*Haemaphysalis longicornis* — United States, August 2017–September 2018

*H. longicornis* is native to eastern China, Japan, the Russian Far East, and Korea. It is an introduced, and now established, exotic species in Australia, New Zealand, and several island nations in the western Pacific Region. Where this tick exists, it is an important vector of human and animal disease agents. In China and Japan, it transmits the severe fever with thrombocytopenia syndrome virus (SFTSV), which causes a human hemorrhagic fever (2), and *Rickettsia japonica*, which causes Japanese spotted fever (3). Studies in Asia identified ticks infected with various species of *Anaplasma, Babesia, Borrelia, Ehrlichia*, and *Rickettsia*, and all of these pathogen groups circulate zoonotically in the United States (4, 5). In addition, parthenogenetic reproduction, a biologic characteristic of this species, allows a single introduced female tick to generate progeny without mating, thus resulting in massive host infestations. In some regions of New Zealand and Australia,
Questions?