IS IT LYME DISEASE, or TICK-BORNE RELAPSING FEVER?

Webinar Presented by
Joseph J. Burrascano Jr. M.D.
Joined by Jyotsna Shah PhD for the Q&A

January 2020
Presenters

Joseph J. Burrascano Jr. M.D.

- Well-known pioneer in the field of tick-borne diseases, active since 1985
- Founding member of ILADS and ILADEF
- Active in physician education on all aspects of tick-borne diseases

Jyotsna Shah, PhD

- President & Laboratory Director of IGeneX Clinical Laboratory
- Over 40 Years of Research Experience in Immunology, Molecular Biology & Microbiology
- Author of Multiple Publications & Holds More Than 20 Patents
- Member of ILRAD as a Post-Doctoral Scientist
- Started the First DNA Sequencing Laboratory in E. Africa
Poll Question

Before we begin, we’d like to ask a poll question.

Which one of these *Borrelia* causes Tick-Borne Relapsing Fever (TBRF)?

a) *B. mayonii*
b) *B. turicatae*
c) *B. burgdorferi*
d) *B. andersonii*
e) *B. garinii*
Poll Question

Before we begin, we’d like to ask a poll question.

Which one of these *Borrelia* causes Tick-Borne Relapsing Fever (TBRF)?

a) *B. mayonii* - Lyme  
b) *B. turicatae* - TBRF  
c) *B. burgdorferi* - Lyme  
d) *B. andersonii* - Lyme  
e) *B. garinii* – Lyme strain in Europe
What is TBRF?

- Has been defined by clinical presentation
- Has been defined by tick vector
- Has been defined by genetics
- Has been defined by serotype

**BUT**

- Each of these has exceptions and limitations!
Clinical Presentation of Classic TBRF

- “Recurring febrile episodes that last ~3 days and are separated by afebrile periods of ~7 days duration.”

- “Each febrile episode involves a “crisis.” During the “chill phase” of the crisis, patients develop very high fever (up to 106.7°F) and may become delirious, agitated, tachycardic and tachypneic. Duration is 10 to 30 minutes.”

- “This phase is followed by the “flush phase”, characterized by drenching sweats and a rapid decrease in body temperature. During the flush phase, patients may become transiently hypotensive. Overall, patients who are not treated will experience several episodes of fever before illness resolves.”
Classic TBRF: Cycles

- TBRF *Borrelia* express surface antigens that undergo cyclic changes
- Cycles of disease are caused by regular variation of these antigens
- These antigens are coded for by plasmid genes (VSP and VLP)
- The ability of a single spirochete to switch expression among antigenically distinct VSP and VLP genes allows escape from an individual host’s immune response and can cause late-appearing IgM antibodies
- Alteration of these proteins prevents elimination of the spirochetes by the immune system, leading to recurrent febrile episodes.
- Allelic polymorphism or genetic variability of VSP and VLP genes within the total spirochete population may help to evade herd immunity
But can also Present like Lyme!

- 543 US patients with suspected Lyme:
  - 29% were positive for Ab to TBRF (tested for 2 species)
- Cohort of 321 California residents:
  - 38% were positive for Ab to TBRF (same 2 species)

These patients did not have the “classic” acute TBRF presentation. Clinically, they resembled Lyme patients

Sero-negative Lyme?
ORNITHODOROS TICKS

- These ticks have a life span of 10 to 20 years and can endure starvation for >5 years.
- Once infected, the ticks remain infected for the rest of their lives!
- “B. turicatae is maintained transovarially …”
- Meaning that larvae may transmit infection.
Soft Tick Vector

ORNITHODOROS TICKS

- Attached ticks are rarely seen because these ticks are rapid feeders- attached for only 5 to 30 minutes
- Bites are **painless** and go unnoticed
- Transmission of *B. turicatae* occurs within seconds of the tick bite
- Can feed **multiple times**
- **Do not live in the grass** - live in crevices which can include wood cracks, leaf litter, caves and small- and medium-size mammal nests and dens- **indoors and outdoors**
- After feeding, ticks return to their crevice
- Campers, hikers, cave explorers; rodent-infested homes and cabins. May emerge when you start a campfire, wood stove or simply turn on the heat!
Ornithodoros Ticks

Before feeding  After feeding
Engorged *Ixodes*

 Might be confused with *Ornithodoros*
But Some Species of TBRF Have Hard Tick Vectors

- *B. miyamotoi* - vector is *Ixodes*
- *B. lonestari* - vector is *Amblyomma americanum*
- *Others??*
Complex Genetics (No Surprise)

- Can characterize an organism by the genetic sequences
- Sequencing is typically done on a specific gene- for example, the flagellin gene
- Can also sequence other genes and even the telomere
- Problem is, the family tree that results looks different for each method, making precise groupings of families of *Borrelia* impossible
- Serotyping (based on expressed surface antigens) is tricky due to antigenic variation- so to be accurate, need to measure multiple types of each surface antigen. This is the basis of advanced immunoblotting.
TBRF - Important Facts

- Transmission within **15 seconds** of tick bite
- **Maternal-fetal passage** well recognized and accepted
  - Spontaneous abortion, premature birth, and neonatal death
- Louse-borne RF (*B. recurrentis*) transmission via **mucous membranes**!!
- **Acute Respiratory Distress Syndrome** has been associated with *B. hermsii* (CDC)
- Ornithodoros- because of transovarial passage of *Borrelia* and its ability to survive for decades, it may **serve as its own reservoir**, and not need to feed on an animal to acquire or maintain infection
- Some TBRF species are immune to complement-mediated killing
- Prolonged QT interval has been reported with TBRF infection
Do we Need to Worry About TBRF?

- “TBRF is typically considered a disease of outdoor enthusiasts and impoverished persons living in primitive conditions”
- “However, our study suggests emergence of *B. turicatae* in metropolitan areas”
- “Evidence indicates the endemicity of *O. turicata* ticks in San Antonio, Dallas, and Austin, the seventh, ninth, and eleventh largest cities in the United States”
- “The University of Tennessee reported that in 2009, during fall hunting season, 58% of turkeys tested positive for *B. miyamotoi*”
Do we Need to Worry About TBRF?


- “In the USA, several species of RFB have been reported to cause disease in humans, including *B. miyamotoi*, *B. hermsii*, *B. lonestari*, *B. parkeri*, and *B. turicatae*, with most cases occurring in the western USA.”
- “In the state of California, *B. miyamotoi*, *B. hermsii*, and *B. parkeri* have been shown to infect humans, and a fourth *Borrelia* species, *B. coriaceae*, infects ticks found in that state, although human infection has not yet been identified.”
“High prevalence of tick-borne co-infections in patients with Lyme-like symptoms”

Abstract, ILADS 2019

“We reviewed results of over 10,000 patients tested for the presence tick-borne disease pathogens by direct or indirect tests.”

Table 1: Patients Positive for exposure to Tick-Borne Pathogens

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<th>Pathogen</th>
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<td>37.3%</td>
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<td>32.1%</td>
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<td>Rickettsia</td>
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<tr>
<td>Ehrlichia chaffeensis (HME)</td>
<td>6.9%</td>
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Table 2: Percentage of Lyme patients with one or more coinfection

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<tr>
<th>Co-infection</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>One Co-infection</td>
<td>40%</td>
</tr>
<tr>
<td>Two Co-infections</td>
<td>15%</td>
</tr>
<tr>
<td>Three Co-infections</td>
<td>4.6%</td>
</tr>
<tr>
<td>Four Co-infections</td>
<td>0.7%</td>
</tr>
</tbody>
</table>
TBRF in Suspected Lyme Patients

543 US patients with suspected Lyme
- 32% were positive for Ab to LB
- **22% were positive for Ab to TBRF**
  - Only tested for 2 species- *hermsii* and *turcica*
- 7% were positive for Ab to both

California cohort- 321 patients
- 33% were positive for Ab to LB
- **27% were positive for Ab to TBRF (2 species)**
- 11% were positive for Ab to both
TBRF Reported in 49 of 50 States
World-wide Distribution

- TBRF has also been reported in **Central and South America**

- *Borrelia hispanica*, *B. persica*, and *B. miyamotoi* are important causes of TBRF in **Europe and Asia**

- *B. hispanica*, *B. crocidurae*, and *B. duttonii* are important causes of TBRF in **Africa**
Clinical Presentations

Two types
- **Classic presentation- acute**- fever, chills, headache, myalgias, arthralgia, nausea
- **Lyme-like presentation**
- *B. miyamotoi* seems to be a blend of the two
  - “*Borrelia miyamotoi* disease”
- Note that GI involvement is more common in TBRF than in Lyme
- Classically presenting TBRF may be confused with Rickettsia, viruses, Babesia and Malaria
## Lyme and Relapsing Fever Symptoms

The table below shows the percentage of patients with various symptoms associated with different Borrelia species:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EM</td>
<td>9</td>
<td>18</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>Multiple EM</td>
<td>0</td>
<td>14</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Fever</td>
<td>98</td>
<td>100</td>
<td>67</td>
<td>32</td>
</tr>
<tr>
<td>Fatigue</td>
<td>98</td>
<td>86</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>89</td>
<td>94</td>
<td>57</td>
<td>63</td>
</tr>
<tr>
<td>Chills</td>
<td>35</td>
<td>88</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>Myalgia</td>
<td>59</td>
<td>92</td>
<td>52</td>
<td>63</td>
</tr>
<tr>
<td>Artralgia</td>
<td>28</td>
<td>73</td>
<td>29</td>
<td>62</td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>76</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>71</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Neck Stiffness</td>
<td>2</td>
<td>24</td>
<td>0</td>
<td>38</td>
</tr>
</tbody>
</table>
TBRF Species (so far…)

1. *Borrelia americana*
2. *Borrelia anserina*
3. *Borrelia coriaceae*
4. *Borrelia crocidurae*
5. *Borrelia duttonii*
6. *Borrelia hermsii*
7. *Borrelia lonestari*
8. *Borrelia miyamotoi*
9. *Borrelia parkeri*
10. *Borrelia persica*
11. *Borrelia recurrentis*
12. *Borrelia sinica*
13. *Borrelia theileri*
14. *Borrelia turcica*
15. *Borrelia turicatae*
16. *Borrelia valaisiana*
17. *Candidatus Borrelia texasensis*
18. *Candidatus Borrelia johnsonii*
Important TBRF Species in USA

1. B. hermsii
2. B. miyamotoi
3. B. turcica-like
4. B. turicatae
5. B. coriaceae?
6. B. parkeri
7. Candidatus Borrelia johnsonii?
Laboratory Testing

BLOOD SMEARS

• Some TBRF species may be visible on blood smears
• Only in acute stage of a crisis
• Cannot determine species
• False positives
• Positive smear may be incorrectly diagnosed as Lyme
Laboratory Testing

PCR
- Large commercial labs - for *B. miyamotoi* only

- IGeneX PCR - Genus-specific
  - Therefore may detect many different species of TBRF
  - Can identify and report *B. miyamotoi*

- PCRs only acceptably sensitive during early or acute stages of the disease and in the immunosuppressed, including very ill, late stage patients
SEROLOGIES

- Most TBRF express p41
  - May give rise to a false positive Lyme ELISA
  - On a Lyme western blot, a single band 41 in a suspected Lyme patient may represent an unexpected TBRF infection

- OspC is present in several TBRF species
  - Another potential reason for false-positive Lyme serologies
Laboratory Testing

**SEROLOGIES**
- Large commercial labs- for *B. hermsii* only!

- Can get a GLP-protein based ELISA for *B. miyamotoi*, but is only one protein antigen and therefore prone to false negatives

- IGeneX offers a variety of advanced serologic tests for TBRF
  - **ImmunoBlots**- provides the most information and is the gold standard
  - **Broad Coverage Antibody Assay**- simple and cost effective but still better than the Large-Lab options
The IGeneX TBRF ImmunoBlot

The most advanced TBRF diagnostic test available to clinicians
Advantages of the ImmunoBlot

- Uses **recombinant antigens** that are specific to multiple individual species
- Unlike western blots, IGeneX ImmunoBlots deliver **precise quantities** of antigen to **specific locations** on the gel - drastically improves sensitivity and specificity
- **A large variety of protein antigens** are included, not just one, as in large-lab testing for *B. miyamotoi*
- Antigens reflect the **seven most commonly found TBRF species**, not just *B. hermsii* or *B. miyamotoi*
Advantages of the ImmunoBlot

USES RECOMBINANT PROTEIN ANTIGENS AND INCORPORATES UNIQUE Ag DELIVERY AND DETECTION METHODS

- Significantly increases real-world sensitivity
- Significantly increases specificity
  - Less likely to cross react with viruses, non-Borrelia bacteria and autoantigens
- Species-specific- no cross reactivity between RF and Lyme *Borrelia*
- IgM and IgG
IDENTIFICATION IS BASED UPON POSITION: MIGRATION-DEPENDENT

However:
• Migration is not an exacting process and the variable location of the bands can make identification of individual antigens very difficult - may not line up.

• Also, some nonspecific or unimportant proteins may co-migrate with important Borrelia proteins, and the WB cannot distinguish these.
SCORING (POS OR NEG) IS BASED UPON BAND INTENSITY

However:
• How dark must a band be to be called positive? Indeterminate? Because protein content can vary, the band intensity can vary, potentially causing false positives and false negatives.

• What does a broad band mean?
  o More antigen?
  o Multiple co-migrating antigens?
  o Stronger host reaction?
  o ??
Scoring the ImmunoBlot

**PRECISE AMOUNT OF ANTIGEN**
- Banding intensity is no longer source-dependent
- Positive bands are more clearly displayed
- Reduces false positives and false negatives

**PLACED AT SPECIFIC LOCATIONS**
- Band locations are no longer migration-dependent
- Know exactly what each positive band represents
- No longer an issue with co-migration of other, non-TBRF antigens (viruses, other bacteria, autoantibodies)
WB vs. IGeneX ImmunoBlot

TBRF Western Blot

TBRF ImmunoBlot

IgM  IgG
MULTIPLE species of TBRF *Borrelia* are included

Between IgM and IgG, one set of IGeneX TBRF ImmunoBlots deliver the equivalent of **TWELVE** individual tests!

**SPECIES:**
- *B. hermsii*
- *B. miyamontoi*
- *B. turcica-like*
- *B. turicatae*
- *B. coriaceae*
- *B. parkeri*
Example of What is Being Seen

<table>
<thead>
<tr>
<th>TBRF Species</th>
<th>TBRF IB (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. hermsii</td>
<td>7</td>
</tr>
<tr>
<td>B. miyamotoi</td>
<td>13</td>
</tr>
<tr>
<td>B. turicatae</td>
<td>13</td>
</tr>
<tr>
<td>B. turcica-like</td>
<td>2</td>
</tr>
<tr>
<td>TBRF Borrelia sp.</td>
<td>26</td>
</tr>
<tr>
<td>B. hermsii and B. miyamotoi</td>
<td>1</td>
</tr>
</tbody>
</table>
## TBRF ImmunoBlot

### Sensitivity

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Number</th>
<th>IgM (+)</th>
<th>IgG (+)</th>
<th>IgM &amp; IgG (+)</th>
<th>Total (+)</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Sample (acute)</td>
<td>15</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>66.7%</td>
</tr>
<tr>
<td>2nd Sample (convalescent)</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>100%</td>
</tr>
</tbody>
</table>

**PCR-Positive patients**

- First sample refers to *early disease*, when serologies are expected to be nonreactive. Note however the sensitivity of 66.7%.
- Second sample, a *convalescent* sample, shows 100% sensitivity.
- Late-appearing IgM is not uncommon.
## Specificity

<table>
<thead>
<tr>
<th>Sample Types</th>
<th>N</th>
<th>IgM (+)</th>
<th>IgG (+)</th>
<th>IgM or IgG (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endemic area control</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mononucleosis</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Non-endemic area control</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Periodontitis</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>13</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>HIV-1 infection</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus infection</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Autoimmune and Allergy</td>
<td>33</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><em>Borrelia burgdorferi</em> infection</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><em>Bartonella henselae</em> infection</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Human granulocytic anaplasmosis</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><em>Babesia microti</em> infection</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><em>Babesia duncani</em> Infection</td>
<td>41</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Human monocytic ehrlichiosi</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total False (+)</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Total True (-)</td>
<td>212</td>
<td>209</td>
<td>209</td>
<td>207</td>
</tr>
</tbody>
</table>

**Specificity**

<table>
<thead>
<tr>
<th></th>
<th>98.6%</th>
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<th>97.6%</th>
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*Note: The table above summarizes the specificity of the TBRF ImmunoBlot test across various sample types and conditions.*
IGeneX TBRF ImmunoBlot Summary

**Provides vital information not previously available**

- Accurately identifies TBRF—especially important in diagnosing “Lyme-like illnesses”
  - Does not cross-react with Lyme *Borrelia*
- Ability to identify multiple clinically relevant TBRF species
- Useful in detecting early disease
- Highly sensitive
- Highly specific
- Rapid turnover
IGeneX Broad Coverage TBRF Antibody Assay
Simple and cost effective
IGeneX TBRF Broad Coverage Antibody Assay

Single serological test that covers multiple, clinically relevant TBRF species

- Highly accurate replacement for standard serologies
  - Think of it as a better ELISA
- Single result includes IgM and IgG
- Simple yes-no results- makes interpretation easy
- Rapid turnover
- Cost effective
Using These New Assays

- **The Broad Coverage Antibody Assay** offers a more sensitive, highly specific and broad-spectrum alternative to standard serologies
  - Tests for multiple TBRF *Borrelia* species
  - Very cost-effective
  - Simple yes-no interpretation; includes both IgM and IgG

- **The IGeneX ImmunoBlots** include broad, multi-species coverage, BUT CAN ALSO IDENTIFY SPECIES*
  - Allows the clinician to identify patterns of presentation and treatment response associated with specific species of TBRF *Borrelia*
  - Provides information not available anywhere else
  - Highly sensitive and specific
  - Extremely useful in selected early cases
  - Replacement for the western blot and all other standard serologies

* Speciation not available in New York
Testing for TBRF

- **In patients with intact immunity, the TBRF ImmunoBlot is always the first choice**
  - Good for all stages of disease
  - Late IgM is still significant
  - Two or more reactive band groups is read as positive
  - One reactive band group is considered a borderline result

- **Immunocompromised**
  - Add the TBRF PCR to catch those who do not have detectable levels of free antibody
  - Reciprocal relationship between serologies and PCR due to this immune system effect
  - By doing both a serology and a PCR, you get a picture of immune responsiveness
Why Test Panels? Results from 10,000 Patients

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<tr>
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</tr>
<tr>
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<td>0.7%</td>
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Why Test Panels

• Nearly all Lyme patients, especially the more ill ones, have co-infections
• In light of the high prevalence of TBRF, which may present acutely and with high fever, more important than ever to distinguish this from acute rickettsial and acute Babesia infections
• Many reports of nervous system involvement by TBRF, making it difficult to separate clinically from tick-borne viral encephalitis
• Positive blood smears for spirochetes or protozoa require more definitive lab testing for confirmation
What About Treatment?
Treating TBRF

• As far as we can tell, treatment regimens for TBRF and Lyme are similar
  o Very few studies on antibiotic susceptibility
  o TBRF can be a chronic illness
  o TBRF can involve the central nervous system
  o TBRF can involve the joints
  o TBRF can induce chronic fatigue

• BE CAREFUL! In the classical form of TBRF, if treated during a crisis, **severe Herxheimer** reactions may ensue- hypotension, cardiac arrhythmias, etc. so be careful!!
Concluding Thoughts

- TBRF is newly recognized as being far more prevalent than previously thought
- May be responsible for many cases of seronegative Lyme
- More difficult to clinically identify this without laboratory confirmation
- Test with ImmunoBlots to learn if there are any important differences among the various *Borrelia* regarding presentation and response to treatment
- Keep records, share your info, and publish!
Line Immunoblot Assay for Tick-Borne Relapsing Fever and Findings in Patient Sera from Australia, Ukraine and the USA

- Published in October 2019
- Lead author is Dr. Shah from IGeneX
- Available on www.igenex.com
NOW TIME FOR QUESTIONS