Modified two-tiered testing for Lyme disease

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Disclosures

• Advisory Board/Consulting:
  • Roche Diagnostics, Accelerate Diagnostics

• Speaker Fee:
  • Bio-Rad Diagnostics

• Research funding:
  • Ortho-Clinical Diagnostics

Laboratory Diagnostic Approaches for Lyme Disease
A New Decade, A New Algorithm

• The Standard Two-Tiered Testing Algorithm (STTTA) has been in use since 1994

• STTTA suffers from multiple limitations
  • Low sensitivity (~35%-60%) during acute disease
    • Primarily due to limited immunoblot sensitivity
  • Challenges with immunoblot result interpretation
    • Banding patterns and specificity concerns

• Best option at that time…and for the last 25 years

• July 30, 2019
  • FDA cleared 4 EIAs from Zeus Scientific for use in a Modified Two-Tiered Testing Algorithm (MTTTA)
  • Historic event in Lyme disease diagnostics!
The Modified Two-Tiered Testing Algorithm

Not one, but two versions available!

• Biggest difference between the STTTA and MTTTA?
  • No more blots!!

• MTTTA is entirely EIA-based
  • 1st and 2nd tier EIAs differ in the B. burgdorferi antigens used

  • Tier 1:
    • VlsE/pepC10 antigen
    • Total IgM/IgG

  • Tier 2:
    • Whole Cell Sonicate (WCS) material
    • IgM and IgG separately, or Total IgM/IgG

The MTTTA: How much better than the STTTA is it?2-4

<table>
<thead>
<tr>
<th>Stage of Lyme Disease</th>
<th>% Positive by the STTTA</th>
<th>% Positive by a 2-EIA MTTTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema migrans (EM)</td>
<td>42%-58%*</td>
<td>53%-67%*</td>
</tr>
<tr>
<td>Early Disseminated Lyme</td>
<td>73%-95%</td>
<td>85%-100%</td>
</tr>
<tr>
<td>Late Lyme</td>
<td>97%-100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

• MTTTA significantly more sensitive vs. the STTTA across studies and EIA combinations in patients with EM and overall
  • Equivalent sensitivity during later stages of Lyme disease

• False positivity rate remains unchanged with similar causes:
  • Mononucleosis, Syphilis, MS
Performance of the Zeus Scientific FDA-Cleared MTTTAs Clinical Trial Data

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late Lyme</td>
</tr>
<tr>
<td>STTTA</td>
<td>63.3%</td>
<td>100%</td>
</tr>
<tr>
<td>MTTTA-1 (3 EAs)</td>
<td>76.7%</td>
<td>100%</td>
</tr>
<tr>
<td>MTTTA-2 (2 EAs)</td>
<td>78.3%</td>
<td>100%</td>
</tr>
</tbody>
</table>

- Improved sensitivity during early stages of infection
- Similar sensitivity to STTTA during later stages of infection
- Overall similar specificity to STTTA
- …more assays will likely be cleared for MTTTA use in the near future!

Advantages and Disadvantages of using the MTTTA

**Advantages:**
- ↑ sensitivity during early disease
- Similar specificity to STTTA
- Ability to detect antibodies to other Lyme disease cause *Borrelia* spp.
- Potentially less expensive
- Ability for smaller laboratories to perform all stages of testing
  - Faster turnaround time
- Less confusion around result interpretation
  - No banding patterns to interpret!

**Disadvantages:**
- Sensitivity during early disease remains imperfect
  - Negative results do not r/o infection
- Inability to follow IgG antibody expansion
- Potential confusion between the multiple MTTTA options
- Similar to STTTA:
  - Cannot use to monitor response to therapy
  - Challenging to diagnose reinfection
**Resources**


THANK YOU!