Comparative Clinical Evaluation of the T2Bacteria Panel versus Blood Culture for the Diagnosis of Bacteremia


University of Pittsburgh, University of Alabama at Birmingham, Henry Ford Hospital, Ochsner Health System, Indiana University School of Medicine, Robert Wood Johnson University Hospital, Tampa General Hospital, Geisinger Health System, Weill Cornell Medicine of Cornell University, New York Presbyterian Hospital, Duke University, Alpert Medical School of Brown University
Disclosures

• This clinical trial was funded by T2 Biosystems
• T2 Biosystems provided assistance with the study design and compiled data from each institution in a central database.
  – The authors performed data and statistical analyses and prepared today presentation without assistance.
Background

• Bloodstream infections (BSIs) are associated with significant morbidity and mortality
  – Timely administration of appropriate antibiotics improves outcomes (Seymour, 2017; Kumar, 2006)
Background

• Bloodstream infections (BSIs) are associated with significant morbidity and mortality
  – Timely administration of appropriate antibiotics improves outcomes (Seymour, 2017; Kumar, 2006)

• Blood culture (BCx) is considered the gold standard for diagnosing BSI, but is limited by
  – Suboptimal sensitivity (Murray, 2014)
    • 10% in suspected bacteremia
    • 30% in febrile neutropenia
    • 35% in severe sepsis
    • 50% in septic shock
  – Slow turnaround time
    • Mean: 84 hours (23-199 hours)
Background

• Several nucleic acid amplification tests (NAATS) for detection of bacteria directly from blood have been developed.

• Given the poor sensitivity of BCx, it may be more accurate to use composite microbiologic and clinical criteria in evaluating the performance of these non-cultural diagnostic tests.
Background

• T2Bacteria Panel (T2B) is an automated, rapid, culture-independent diagnostic test that identifies microbes directly from whole blood
• T2B runs on a fully automated T2Dx Instrument
• Results available as early as 3.5 hours
Background

– T2B identifies 6 target organisms responsible for ≥50% of BSI
  • can detect bacteria at a density as low as 2 colony forming unit (CFU) per ml of whole blood

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>LoD (CFU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>3</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em></td>
<td>5</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>11</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>2</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>5</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>2</td>
</tr>
</tbody>
</table>
Goal

• To evaluate the performance of T2B for diagnosing BSI
Methods

• Prospective study with sample collections from Dec 2015 – August 2017
  – 11 centers throughout the US

• Inclusion criteria
  – Patients (18-95 years of age) with a diagnostic BCx ordered per standard of care

• Process:
  – Paired BCx and T2B blood drawn, with BCx always drawn first
Results

- Paired samples from 1,427 unique patients were obtained
- 6% (82) of BCx were positive
  - 47% (39) were due to 5 target T2B
  - No BSI due to A. baumannii recovered from BCx
- Mean time to BCx+: 72 hours (24 - 177 hours)
Sensitivity of T2B compared with BCx

<table>
<thead>
<tr>
<th>T2B Target</th>
<th>Sensitivity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>90% (35/39)</td>
<td>75-97%</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>91% (10/11)</td>
<td>62-98%</td>
</tr>
<tr>
<td><em>E. faecium</em></td>
<td>100% (1/1)</td>
<td>21-100%</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>100% (6/6)</td>
<td>61-100%</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>100% (5/5)</td>
<td>57-100%</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>81% (13/16)</td>
<td>57-100%</td>
</tr>
</tbody>
</table>

BCx+ for T2B targets
N=39

T2B+ match
N=35

T2B-
N=4
Sensitivity of T2B compared with BCx

<table>
<thead>
<tr>
<th>T2B Target</th>
<th>Sensitivity</th>
<th>False Negative Paired T2B Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>91% (10/11)</td>
<td>1</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>81% (13/16)</td>
<td>3</td>
</tr>
</tbody>
</table>

T2B retest using archived tubes

<table>
<thead>
<tr>
<th>Paired BCx Result</th>
<th>Paired T2B Result</th>
<th>Archived Sample T2B Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td><em>E. coli</em> NEGATIVE</td>
<td><em>E. coli</em> POSITIVE</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td><em>S. aureus</em> NEGATIVE</td>
<td><em>S. aureus</em> POSITIVE</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td><em>S. aureus</em> NEGATIVE</td>
<td><em>S. aureus</em> NEGATIVE</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td><em>S. aureus</em> NEGATIVE</td>
<td><em>S. aureus</em> NEGATIVE</td>
</tr>
</tbody>
</table>
Specificity of T2B compared with BCx

1,427 blood samples from unique patients

BCx+ for T2B targets (N=39)
- True T2B+ (N=35)

BCx- (N=1,388)
- BCx-/T2B+ (N=166)
- True T2B- (N=1,222)

Specificity = 88% if BCx was used as gold standard
## Composite Clinical/Microbiologic Criteria

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Clinical/Microbiologic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proven</strong></td>
<td>Paired BCx+ and T2B+ for same organism</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td>BCx-/T2B+ but with positive culture for T2B organism in 1) blood or 2) extra-blood site within 14 days of paired sample</td>
</tr>
<tr>
<td><strong>Possible</strong></td>
<td>BCx-/T2B+ associated with infectious syndromes that fit clinical scenario of T2B+ result, but cultures were either not performed or negative</td>
</tr>
</tbody>
</table>
Analysis of Discordant BCx- /T2B+

- Probable BSI: 39%
- Possible BSI: 21%
- T2B+ of unclear significance: 40%

52% (86/166) of samples were associated with antecedent antibiotics that potentially had activity against T2B identified organisms.
Analysis Discordant BCx-/T2B+

- Probable BSI: 39%
- Possible BSI: 21%
- T2B+ of unclear significance: 40%
- Other, Non-Paired BCx: 59%
- Extra-blood site culture, 41%
Analysis of Discordant BCx-/T2B+

- **Probable BSI** (39%)
- **Possible BSI** (21%)
- **T2B+ of unclear significance** (40%)
- **Known site of infection** (90%)
  - Lungs (36%)
  - Hepatobiliary (24%)
  - Intra-abdominal (15%)
  - Vascular catheter (9%)
  - Kidney (9%)
  - Bone/Soft tissue (6%)
- **Unclear site** (10%)
## Specificity analysis

<table>
<thead>
<tr>
<th>T2B Target Organism</th>
<th>Proven BSI</th>
<th>Proven and probable BSI</th>
<th>Proven, probable and possible BSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>88.0%</td>
<td>92.6%</td>
<td>95.2%</td>
</tr>
</tbody>
</table>

- Data suggest that T2B detected at least some BSIs that were missed due to the poor sensitivity of BCx.
Conclusions

• T2B demonstrates excellent performance in detecting BSI
  – Overall sensitivity: 90%
  – Detects 5 bacteria accounting for ≥50% of BSI
    • Use T2B in conjunction with BCx

• The specificity of T2B was:
  – 88% when BCx was used as gold standard comparator
  – >95% when composite clinical/microbiologic criteria was used
Conclusions

• Our data clearly demonstrate the limitations of BCx as gold standard for both diagnostic and study design purposes

• Among the patients with discordant BCx-/T2B+ samples, evidence of infection were identified in 60%
  – Had the same bacteria recovered from blood or non-blood site cultures
  – Had clinical pictures that fit infection syndromes caused by bacteria identified by T2B
  – 52% of patients received antecedent antibiotics
Conclusions

• Potential sources of T2B+ results of unclear significance:
  – Non-viable bacteria in patient’s blood
    • Transient bacteremia
    • Antibiotics
  – Contamination (environment, reagent, during blood drawn):
    • 88% of BCx-/T2B+ were negative upon retesting and sequencing (data not shown)
Conclusions

• Potential advantages of T2B over BCx
  – detect bacteremia several days before BCx (3-5 hours versus 2-3 days)
  – diagnose infections missed by BCx
    • Patients with antecedent antibiotics
    • Patients with extra-blood site infections
  – informed target of therapy within hours of blood drawn

• In the future, it is important to evaluate how to strategically incorporate this assay in clinical practice