T2Bacteria® Panel RUO Detects Clinically Important Infections Missed by Blood Culture

Summary findings from a retrospective study at Northwestern University Feinberg School of Medicine
The T2Bacteria Panel identifies five of the most deadly and prevalent bacteria species, including: *Escherichia coli; Klebsiella pneumoniae; Pseudomonas aeruginosa; Staphylococcus aureus; and Enterococcus faecium*. The Panel developed by T2 Biosystems provides species-specific results directly from whole blood, making results available within hours of patient presentation without waiting for blood culture-based results that can take one to five or more days.

In a retrospective study conducted by Chiagozie Pickens, MD, at the Northwestern University Feinberg School of Medicine and presented at the Association for Molecular Pathology (AMP) 2017 conference, T2Bacteria Panel RUO results were compared to cultures of blood, bronchial lavage (BAL), and urine samples in addition to the true infection status of the patient.

The study findings indicate that the T2Bacteria Panel RUO is able to detect clinically important infections more reliably than blood cultures, and that an early result from the T2Bacteria Panel RUO could enable clinicians to treat the source of infection faster. Further, a positive T2Bacteria Panel RUO result where the companion blood culture was negative correlated with infections that progressed, suggesting that T2Bacteria may serve as a positive marker of a more serious disease, indicating the need for more aggressive management—despite a negative blood culture.
Study Methodology

The retrospective study included 61 frozen whole-blood specimens previously collected from patients admitted to the medical intensive care unit in 2012 with suspected sepsis or septic shock.

- The study samples were collected immediately after blood culture bottles were filled and then stored at -80°C for future diagnostic testing.
- The sample identification and corresponding culture data was stored in a Northwestern database.
- Samples were sorted according to their corresponding culture results and screened for volume.
- Samples selected for inclusion in this retrospective study were removed from the freezer and thawed at room temperature for at least 30 minutes and then tested using the T2Bacteria Panel RUO on the T2Dx® Instrument.

Results

Northwestern University tested 61 patient samples with the T2Bacteria Panel RUO. The findings showed that the T2Bacteria Panel RUO detected more confirmed bacterial infections than blood culture.

There were 25 patients with confirmed infections as defined by a positive blood culture or BAL or urine culture that had a clinically relevant titer level above the threshold of 10,000 CFU/mL (Table 1).

- 40% were positive by blood culture
- 64% were positive by urine or BAL cultures
- 72% were positive by T2Bacteria Panel RUO

These data show that T2Bacteria not only detects bloodstream infections like blood culture, but also detects localized infections not detected by blood culture.

Table 1: Infected status of patient vs. blood culture, other culture, and T2Bacteria Panel RUO

<table>
<thead>
<tr>
<th>T2Bacteria Target Organism</th>
<th>Number of Confirmed* Infections</th>
<th>Blood Culture Positive (%)</th>
<th>Other Culture PPA (N pos/N total)</th>
<th>T2Bacteria PPA (N pos/ N total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. faecium</td>
<td>4</td>
<td>2 (50%)</td>
<td>2 (50%)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>S. aureus</td>
<td>9</td>
<td>6 (67%)</td>
<td>3 (33%)</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>2</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>3</td>
<td>0 (0%)</td>
<td>3 (100%)</td>
<td>2 (67%)</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>4</td>
<td>0 (0%)</td>
<td>4 (100%)</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>E. coli</td>
<td>3</td>
<td>1 (33%)</td>
<td>3 (100%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>Overall</td>
<td>25</td>
<td>10 (40%)</td>
<td>16 (64%)</td>
<td>18 (72%)</td>
</tr>
</tbody>
</table>

*Confirmed Infection defined as positive blood culture OR clinically relevant urine or BAL culture (e.g. >10,000 CFU)
Discussion
The discordant results between the T2Bacteria Panel RUO and blood culture were a focus of the data analysis for this study. The following discussion provides clarity around discordant results by identifying characteristics of the T2Bacteria Panel RUO that appear to explain the discrepancies.

T2Bacteria Panel RUO results are more sensitive than blood culture and unaffected by the presence of antibiotics.

- While culture is considered the gold standard for pathogen identification, it does have limitations such as the following:
  - Lengthy time to result
  - Antibiotics can limit bacteria growth
- Gram-positive growth can be suppressed by Gram-negative organisms in polymicrobial infections, resulting in the inability to culture

The T2Bacteria Panel RUO is powered by T2 Magnetic Resonance (T2MR) technology, which is unaffected by the presence of antibiotics.

The T2Bacteria Panel RUO helps distinguish between complicated and uncomplicated infections.

- For cases in the retrospective study that were not identified by blood culture, the T2Bacteria Panel RUO seemed to identify ineffectively treated infections and those that could have been better contained and cured.

The retrospective approach to this study provided an ideal opportunity for detailed case studies, comparing the results using the available standard of care at the time (culture on blood, urine and BAL samples) against more sensitive testing, the T2Bacteria Panel RUO, five years later. This comparison allows an analysis of how the use of the T2Bacteria Panel could have potentially changed clinical practice and outcomes.

Case Study
25-year-old female with cerebral palsy diagnosed with duodenal pneumatosis
Patient was admitted to the hospital for gastrointestinal (GI) issues and started on empiric vancomycin and Zosyn.

- **Day 8**: The patient developed tachypnea and hypoxia and was diagnosed with aspiration pneumonia. Patient’s respiratory culture grew 15,000 CFU/mL *Pseudomonas aeruginosa* and 1,000 CFU/mL *Klebsiella pneumoniae*, both pan-sensitive, so she was appropriately treated.
  - The T2Bacteria Panel RUO result from blood drawn on day 8 was negative
  - Blood culture drawn on day 8 was negative.
- **Day 35**: The patient was discharged after prolonged GI complications.

**Analysis**: The negative T2Bacteria Panel RUO result most likely indicates an appropriately managed infection in the lung that was contained and did not progress, and that did not require a change in antibiotic treatment.
Case Study

73-year-old female with lymphoma in hospital on chemotherapy and diagnosed with pneumonia and septic shock

- **Day 1**: The blood culture tested positive for *Pseudomonas aeruginosa*. The patient was given cefepime and ciprofloxacin.
  - Subsequent blood cultures were negative, but the patient deteriorated, developed septic shock, and required intubation.
- **Day 17**: The patient’s bronchoalveolar lavage (BAL) cultures showed 100 CFU/mL Achromobacter and 100 CFU/mL *Pseudomonas aeruginosa*, below the threshold for clinically relevant titer level of 10,000 CFU/mL set by the laboratory. The results were not alarming, and the antibiotic regimen was not changed.
  - T2Bacteria Panel RUO identified *Pseudomonas aeruginosa* from blood drawn on day 17.
  - Blood culture drawn on day 17 was negative.
- **Day 20**: The BAL cultures grew significantly to 100,000 CFU/mL Achromobacter and 100,000 CFU/mL *Pseudomonas aeruginosa*.
- **Day 23**: The patient expired under palliative care.

Analysis: The T2Bacteria Panel RUO’s identification of *Pseudomonas aeruginosa* 3 days earlier than the BAL cultures and in the absence of positive blood cultures likely indicates the progression of an infection due to both ineffective source control and inappropriate antimicrobial therapy. The T2Bacteria Panel RUO result may have led to faster targeted therapy, such as the addition of an aminoglycoside to better treat this patient’s septic shock, potentially impacting the outcome.

(Discussion continued)

- In many of the cases in which the T2Bacteria Panel RUO was negative along with blood culture, respiratory cultures had a low rate of growth (<15,000 CFU/mL), indicating an appropriately managed and contained infection that had not disseminated into the bloodstream.
- In cases where the T2Bacteria Panel RUO and respiratory cultures were positive but blood culture was negative, it could be an indication of poor antibiotic management of an infection with a higher colony count that had disseminated into the bloodstream at levels not detectable by blood culture.

Implications

The results of this retrospective study indicate the promising potential for use of the T2Bacteria Panel. In addition, the T2Bacteria Panel RUO appears to have detection advantages over blood culture, the current standard of care diagnostic for bacteremia.

The T2Bacteria Panel RUO performance characteristics indicate the following clinical impact:

- Positive T2Bacteria results may add timely information for treating critically ill patients with negative cultures and suspected sepsis or septic shock;
- Positive T2Bacteria results may be a marker of more serious disease in patients with known infections (e.g., pneumonia, UTI) but negative blood cultures;
- Persistently positive T2Bacteria results may indicate poor source control or ineffective antibiotics; and
- T2Bacteria positive results may prompt consideration of more targeted antibiotic therapy.
Conclusion

Rapid detection and identification of sepsis-causing pathogens are critical for optimizing antimicrobial therapy to improve patient survival and substantially reduce healthcare costs. In this study, the T2Bacteria Panel RUO detected infections faster than blood culture and identified more infections than blood culture. In addition, a positive T2Bacteria Panel result may serve as a positive marker of a more serious disease, suggesting the need for more aggressive management—despite a negative blood culture. These results indicate that the T2Bacteria Panel may enable patients with infections to receive early targeted therapy, thereby having a significant impact on patient outcomes.

Detailed case studies identified the multiple situations where the T2Bacteria Panel could impact clinical decision-making by helping get patients on the right therapy faster or confirming that an infection is being effectively treated.

The T2Bacteria Panel shows promise for broad application for patients suspected of an infection in the emergency department and ICU, and suspected sepsis patients throughout the hospital. The ability to access clinically relevant results within hours offers an opportunity to improve patient outcomes and the quality of care.

Watch the complete AMP presentation at http://info.t2biosystems.com/amp17

1. Dr. Pickens is the Ruth L. Kirschstein National Research Service Award Research Fellow, Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL.