Blood culture-independent rapid diagnostic technology for improvement of time to bacterial species ID and earlier targeted antibiotic therapy.

Oscar Guzman[1], Sandy Estrada[1], Jessica Clark[1], Dina Besece[1], Christopher Voigt[2], Deborah Ashcraft[2], George Pankey[2] ,Suzane Silbert[3], Raymond H. Widen[3]

[1]T2 Biosystems, Lexington, MA, USA [2]Ochsner Medical Center, New Orleans, LA, USA; [3]Tampa General Hospital, Tampa, FL, USA;

Introduction

Early appropriate empirical antibiotic treatment is associated with reduced all-cause mortality in septic patients.[1,2] Delays in antibiotic administration have also been associated with increases in long-term, risk-adjusted sepsis mortality in patients admitted to the emergency department.[3] However misuse and overuse of antibiotics contributes to increased drug related toxicity, the selection of pathogenic organisms (such as Clostridium difficile) and the emergence of resistance[4]. Therefore a balance between prevention of infection related mortality and judicious antibiotic use should exist.

The Infectious Diseases Society of America/Society for Healthcare Epidemiology of America Stewardship Guidelines suggest various strategies to promote judicious use of antimicrobials in order to improve patient outcomes, control resistance and decrease healthcare expenses.[4,5] One strategy the guidelines suggest is antibiotic streamlining based on diagnostic results. Blood cultures, the gold standard in bacteremia diagnostics, however detect bacteremia in only about 50% of patients who are clinically suspected of having sepsis and that value may decrease after antibiotic administration.[6,7] In addition, blood culture and subsequent antimicrobial susceptibility testing, can take 2-5 days.[8] During this time no clinical data is available to support patient treatment, therefore patients are typically treated empirically. However, in a meta-analysis of 70 studies, empiric antibiotic therapy was not appropriate in 46.5% of patients, indicating that nearly half of infected patients are not treated optimally in the absence of diagnostic information. In addition, these patients showed over two times higher odds of death.[2]

Rapid diagnostic assays have been associated with improvements in time to appropriate antibiotic therapy by enhancing early identification of causative organisms.[9,10] Data supports bundling rapid diagnostic technology and antimicrobial stewardship programs to reduce antibiotic utilization and improve empirical therapy and time to de-escalation.

Research Question

- The T2Bacteria Panel is an FDA and CE Mark cleared and blood culture-independent assay for detection of bacteremia due to the most common ESKAPE pathogens: *Escherichia coli, Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, and provides species identification within 3 to 5 hours after blood culture.
- In this study, we hypothesize that the T2Bacteria Panel, a direct-from-whole blood diagnostic assay, has the potential to provide accurate and timely diagnosis of bacteremia, which might support the direct therapeutic management of BSI patients in the emergency department.

Methods

As part of the prospective, non-interventional T2Bacteria Panel clinical study, a subset of ED patients were enrolled from Ochsner Medical Center (New Orleans, LA) and Tampa General Hospital (Tampa, FL). The study was approved by the review boards of both institutions.

Inclusion Criteria

- Patients ≥ 18 years old with blood culture ordered per standard of care

Exclusion Criteria

- Patients who could not provide consent
- Any subject that was previously enrolled in the study (i.e., subjects were unique and had exactly one result)
- Patients that did not have sufficient blood collected for T2 testing (at least one tube ≥3 mL)

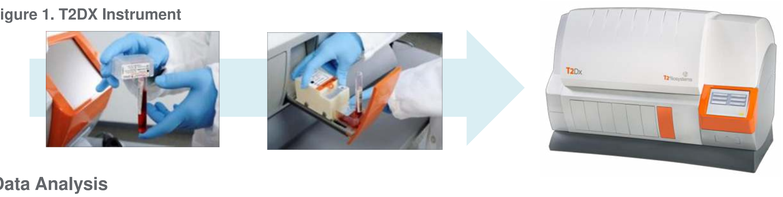
Blood Collection

Two blood cultures (BC) bottles with 5 to 10 mL of blood were drawn first.

Immediately following, three K2EDTA vacutainers with 3 to 4 mL of blood from the same line were collected for T2Bacteria testing.

The T2 vacutainers were then either run within 72 hrs. or frozen and run months later on the FDA cleared T2Dx instrument, a fully automated system with minimal hands on time (Figure 1). Only 1 of the 3 T2 vacutainers was used for performance evaluation.

Figure 1. T2DX Instrument



Data Analysis

- Samples were analyzed for bacterial growth using both methods and both positive percent agreement (PPA) and negative percent agreement (NPA) were calculated for each species.
- T2Bacteria results were compared against: (i) the "matched" blood culture drawn concurrently with T2Bacteria, (ii) other blood cultures within ±14 days of the T2 draw, (iii) other cultures in non-blood matrices within ±14 days of the T2 draw, and (iv) against a Sanger sequencing method.
- Time required to species identification were also compared.
- This was a non-interventional study and thus we reviewed patient history to assess potential impact of the T2Bacteria result.
- Data were retrospectively analyzed for opportunities for antimicrobial escalation or de-escalation. Opportunities for antimicrobial stewardship intervention were defined as:
  - Escalation of therapy including initiation of effective antimicrobial therapy (based on antibiogram and spectrum of activity of active antibiotic at time of T2 result)
- De-escalation of therapy
  - Discontinue MRSA coverage when S. aureus negative
  - Discontinue/narrow anti-Pa coverage when Pa negative
  - Discontinue gram negative coverage when S. aureus positive

Results

Figure 2. Positive percent agreement (PPA) and negative percent agreement (NPA) of the T2Bacteria Panel against matched blood culture

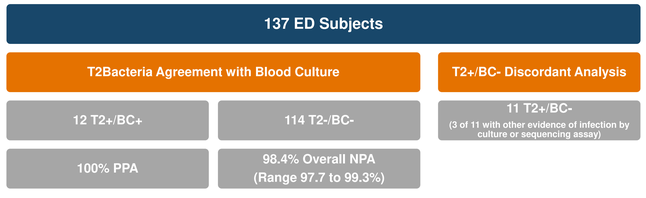
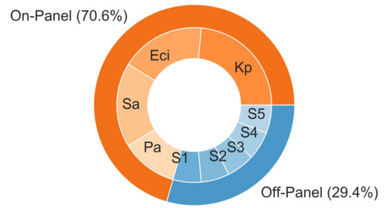


Figure 3. T2Bacteria panel coverage of blood culture positive species



- Total of n = 17 positive blood cultures from the matched T2/BC draws
- 70.6% (12/17) were species on the T2Bacteria Panel, most common were *K. pneumoniae*, *E. coli*, and *S. aureus*
- Remaining 29.4% (5/17) were off-panel: Group A beta-hemolytic *Streptococcus*, *C. freundii*, *E. faecalis*, *S. anginosus*, and *S. schleiferi*

Time to species ID, blood culture vs. T2Bacteria

- Difference in mean time to ID between blood culture and T2Bacteria was 66.1 hrs. (Table 1)
- When considering only species on the T2Bacteria Panel, the mean time difference was 56.6 hrs. This difference was significant with either all BC species or only species on the T2Bacteria Panel ($p < 0.001$).

Table 1: Comparison of T2Bacteria Panel and blood culture time to result

	T2Bacteria Panel Result mean ± SD	Blood Culture Result mean ± SD	Difference (hrs)	P-value
Time to species identification (hrs)	6.1 ± 1.9	72.2 ± 31	66.1	<0.001
Time to final negative (hrs)	6.1 ± 1.9	124.6 ± 4.4	118.5	<0.001

Potential impact of T2Bacteria results on patient care

- A total of 29 potential opportunities for antimicrobial stewardship intervention were identified for the 23 patients with a positive T2 result
- 43% (10/23) of patients with positive T2 results had opportunity for earlier escalation of antibiotics/initiation of effective therapy based on institutional antibiograms
- 19 opportunities for S. aureus and P. aeruginosa de-escalation were identified

Table 2: Patient examples of the potential for impact of positive and negative T2Bacteria results

26-091	**K. pneumoniae T2+/BC-** (evidence of infection: urine cx+)	Intervention Opportunity: 1. Initiate effective abx therapy
26-018	**P. aeruginosa T2+/BC+** (36.6 hr difference in time to species ID)	Intervention Opportunity: 1. Escalate anti-Pa abx coverage 2. De-escalate anti-MRSA therapy
25-057	**E. faecium T2+/BC-** (evidence of infection by sequencing assay)	Intervention Opportunity: 1. Initiate effective abx therapy
25-034	**K. pneumoniae T2+/BC+** (50 hr difference in time to species ID)	Intervention Opportunity: 1. Initiate effective abx therapy 2. De-escalate anti-MRSA therapy

Conclusions

- T2Bacteria provides rapid and sensitive detection of bloodstream infections caused by the majority of concerning pathogens most commonly identified in ED patients
- The T2Bacteria assay can be a useful antimicrobial stewardship tool that has the potential to impact the care of patients, including reduction in time to effective therapy and antimicrobial streamlining.

Disclosures

OG, SE, JC and DB are employees of T2 Biosystems, Inc, the manufacturer of the T2Bacteria Panel.

References

1. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589-96. Epub 2006/04/21.
2. Paul M, Shani V, Muchtar E, et al. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother. 2010;54(11):4851-63. Epub 2010/08/25.
3. Peltan ID, Brown SM, Bledsoe JR et al. ED Door-to-Antibiotic Time and Long-term Mortality in Sepsis. Chest. 2019 Feb 16. pii: S0012-3692(19)30157-6. doi: 10.1016/j.chest.2019.02.008. [Epub ahead of print]
4. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007; 44:159–77.
5. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10):e51–e77.
6. Brun-Buisson C, Doyon F, Carlet J, et al. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. JAMA. 1995;274(12):968-74.
7. Grace CJ, Lieberman J, Pierce K, et al. Usefulness of Blood Culture for Hospitalized Patients Who Are Receiving Antibiotic Therapy. Clin Infect Dis. 2001; 32 (11):1651–1655.
8. Doern GV, Brueggemann AB, Dunne WM, et al. Four-day incubation period for blood culture bottles processed with the Difco ESP blood culture system. J Clin Microbiol. 1997 May;35(5):1290-2.
9. Buehler SS, Madison B, Snyder SR, et al. Effectiveness of Practices To Increase Timeliness of Providing Targeted Therapy for Inpatients with Bloodstream Infections: a Laboratory Medicine Best Practices Systematic Review and Meta-analysis. Clin Microbiol Rev. 2016 Jan;29(1):59-103.
10. Bookstaver PB, Nimmich EB, Smith TJ, 3rd, et al. Cumulative Effect of an Antimicrobial Stewardship and Rapid Diagnostic Testing Bundle on Early Streamlining of Antimicrobial Therapy in Gram-Negative Bloodstream Infections. Antimicrob Agents Chemother 2017; 61(9).