Impact of Blood Culture Independent Rapid Diagnostics and Early Identification of Sepsis Causing Pathogens

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Background

Sepsis contributes between one-third to one-half of all hospital deaths in the USA and accounts for a significant part of the overall costs of healthcare. The incidence of severe sepsis and septic shock in developed countries has been reposted as increasing steadily over recent decades.[1]

A study by Pruinelli, L et al., demonstrated that no delay is safe for patients with severe sepsis and septic shock. The longer the delay, the more harm. For example, a delay of 50 minutes, increases the patient's risk of mortality by 0.028 (CI = 0.004, 0.058) suggesting that a delay of 50 minutes significantly increases the risk of mortality.[2]

Prompt treatment with targeted antibiotics affects both the financial impact and the clinical outcome of blood stream infection (BSI). Every hour gained in initiating the correct antimicrobial therapy significantly increases the probability of patient survival. Although many infections can be detected after 24 to 48 hours, it may take up to 5 days of incubations to capture most slow-growing bacteria and fungi associated with BSI, and the antibiotic susceptibility determination require an additional 6 to 24 hours. Therefore, a targeted therapy is usually initiated after several days of empirical treatment with broad-spectrum antibiotics. The empiric use of antibiotics results in a 15 to 30% rate of inappropriate treatment, which is associated with a 2 to 5-fold increase in the mortality risk of septic patients and a contributing factors in the recent increases in antimicrobial resistance. [3-6]

T2MR Technology Method

T2 Magnetic Resonance (T2MR) technology from T2Biosystems employs culture-independent testing, providing species identification directly from whole blood samples in 3 to 5 hours without the wait for a positive blood culture.

T2Candida and T2Bacteria Panels are the only FDA cleared, commercially available assays for direct-from-blood detection of *Candida* and bacterial species most commonly implicated in BSI that progress to sepsis.

Figure 1. T2DX Workflow

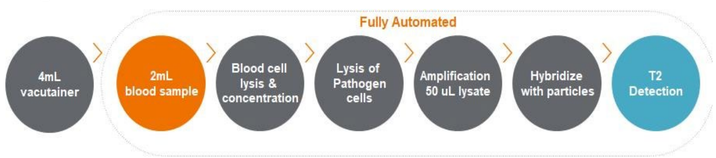


Figure 2. T2Biosystems FDA Cleared Assays

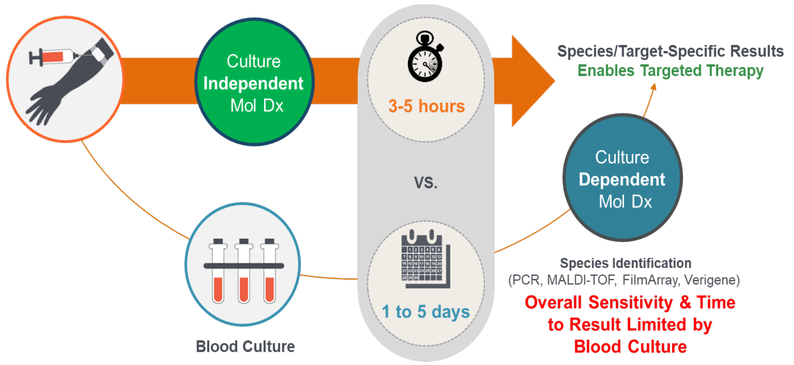
T2Candida® Panel	T2Bacteria® Panel
Sensitivity: 91%[8] Specificity: 99%[8]	Sensitivity: 90%[2] Specificity: 98%[2]
C. albicans *C. tropicalis* *C. parapsilosis* *C. krusei* *C. glabrata*	*E. faecium* *S. aureus* *K. pneumoniae* *P. aeruginosa* *E. coli*
FDA-cleared 1-3 CFU/mL LoD	FDA-cleared 2-11 CFU/mL LoD

T2Candida and T2Bacteria Panel Pathogens

- T2Candida Panel pathogens cover 90% of all *Candida* blood stream infections[9]
- T2Bacteria Panel pathogens cover 50%-70% of all bacterial blood stream infections[8,10] and ~90% of ESKAPE pathogens.[11]
- ESKAPE pathogens are concerning due to their ability to "escape" and survive antibiotic therapy and are associated with increased morbidity and mortality.[12]

Impact on Lab Results

Figure 3. Culture-Independent Molecular Diagnostic vs Blood Culture Workflow



Faster Time to Species Identification

Table 1: Comparison of T2Bacteria and T2Candida Panels and Blood Culture Time to Result

	Positive Results	T2Candida Panel (hrs.)	Blood Culture (hrs.)	Differenc (hrs.)
Mylonakis et al., 2015[7]	Time to Species ID [mean ±SD]	4.4 ± 1	129.9 ± 26.3	103.6
Wilson et al., 2017[13]	Time to Species ID [median (IQR)] ‡	11 (6, 23)	36 (25, 46)	25
Nguyen et al., 2019[8]	Time to Species ID [mean ± SD]	3.61 ± 0.2 to 7.70 ± 1.38†	71.7 ± 39.3 (with MALDI-TOF or VITEK2)	68.09
De Angelis et al., 2018[14]	Time to Species ID [mean ± SD]	5.5 ± 1.4	25.2 ± 15.2 (with MALDI-TOF and Film Array BCID)	19.7

†Depending on how many samples were loaded for testing
‡Data presented as median (25th percentile-75th percentile)

Improved Diagnosis of Bloodstream Infection

Table 2: T2Candida and T2Bacteria Panels Detect More On-Panel Pathogens Compared to Blood Culture

T2Candida

Clancy et al., 2019[15]

- 14-center, prospective trial of hospitalized patients with candidemia (n=152)
- T2Candida was significantly more likely to be positive that companion blood cultures (cBCs) (45% vs 24%; P<0.0001)
- Prior antifungal therapy, neutropenia, and *C. albicans* candidemia were independently associated with T2Candida positivity and T2+/cBC- results (P values <0.05)

Wilson et al., 2017[13]

- 1789 bed, 4 hospital health system; pre-post-test quasi experimental study of hospitalized patients with candidemia (n=161)
- Candida species were identified in 57% (50/87) patients in the pre-T2Candida group compared to 93% (69/74) in the post-T2Candida group (p<0.001)
- Median time to appropriate antifungal therapy was reduced from 39 hours to 22 hours (p=0.003)
- Candida eye involvement was diagnosed in 30% (16/53) in the pre-T2Candida group vs. 12% (4/49) of patients in the post-T2Candida group (P=0.028)

T2Bacteria

De Angelis et al., 2018[14]

- 1200-bed tertiary-care teaching hospital; prospective observational evaluation of Emergency Department, Infectious Diseases Unit, and ICU patients (n=140samples)
- T2Bacteria detected 20 positive cases missed by blood culture
- T2+/BC- results significantly more likely in patients receiving antibiotics (p<0.001)
- 66.7% of infected patients missed by BC and detected by T2Bacteria were being inappropriately treated at time of T2Bacteria result

Kalligeros et al., 2020[16]

- Retrospective evaluation of a subset of patients from the T2Bacteria pivotal trial with discordant T2+/BC- results (n=20 patients, 21 results)
- 52.5% (11/20) of patients had probable BSI (supported by same organism isolated by at least 1 clinical culture); 19.6% (4/20) possible BSI; 28.5% (6/20) presumptive false-positive
- 80% (16/20) of patients received active antibiotic within 48 hr of sample
- 14/20 patients were diagnosed with closed-spaced or localized infection (pyelonephritis n=7; abscess n=4; pneumonia n=1; infected hematoma n=1; osteomyelitis n=1)

Impact on Patient Care Results

Table 3. T2Candida: Economic and Clinical Outcomes

Steuber et al., 2019[19]

- **Antifungal optimization** occurred in 54% of patients with antifungal orders at time of T2Candida (T2C) test
- Antifungal therapy was avoided in 60.4% of negative cases
- Patients with **negative T2C results had significantly fewer days of antifungal therapy** compared to those with positive results (4.9±6.3 vs 10±10 days, respectively; p=0.03)

Patch et al., 2018[20]

- **Faster time to appropriate therapy** post-T2C implementation (34 hours to 6 hours, p=0.00147)
- **Unnecessary antifungal therapy avoided** in 42.8% and discontinued after 1 dose in another 15.6% of patients with negative T2C results
- **Average length of stay per patient reduced** by 8 days
- Average net **antifungal savings** of ~$280 for every patient tested

Kenney et al., 2016[21]

- Study demonstrated $2.3MM in annual **hospital savings**
- **Reduced median ICU length of stay** per patient by 7 days (p=0.009)
- **Reduction in total length of stay** by 4 days/patient (p=0.164)
- 75% of T2C negative patients had **antifungals discontinued or deescalated**

Patel et al., 2016[22]

- 83% of patients who tested positive received appropriate therapy within 6 hours of the blood draw and 100% in under 9 hours
- Therapy was discontinued for 100% of the patients who tested negative

Table 4. T2Bacteria: Clinical Outcomes

Seitz et al., 2019[23]

- Prospective, single center study of newly admitted patients to Infectious Diseases department (n=44)
- T2Bacteria (T2B) detected more pathogens than blood culture (BC): 41% (9 of 22) vs 14% (3 of 22) of samples, respectively
- Faster time to species ID (difference of 59.3 hrs; p 0.01) **and faster time to targeted antibiotic therapy** (median 6.6 hrs T2B+BC vs 77.7 hrs BC alone)
- **Length of stay was shorter** in the T2B+BC group (10.6 days) vs BC alone group (13 days)

Horowitz et al., 2020[24]

- Prospective cohort analysis of Hematopoietic Stem Cell Transplantation patients with febrile neutropenia (n=39, 59 tests)
- 29 patients had **early de-escalation of empiric anti-pseudomonal therapy**
- Total of 124 days of anti-pseudomonal therapy saved; (5.2 days saved per patient)

Walsh et al., 2019[25]

- Prospective cohort analysis of Hematologic Malignancy/ HSCT patients (n=94)
- **Faster time to species ID** with T2Bacteria 3.7h vs 12.5h with standard blood culture methods (MALDI/BioFire), (*p*=0.002)
- T2Bacteria could have potentially influenced care and provided an **opportunity to place (T2+/BC-) patients on effective therapy faster** than with culture dependent methods

Voight et al., 2020[26]

- Retrospective evaluation of a subset of Emergency Department patients included in the T2Bacteria Pivotal Trial (n=137)
- **Faster time to species ID** with T2B (mean 56.6 hours faster) compared to BC
- **T2Bacteria detected 25% more pathogens** associated with infection than BC
- **T2Bacteria provided potential opportunity to influence therapy**; focus therapy (8 patients), reduce time to species ID (4 patients); reduce time to effective therapy (4 patients)

Conclusion

WHO WE ARE	WHAT WE DO	ENABLING CHANGES IN CLINICAL DECISIONS AND OUTCOMES	WHY WAIT DAYS FOR RESULTS?
T2 Biosystems offers an FDA-cleared diagnostic test for the detection of sepsis-causing bacterial and fungal pathogens, **directly from whole blood**	Species ID within **3-5 hours of first blood draw** enables timely therapy when patients need it most	Lab results are often available **before the second dose** of broad-spectrum antibiotics is delivered	The current blood culture-based standard of care provides **species ID results in 2-7 days**[1]

Disclosures

AA, DM, and EO, are employees of T2 Biosystems, Inc, the manufacturer of the T2Bacteria and T2Candida Panels.

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