Application of Rapid and Innovative Molecular Diagnostic Assays to Identify Sepsis-causing *Candida* Pathogens

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Background

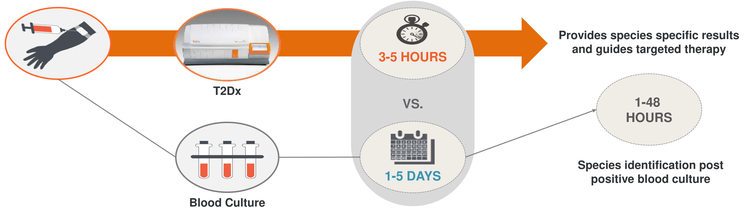
Bloodstream infections are a significant source of morbidity and mortality worldwide with *Candida* contributing to more than 90% of fungal bloodstream infections[1,2]. In fact, bloodstream infections due to *Candida* are classified as the fourth most common isolate in the United States and seventh most common in Europe[2,3]. Globally, the most common fungal disease among hospitalized patients is invasive candidiasis. These acute infections may lead to sepsis resulting in organ dysfunction and death[4].

The early diagnosis and administration of antimicrobial therapy can alleviate the mortality trends of this burdensome condition, thus improving patient outcomes. Majority of literature on bloodstream infections focus on bacteria pathogens with less attention to fungal etiologies[2]. The detection of fungal pathogens in bloodstream infections poses as a challenge as blood cultures have poor sensitivity and slow turnaround time[5]. Furthermore, administration of empiric antifungal therapy may hinder the detection of *Candida* in blood cultures and subject *Candida* negative patients to unnecessary empiric therapy which may contribute to antimicrobial resistance (AMR).

T2Candida® is a cartridge-based test that requires collection of samples directly from whole blood and employs T2 Magnetic Resonance (T2MR) technology. This FDA cleared panel is a rapid and nonculture-based test that provides results in 3 to 5 hours. These results that are highly sensitive (91%) and specific (99%) as compared to blood culture and detect pathogens with no interference from prior antimicrobial intake. This technology simplifies processes by eliminating steps such as extraction as well as purification of targets. This assay detects the five most common *Candida* species which include: *Candida albicans*, *Candida tropicalis*, *Candida parapsilosis*, *Candida glabrata* and *Candida krusei*. The application of a rapid and culture-independent test to detect *Candida* in whole blood samples may improve clinical outcomes and AMR by allowing the administration of earlier targeted therapy.

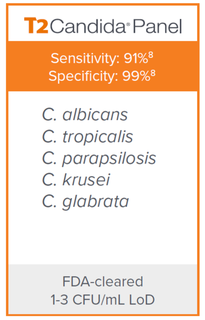
Figure 1: T2 Magnetic Resonance (T2MR) technology

Figure 2: T2 Workflow – Culture Independent vs. Culture Dependent tests



- T2Dx is a fully automated multiplex diagnostic instrument that provides species specific results in 3-5 hours without waiting for the result of a blood culture
- This instrument performs with no sample preparation and tests samples directly from whole blood

Figure 3: T2Candida® Panel



- T2Candida® Panel is FDA cleared and CE marked culture independent assay that detects *Candida* directly from whole blood
- Multiplex identification of 5 species from a single sample of whole blood
- This panel detects the five most common pathogens contributing to more than 90% of invasive candidiasis[8,14]
- This assay has a low Limit of Detection (LoD) of 1-3 CFU/mL for all five target species

Methods

A literature review was collated to examine the clinical impact of the T2Candida assay in detecting *Candida* in whole blood samples as compared to blood culture

Impact on Time to Results and Species Identification

Mylonakis et al., 2015[8]	
Study Design	• Prospective multicenter study conducted at 12 sites • Clinical trial to validate the sensitivity and specificity
Outcomes	• T2MR demonstrated overall sensitivity and specificity of 91% and 99% respectively. • Mean time to negative result was 4.2 ± 0.9 hours for T2MR and ≥120 hours for blood culture per institutional protocols • Mean time for detection and species identification was 4.4 ±1.0 hours for T2MR and 129.9 ± 26.3 hours for blood cultures

Quirino et al., 2022[9]	
Study Design	• Retrospective, observational, matched case–control study • T2Candida (n=35) in Italy
Outcomes	• **Concordance of 91.4%** for T2 and blood culture • Inappropriate empiric therapy was administered less frequently in cases than in comparators **(5.5% vs. 38.8%)**

Giannella et al., 2021[10]	
Study Design	• Meta-analysis of 14 controlled Studies
Outcomes	• Time to Detection with T2MR: **81 hours** faster (p <0.001) • Time to Species ID with T2MR: **77 hours** faster (p <0.001) • Patients testing positive on T2MR: received targeted antimicrobial therapy **42 hours** faster (p <0.001) • Patients testing negative on T2MR: de-escalated from empirical therapy **7 hours** faster (p =0.02) • Length of Stay: intensive care stay was **5 days** shorter (p=0.03), and length of hospital stay was **4.8 days** shorter (p=0.04)

Impact on Antifungal Stewardship

Steuber et al., 2020[11]	
Study Design	• Retrospective, single-center, observational study • n=628 in United States
Outcomes	• Antifungal therapy was optimized in **54%** of patients with antifungal orders at time of T2Candida® test • Antifungal therapy was avoided in **60.4%** of negative cases • Patients with a negative T2Candida® had **fewer days** of antifungal therapy compared to positive tests (4.9±6.3 vs 10±10 days, respectively)

Patch et al., 2018[12]	
Study Design	• Two-phase retrospective analysis in United States
Outcomes	• Time to appropriate therapy was faster after T2Candida test (**6 hours** vs 34 hours) • Average antifungal savings of ~**$280** for per patient tested • Antifungal therapy was avoided in **42.8%** and discontinued after a single dose in 15.6% patients

Francois et al., 2021[13]	
Study Design	• Retrospective, observational study • n=210 in the France
Outcome	• Average turnaround time T2Candida vs Blood Culture: 13 h (5-10 h) versus 34h (21-109) (initial blood culture) and 4 days (final blood culture) • In 6 of 13 cases, positivity of T2Candida panel preceded blood culture by 1-5 days

Conclusion

T2Candida is a novel and innovative test that accurately identifies the five most common pathogens contributing to more than 90% of invasive candidiasis. This technology is highly sensitive and specific for detecting *Candida* causing bloodstream infections that may otherwise be missed by blood culture. The utilization of this culture independent rapid molecular test can provide opportunities for antifungal stewardship by preventing the administration of unnecessary empiric therapy, optimizing appropriate antifungal therapy sooner, and aid in curbing the spread of AMR.

Disclosures

SV and AA are employees of T2 Biosystems, Inc, the manufacturer of the T2Candida Panel

References

1. Leal HF, et al. Bloodstream infections caused by multidrug-resistant gram-negative bacteria: epidemiological, clinical and microbiological features. BMC Infect Dis. 2019;19(1):609. Published 2019 Jul 11. doi:10.1186/s12879-019-4265-z
2. Kotey FC, el al. Candida Bloodstream Infections: Changes in Epidemiology and Increase in Drug Resistance. Infect Dis (Auckl). 2021;14:11786337211026927. Published 2021 Jun 24. doi:10.1177/11786337211026927
3. Delaloye J, el al. Invasive candidi`asis as a cause of sepsis in the critically ill patient. Virulence. 2014;5(1):161-169. doi:10.4161/viru.26187
4. Vincent JL. The Clinical Challenge of Sepsis Identification and Monitoring. PLoS Med. 2016;13(5):e1002022. Published 2016 May 17. doi:10.1371/journal.pmed.1002022
5. Clancy CJ, et al. Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin Infect Dis. 2013;56(9):1284-1292. doi:10.1093/cid/cit006
6. Boucher HW et al. Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America. Clinical Infectious Diseases 2009; 48:1–12
7. Zeng ZR, et al. Surveillance study of the prevalence, species distribution, antifungal susceptibility, risk factors and mortality of invasive candidiasis in a tertiary teaching hospital in Southwest China. BMC Infect Dis. 2019;19(1):939. Published 2019 Nov 7. doi:10.1186/s12879-019-4588-9
8. Mylonakis E, et al. T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. Clin Infect Dis. 2015 Mar 15;60(6):892-9
9. Quirino A, et al. Role of the T2Dx magnetic resonance assay in patients with suspected bloodstream infection: a single-centre real-world experience. BMC Infect Dis. 2022;22(1):113. Published 2022 Feb 1. doi:10.1186/s12879-022-07096-w
10. Giannella M, et al. Antimicrobial and resource utilization with T2 magnetic resonance for rapid diagnosis of bloodstream infections: systematic review with meta-analysis of controlled studies. Expert Rev Med Devices. 2021;18(5):473-482. doi:10.1080/17434440.2021.1919508
11. Steuber T, et al. Utilization and impact of a rapid Candida panel on antifungal stewardship program within a large community hospital. Diagnostic Microbiology and Infectious Disease 2020; 97
12. Patch M, et al. Impact of rapid, culture-independent diagnosis of candidaemia and invasive candidiasis in a community health system. J Antimicrob Chemother 2018; 73:4, iv27-iv30
13. Francois N et al. Preliminary evaluation of T2 Candida Panel for the diagnosis of invasive candidiasis in critically ill patients. Poster presented at: ECCMID July 2021; online
14. Pappas PG, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1-e50. doi:10.1093/cid/civ933