T2Candida® Panel

Antimicrobial Stewardship Implications

Review of current published data on antifungal stewardship with use of the T2Candida Panel

WHITE PAPER

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Key Points

- ***Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis, and Candida krusei* cause >90% of invasive candidiasis infections (ICI)[1].**
- **Immunocompromised individuals are the most at risk for ICIs.**
- **Morbidity due to IC ranges anywhere from 30-81%[2-6].**
  - » Early and effective use of antifungal therapy has been documented as an important strategy to improve survival, however, has also lead to overuse of antifungals in certain patients.
- **Antifungal stewardship faces challenges compared to antimicrobial stewardship.**
  - » Challenges such as the lack of reliable rapid diagnostic tests that can aid in the prompt detection; and assistance in decreasing overuse of antifungal therapy in patients.
- **Several peer reviewed clinical studies and posters have been published to demonstrate clinical utility of the T2Candida Panel aiding in antifungal stewardship initiatives.**
  - » All studies identified faster identification of *Candida spp.* as well as a faster TAT of positive and negative patient blood samples when compared to BC.
  - » Numerous studies demonstrated that avoidance or discontinuation of antifungal therapy can be achieved with the T2Candida Panels negative results.
  - » A number of studies identified a reduction of LOS in their floor and ICU patients when utilizing the T2Candida Panel.

Background

Fungi can cause a broad spectrum of host responses including infection and sepsis leading to septic shock and death. Fungal bloodstream infections, primarily those caused by *Candida* species, are the fourth most common bloodstream infection in the United States and seventh in a nationwide survey of 17 hospitals in Switzerland[7,8]. There are many *Candida* species that have been identified to cause infections in humans, however, >90% of invasive candidiasis (IC) are caused by 5 pathogens, *Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis, and Candida krusei*[1].

Epidemiology of Invasive Candidiasis

Immunocompromised hosts such as transplant and oncology patients, and those undergoing abdominal surgery are the primary hosts for IC with a prevalence ranging from 2-11%[3,10]. Due to the rapidly expanding population of immunocompromised patients, the amount of IC has increased considerably. *Candida* is the most frequent cause of fungal sepsis or fungal septic shock in nosocomial blood stream infections (BSI's) particularly in the intensive care units (ICUs)[11]. A recent registry study noted that the proportion of non-*Candida albicans* infections was increasing and was higher than that caused by *Candida albicans* infections (57.9 vs. 42.1%, respectively)[2]. Additionally, several retrospective studies involving patients with a variety of diseases with candidemia had revealed significant morbidity and crude and attributable mortality rates of anywhere from 30%–81% and 5%–71%, respectively[2-6].

Administration of early and effective antifungal therapy has been documented as an important strategy to improve survival of candidemia[5,12]. One study verified that patients who received antifungal therapy less than 24 hours from candidemia onset had a 15.4% mortality rate versus patients who were delayed greater than 72 hours had a 41% mortality rate[5]. Additional studies have echoed that early antifungal therapy is an independent predictor of survival for critically ill patients with septic shock due to candidemia[11]. However, empiric therapy does not guarantee appropriate therapy for affected candidemic patients.

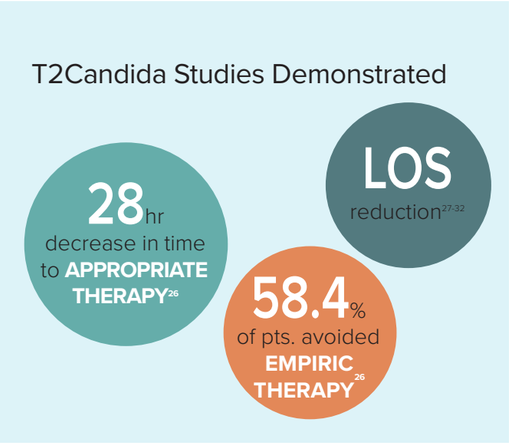
Increased use of empiric antifungals in this population has been shown to impact blood culture sensitivity in infected patients and also expose non-infected patients to unnecessary antifungal therapy contributing to adverse drug effects and likely contributing to antifungal resistance[13,14]. Blood cultures remain the gold standard for detection of candidemia, however, are limited for diagnosing IC due to their poor sensitivity and slow time to growth and species identification. It has been acknowledged that blood cultures may miss approximately 50% of episodes of invasive candidiasis[15]. Due to these limitations of traditional diagnostic methods, early use of antifungals may continue to be delayed.

T2 Rapid Diagnostics in Candida BSI's and Antifungal Stewardship

Antimicrobial stewardship is comprised of a multidisciplinary group that performs activities that evaluate and augment antimicrobial use to improve clinical outcomes and minimize consequences of inappropriate antimicrobials. Antimicrobial stewardship programs (ASP) have traditionally focused on the optimal use of antibacterial agents, with much less emphasis on the optimal use of antifungals. Recently, there has been a significant shift in focus for optimal use of antifungals. The high mortality and emergence of resistance in invasive infections due to *Candida* species presents a critical opportunity for antifungal stewardship[16]. Antifungal stewardship faces additional challenges compared to antimicrobial stewardship due to the lack of reliable rapid diagnostic tests that can aid in the prompt detection and lead to overuse of antifungals[17]. As stated previously, blood cultures remain the gold standard for diagnosis, but many fungi do not grow in blood culture media and have insufficient diagnostic accuracy[18]. Fungal cultures can take days or weeks to detect growth, resulting in prolonged inappropriate or unnecessary antifungal therapy[19]. Additionally, IC is typically over suspected and underdiagnosed, which leads to both unnecessary empiric therapy in those patients without invasive infection and a lack of therapy in patients with infection[20,21]. One of the objectives of antifungal stewardship programs is to reduce empirical prescribing in clinical settings where the benefits of this approach are uncertain.

Rapid diagnostics combined with antimicrobial stewardship intervention have previously demonstrated improved antimicrobial use and reductions in mortality for patients with both bacterial and *Candida* BSIs[22,23]. The T2Candida Panel (T2Biosystems, Lexington, MA), is a novel cartridge-based rapid diagnostic assay that utilizes a polymerase chain reaction and nuclear magnetic resonance to identify the five most common *Candida* species which include: *Candida albicans, Candida tropicalis, Candida parapsilosis, Candida glabrata and Candida krusei*. A blood sample from the patient is obtained and put directly on the instrument. There is no need for a positive blood culture and results are obtained in approximately 3 to 5 hours with sensitivity and specificity of 91.1% and 99.4%, respectively[24].

Several peer reviewed clinical studies and posters have evaluated T2MR® diagnostic performance as well as clinical utility of the T2Candida Panel. A recent quasi-experimental multi-center study evaluated the impact of T2Candida Panel implementation with ASP review as compared with standard of care with routine blood cultures on clinical outcomes. Investigators found a difference in median time to appropriate antifungal therapy of 17 hours and no difference in LOS or mortality. However, there were a subset of patients that were diagnosed with an infection by the T2Candida Panel only and a difference in median time to appropriate antifungal therapy of 34 hours was identified. Subsequently, fewer cases of metastatic Candida ocular infections were noted among the patients in the post-T2MR implementation group possibly due to the fact that patients with infections diagnosed by T2Candida Panel were placed on earlier and effective therapy[25]. Although a mortality benefit was not observed due to the small sample size, alternate studies have associated mortality benefits with accelerated time to effective therapy among candidemia patients[5,12]. Another study conducted a two phase retrospective analysis was able to showcase a significant decrease in time to appropriate therapy in the post-T2Candida Panel implementation arm of 28 hours as well as avoidance of empirical antifungal therapy in 58.4% of the T2Candida Panel



negative patients[26]. Additional single center studies have been performed and were able to demonstrate that T2Candida Panel aided in timely administration of antifungal therapy as well as a length of stay (LOS) reduction in their patients, which led to significant cost savings for these institutions[27-32]. A brief outline of these studies can be found in Table 1.

Conclusion

The treatment of candidemia and IC have become increasingly complicated, mainly due to the increased numbers of immunocompromised patients and the lack of reliable rapid diagnostics for identification of Candida infections. Candidemia and IC are treated either preemptively, empirically, or prophylactically with antifungals because of the potential for serious complications as well as their high morbidity and mortality. With these known threats, rapid diagnostics paired with antifungal stewardship have been shown to provide guidance and improvements in the timeliness and overall use of antifungals, aid antifungal stewardship initiatives and show significant hospital savings in patients with candidemia. Identification of patients with or without candidemia within 3-5 hours using the T2Candida Panel has the potential to significantly improve patient outcomes and overall hospital expenditure.

Table 1. T2Candida Literature Specific to Antimicrobial Stewardship

Author/ Location	Objective(s)	Main Findings	Conclusion/Comments
Kenney R, et al. 2016. Detroit, MI, USA[28]	To improve early detections, treatment and outcomes of patients with Candida bloodstream infections (BSI) through implementation of T2Candida N= 120	• T2Candida showed significantly shorter time to candidemia diagnosis vs standard of care (6.5 hrs vs. 42.5 hrs; $p < 0.001$) • T2Candida showed a significantly reduced time to antifungal therapy vs. standard of care (6.5 hrs vs. 37 hrs; $p < 0.001$) • ICU length of stay after candidemia onset was reduced by 4 days when T2Candida was compared to standard of care (8 days vs 12 days, respectively) • Antifungal therapy was discontinued in 71% of the patients in response to the T2Candida; 4% of patients received narrowing of antifungal therapy (anidulafungin to fluconazole	• Implementation of T2Candida in combination with ASP intervention positively impacted patient management and outcomes • T2Candida reduced the time to diagnosis of candidemia and time to initiation of antifungal therapy • For patients with negative T2Candida results: antifungal therapy was rapidly discontinued after a single significant hospital cost savings were associated with the use of T2Candida (ROI of $1.99 million per year)
Patel F, et al. 2016. Riverside, CA, USA[27]	To evaluate antifungal prescribing practices after implementation of T2Candida N= 59	• Micafungin or fluconazole were ordered in response to positive T2Candida results • Of the 53 patients with negative T2Candida results, none had positive blood culture (BC) during their hospital admission • Clinicians were able to discontinue antifungal therapy in 8 of the 53 patients due to T2Candida results	• T2MR resulted in early detection and identification of *candida* BSI • ASP with T2MR resulted in optimal drug management of invasive *candida* BSI
Bhowmick T, et al. 2017. New Brunswick, NJ, USA[32]	To evaluate the effects of a negative T2Candida Panel result N=90	• Of the 40 patients on empiric therapy 10 (25%) were successfully discontinued due to the T2Canidda Panel. • The average time to discontinue therapy was 3 days (range 1-23 days)	T2Candida Panel led to a number of cessations of empirical antifungal therapy which can aid in the overuse of antifungal agents
Hayes J, et al. 2017. Birmingham, AL, USA [29]	To evaluate the influence of T2Candida Panel for rapid diagnosis of *Candida* infections on antifungal stewardship efforts N=214	• Time to initiation of antifungal therapy with the T2Candida Panel vs. no T2MR technology was 1.15 days vs. 2.02 days, respectively	A significant decrease in time to initiation of antifungal therapy was observed, minimizing potentially unnecessary empiric therapy in some patients
Wilson NM, et al. 2017. Detroit, MI, USA[25]	To evaluate the time to appropriate antifungal therapy, time to candidemia detection, and patient outcomes before and after T2MR. (37% patients Cancer/Transplant) N=161	• Median hospital length of stay after candidemia onset was 12 (8, 23 in the pre-T2MR group vs. 11 (7, 23) days in the post-T2MR group, P=0.816 • Median ICU length of stay after candidemia onset was 12 (4, 18) compared to 7 (4, 18) days, P=0.562 • Median ICU length of stay after candidemia onset was 12 (4, 18) compared to 7 (4, 18) days, P=0.562	T2MR is a valuable clinical tool to aid antifungal stewardship and to improve timely antifungal therapy for candidemia
Chaudhry Z, et al. 2018. Detroit, MI, USA[31]	To evaluate the impact of T2Candida Panel on Species Specific Anti-fungal De-escalation (patients with malignancy/ chemotherapy 13%, transplant 36% immunosuppression 40%) N=70	• T2Candida testing decreased turnaround time for results compared to BC from 3 days to less than 10 hours • For C. *albicans/tropicalis*, 50% of patients de-escalated to fluconazole in 4 days	• T2MR proved useful in promoting de-escalation from echinocandin to fluconazole therapy in fluconazole-susceptible species • Overall mortality unaffected despite rapid diagnostic driven de-escalation
Hassoun A, et al. 2018. Huntsville, AL, USA[33]	To evaluate the utility of the T2 Candida Panel in ICU and febrile neutropenic patients	• T2MR demonstrated a sensitivity similar to that found in published studies (94.4%) • 129/311 (41%) of patients were able to avoid antifungal therapy initiation based on negative T2 results • Negative T2Candida tests resulted in discontinuation of antifungal therapy in 71/311 (23%) of patients	• T2MR demonstrated greater sensitivity to *Candida* infection and produced results much quicker when compared to BCx • Authors concluded despite the test's rapid turnaround time and high sensitivity, time to de-escalation remains at 2 days suggesting variations in physicians' utilization of T2MR test results
Chaudhry Z, et al. 2019. Detroit, MI, USA[30]	To evaluate the utility of T2 as an antifungal stewardship tool to support the guidelines in transplant and non-transplant patients N=472	• Median turnaround time in hours of T2 was 6 hrs (±2) vs. 123hrs (±25) for final BC (-) result • 264/472 (56%) pts were initiated on empiric AF • In pts with T2 (-) result, AF was d/c within 7 days in 97% of patients; time to d/c of AF was 72 hr in 50% transplant pts and 48 hr in 50% of non-transplant pts respectively • No episodes of candidemia was diagnosed after d/c of AF • All-cause mortality was lower in transplant pts (14%) vs. non-transplant pts (34%) (P-value 0.0002 • Likelihood of mortality did not increase after d/c of AF (OR1.3, 95% CI 0.913 - 2.064)	This study demonstrated that T2 can promote discontinuation of empiric AF in transplant and non-transplant pts with suspected invasive candidiasis without a negative impact on clinical outcomes
Steuber TD, et al. 2020. Huntsville, AL, USA[34]	To describe and evaluate provider-utilization & patient-related factors that were associated with appropriate or inappropriate utilization of T2CP and AF therapy N=628	• Antifungal optimization occurred in 54% of patients who had antifungal orders at the time of T2Candida • Antifungal therapy was avoided in 60.4% of negative cases • Patients with negative T2CP had significantly fewer days of therapy compared to positive tests	Significant number of antimicrobial stewardship opportunities were identified with the use of T2Candida

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