T2Biosystems®

White Paper

T2Candida® for Critically Ill Patients: Clinical Outcomes, Testing and Treatment Algorithms

Contents

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 eighth most common ICU-acquired blood stream infection in Europe.[1,2] A *Candida* bloodstream infection, also called candidemia, is the most common form of invasive candidiasis (IC). There are many *Candida* species that have been identified to cause infections in humans; however, >90% of IC are caused by 5 pathogens, *Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis, and Candida krusei*.[3]

Epidemiology of Invasive Candidiasis

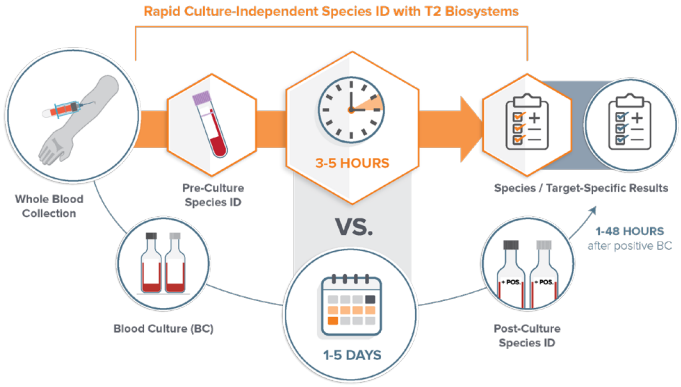
Immunocompromised hosts such as transplant and oncology patients and those undergoing abdominal surgery are the primary hosts for IC, with a prevalence ranging from 2-11%.[4,5] Due to the rapidly expanding population of immunocompromised patients, the amount of IC has increased considerably. *Candida* is the most frequent cause of fungal sepsis or fungal septic shock in nosocomial blood stream infections (BSIs), particularly in the intensive care units (ICUs)[6]. 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)[7]. Additionally, several retrospective studies involving patients with a variety of diseases with candidemia had revealed significant morbidity and crude, attributable mortality rates of anywhere from 30%–81% and 5%–71%, respectively.[7-11]

Administration of early and effective antifungal therapy has been documented as an important strategy to improve survival of candidemia.[10,12] 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 and had a 41% mortality rate.[10] Additional studies have echoed that early antifungal therapy is an independent predictor of survival for critically ill patients with septic shock due to candidemia.[6] 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] With the noted rise in antifungal use it is estimated that approximately 3% of all hospital admission and 8% of ICU admissions include antifungal administration.[15] This increased use of antifungals may result in as much as **10 billion per year** in antifungal cost in the US. Additionally, it is estimated that as much as **50% of this antifungal use is inappropriate**. Given these challenges, the need for diagnostics that provide rapid and sensitive results is paramount.

Diagnosis of Invasive Candidiasis

Blood cultures remain the gold standard for the detection of candidemia, however, are limited for diagnosing IC due to their poor sensitivity and slow time to growth and subsequent species identification. It has been acknowledged that blood cultures may miss approximately 50% of episodes of invasive candidiasis.[16] These limitations of conventional diagnostic methods may delay the initiation of antifungals and have urged the development of alternative, culture independent diagnostic tests for candidiasis. Other non-culture diagnostic tests, such as 1,3-β-D-glucan, are limited by sensitivity as low as 57% and the risk of false-positives in at-risk populations.[16] Currently, the only FDA-approved blood culture independent diagnostic test that can provide identification of the 5 most common *Candida* species is the T2Candida Panel.



T2Candida Panel Rapidly and Reliably Identifies 5 *Candida* Species from Whole Blood

The T2Candida Panel identifies *Candida albicans, Candida tropicalis, Candida parapsilosis, Candida krusei*, and *Candida glabrata* from whole blood in 3 to 5 hours.[17] The pivotal DIRECT1 study demonstrated that the T2Candida Panel was able to detect 5 species of *Candida* with a sensitivity of 91.1% and a specificity of 99.4%.[18] The mean time to species identification was 4.4 ± 0.9 hours with T2Candida compared to 129.9 ± 26.3 hours with conventional blood cultures. T2Candida reduced time to species identification by 125.5 hours or 5.3 days compared to blood culture standard of care testing. The subsequent DIRECT2 trial demonstrated the ability of T2Candida to detect 5 *Candida* species in patients with previously diagnosed candidemia that were receiving antifungal therapy prior to testing.[19] Compared to conventional blood cultures, T2Candida identified 86% more persistent episodes of candidemia. These data confirmed that T2Candida is able to detect candidemia and suggest that T2Candida is less susceptible to interference from antifungal therapy than conventional blood cultures.

T2Candida Panel

- *Candida albicans*
- *Candida tropicalis*
- *Candida parapsilosis*
- *Candida krusei*
- *Candida glabrata*

SAMPLE TYPE: Whole Blood

SAMPLE VOLUME: 4 mL

PERFORMANCE: 91% sensitivity & 99% specificity[18]

LIMIT OF DETECTION (LOD): 1-3 CFU/mL[18]

T2Candida Advances Patient Care and Antimicrobial Stewardship Initiatives

Several clinical trials have demonstrated that T2Candida is highly sensitive, specific, and routinely detects candidemia. Multiple real-world studies have also looked to assess the impact of T2Candida on patient care and antimicrobial stewardship goals.

Steuber and colleagues described the implementation of the T2Candida panel at Huntsville Hospital, a 971-bed community hospital.[20] Patients with positive T2Candida results received appropriate antifungals rapidly with an average time to initiation of 2.3 hours for patients that were not receiving antifungal therapy at the time of the result. In addition to the clear value of a positive test, patients with a negative T2Candida result received fewer days of antifungal therapy (5.1 days) compared to those with a positive test. Overall, de-escalation (including discontinuation) occurred in 54% of cases.

The implementation of the T2Candida Panel in the intensive care population, at Henry Ford Health, was initially described by Wilson and colleagues.[21] Following implementation of T2Candida, the median time to appropriate antifungal therapy was reduced from 39 to 22 hours, P=0.003. Patients with a diagnosis of candidemia by T2Candida had a 5.8 times greater likelihood of receiving empiric antifungal therapy within 12 hours (95% CI 2.5-13.6). Median ICU length of stay after candidemia onset was 12 days prior to T2Candida implementation and 7 days following implementation. Ocular candidiasis was diagnosed in 30% of patients prior to T2Candida implementation and 12% of patients following T2Candida implementation. A subsequent evaluation assessed the impact of negative T2Candida Panels in the intensive care population.[22] Compared to 1,3-β-D-Glucan, negative T2Candida results led to a median reduction of echinocandin days of therapy (DOT) from 2 to 1 days and a negative T2Candida result was independently associated with early discontinuation of antifungal therapy, aOR 3.1 (95% CI1.7-5.6). These data show that, in the intensive care population, T2Candida led to reduced ICU length of stay, reduced hospital length of stay, reduced time to appropriate therapy, reduced antifungal use, and enabled earlier detection of candidemia.

In a medical intensive care population, at University of Pittsburgh Medical Center, T2Candida was piloted specifically in patients with septic shock.[23] Following implementation, a reduction from 26 to 15 antifungal DOT per month, or a 42% reduction was observed. Additionally, investigators reported a reduction in antifungal expenditure by 47%. These data further suggest that T2Candida is an essential tool in improving antifungal use in the intensive care population.

While much of the data previously discussed has involved academic sites, T2Candida has also been successfully implemented in many community hospitals and health-systems, such as Lee Health in Fort Myers, Florida. Patch and colleagues described the implementation of T2Candida at Lee Health.[24] After implementation, time to appropriate antifungal therapy for invasive candidiasis cases was reduced from 34 hours prior to implementation to 6 hours following implementation, P=0.0147. The authors also noted that empiric antifungal therapy was avoided in 58.4% of patients with a negative T2Candida result. These data demonstrate that T2Candida can impact patient care in both academic and community settings.

An independent meta-analysis was published in 2021 assessing the impact of both T2Candida and T2Bacteria® on patient care.[25] A total of 14 studies were included with outcomes related to T2Candida being assessed in 6 of the included studies. T2Candida and T2Bacteria were associated with reduced time to species identification by 77.45 hours (95% CI 114.1, 40.79), reduced time to targeted therapy by 42.48 hours (95% CI 61.52, 23.45), reduced hours to de-escalation of empiric therapy in the setting of a negative result by 6.84 hours (95% CI 12.73, 0.95), reduced ICU length of stay by 5.04 days (95% CI 9.55, 0.46), and reduced hospital stay by 4.83 days (95% CI9.39, 0.28). These data highlight that across multiple studies T2Candida consistently reduces time to optimizing therapy and length of stay.

Guidelines Recommend Rapid Identification of Causative Pathogens

Guidelines are increasingly recognizing the need for improved diagnostics for invasive candidiasis. The 2016 IDSA candidiasis guidelines note the poor sensitivity of blood cultures and discuss non-culture diagnostic methods however provide no recommendation for or against the use of T2Candida at the time of publication.[3] It should be noted that there was significantly less data at the time these guidelines were published than is available now. The 2016 IDSA "Implementing an Antibiotic Stewardship Program" guidelines suggest that rapid diagnostic tests should be utilized in addition to culture on blood specimens.[26] The 2020 recommendations from the Mycoses Study Group Education and Research Consortium includes an achievable recommendation that centers managing fungal infections should implement non-culture based diagnostic tests with timely results available for both *Candida* species and *Aspergillus* species.[15] T2Candida is the only FDA-approved direct from blood non-culture based diagnostic test that identifies the five most common pathogenic *Candida* species in 3 to 5 hours.

Deploying T2Candida in Patient Care

The previously discussed clinical trial data and real-world evidence clearly highlight that T2Candida has a role in improving patient care. The logical next question is how to implement this technology into clinical practice. Implementation should be specified to the needs of each hospital or health-system and can be supported by the following algorithms adapted from experts currently utilizing T2Candida in their clinical practice.

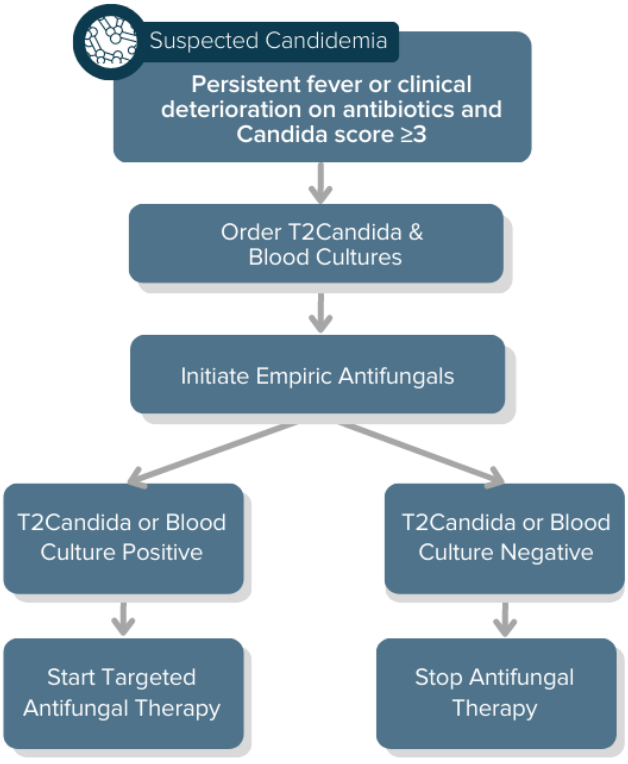
Example Ordering Protocol for T2Candida[28]

Population	Suggested Panel
Oncology & Transplant	T2Candida
Infectious Diseases	T2Bacteria, T2Candida, or Both

Adapted from University of Louisville Health

In these three algorithms, a hospital wide approach and two intensive care specific approaches have been detailed. T2Candida has also been positioned in oncology units, transplant units, and at the discretion of infectious disease clinicians in other practice settings.[28] These provide a starting point for practitioners planning to utilize T2Candida in their own practices.

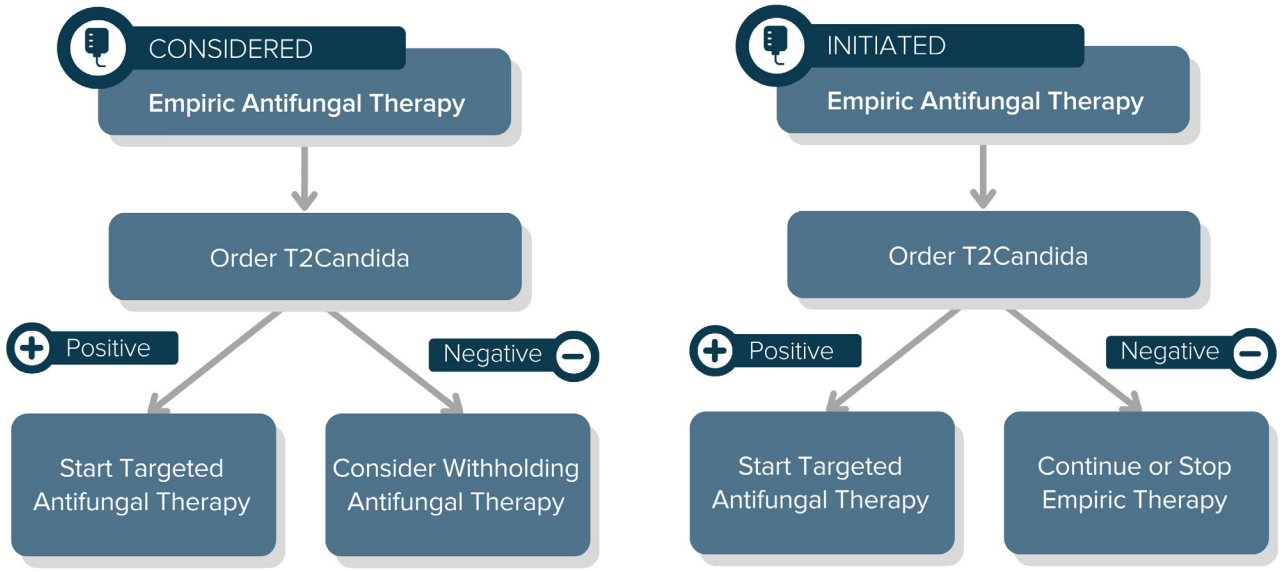
Algorithm 1.[27]
This algorithm is focused on intensive care patients, however, it incorporates clinical criteria and a risk score to guide usage, but do not replace provider judgement.



Adapted from Henry Ford Health

Algorithm 2.[27]

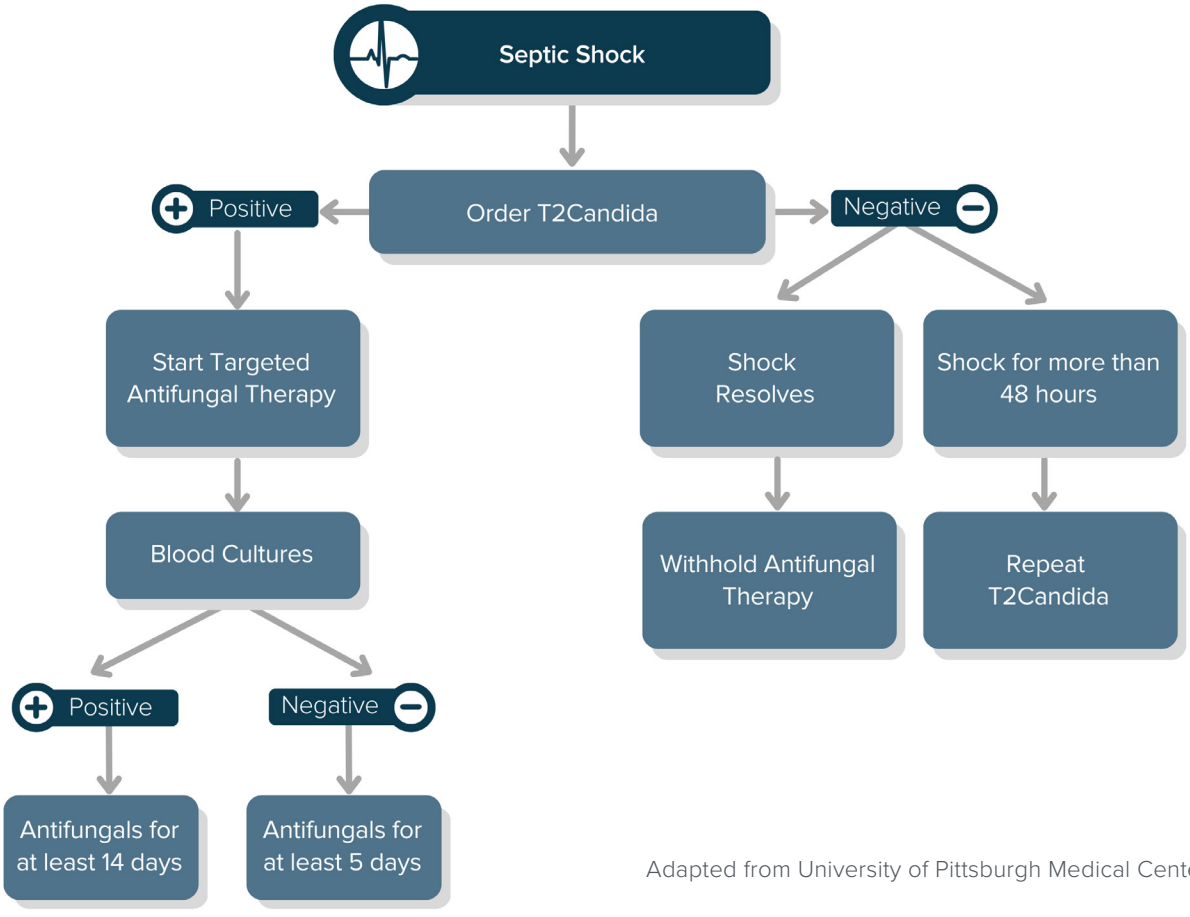
A provider friendly approach was taken that encourages providers to use their clinical judgment to determine whether invasive candidiasis is suspected and subsequently test from there.



Adapted from RWJ University Hospital

Algorithm 3.[23]

Focuses on critically Ill patients in the Medical Intensive Care Unit, provides specific guidance around when to order the test, in septic shock, and how to respond to both positive and negative results specifically.



Adapted from University of Pittsburgh Medical Center

T2Candida in Practice: Example Case Studies from the Field

Case #1:[29] A patient was admitted to Lee Health with PCR-confirmed COVID-19. This patient required oxygen support via nasal cannula, had bibasilar infiltrates on a chest X-ray, and had negative blood cultures from admission. On hospital day 14, the patient developed a new fever and antibacterial therapy was started for suspected bacterial pneumonia. On hospital days 15 and 16, the patient's fever persisted prompting the team to order T2Candida and additional blood cultures. T2Candida returned positive for *Candida albicans/tropicals* 29 hours prior to the positive blood culture. Anidulafungin was subsequently administered following the positive T2Candida. The patient then defervesced on hospital day 18 and was discharged to a long-term acute care center on hospital day 30. T2Candida facilitated the timely administration of appropriate therapy in this critically ill patient with COVID-19.

Case #2:[30] A patient was admitted to the oncology ward, at University of Louisville Hospital, developed persistent fevers. Broad spectrum antimicrobials were administered. Blood cultures were sent as routine workup and remained negative despite continued fevers, notably a port was in place. The team planned to remove the port as no identifiable cause of fever was determined. A T2Candida was subsequently sent that resulted positive for *Candida albicans/tropicalis*. The patient was subsequently started on targeted antifungals and the port was removed. The patient then defervesced and was discharged from the hospital. T2Candida enabled the team to quickly target therapy and increase confidence in the suspected source of infection, the patients port.

T2Candida Improves Patient Care in Invasive Candidiasis

In summary, invasive candidiasis is associated with high morbidity and mortality but conventional diagnostic tests, including blood culture, have low sensitivity and long turnaround times.[7-11] T2Candida panel is the only direct from blood, culture independent diagnostic test that provides rapid identification of the five most common pathogenic *Candida* species.[3] T2Candida provides results in 3 to 5 hours with a sensitivity of 91.1% and a specificity of 99.4%.[18] T2Candida has also been associated with reduced time to reduced antifungal DOT, appropriate therapy, reduced ICU length of stay, reduced hospital length of stay, and reduced time to de-escalation in several peer reviewed clinical studies.[18-22,25] With the ability to identify the five most common *Candida* species directly from whole blood, the T2Candida panel is an essential tool for optimizing treatment and improving care of patients with invasive candidiasis.

KEY FACTS

- Candidemia is associated with mortality rates from 5-71%.[7-11]
- Antifungals account for as much as 10 billion per year in cost in the US with as much as 50% of antifungal use being classified as inappropriate.[15]
- *Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis*, and *Candida krusei* account for over 90% of cases of invasive candidiasis.[3]
- Blood cultures, the standard for detection of candidemia, are limited by poor sensitivity and slow time to growth and subsequent species identification.[16]
- T2Candida is the first, and only, FDA-approved culture independent diagnostic test that can provide rapid identification of the most common *Candida* species in 3-5 hours.
- T2Candida is highly sensitive, 91.1%, and specific, 99.4% for identification of the five most common *Candida* species direct from whole blood.[18]
- T2Candida is able to routinely identify candidemia and is less susceptible to inhibition of growth by antifungals than conventional cultures.[19]
- T2Candida has proven to be an essential tool for antifungal stewardship, demonstrated by 54% of patients with negative tests de-escalated at large community Hospital.[20]
- A 42% reduction in antifungal DOT and 47% reduction in antifungal expenditure in a medical intensive care population at a large academic medical center following implementation of T2Candida.[23]
- Decreases in ICU length of stay, hospital length of stay, time to appropriate antifungal therapy, and rates of ocular candidiasis were observed following implementation of T2Candida at another large academic medical center.[22]
- Compared to 1,3-β-D-Glucan, negativeT2Candida results were associated with decreased antifungal DOT and more frequent early de-escalation.[23]
- Decreases in time to species identification, time to targeted therapy, time to de-escalation of therapy, ICU length of stay, and hospital length of stay were associated with implementation of T2Candida and T2Bacteria by and independent systematic review and meta-analysis.[24]
- T2Candida is an essential tool to improving care for patients with invasive candidiasis and promoting optimal antifungal use.

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