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T2 Candida versus beta-D-glucan to facilitate antifungal discontinuation in the intensive care unit

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ABSTRACT

T2 Magnetic Resonance Candida Panel (T2MR) detects *Candida* directly in blood. Rapid turnaround time and high negative predictive value make it a useful diagnostic test to support antifungal discontinuation.
This retrospective quasi-experiment compared empiric anidulafungin days of therapy (DOTs) in intensive care unit (ICU) patients with suspected candidemia that had negative blood cultures and negative 1,3-β-D-glucan (BDG) versus negative blood cultures and negative T2MR. In 206 ICU patients, median anidulafungin DOTs were 2 (1, 5) compared to 1 (1, 2), respectively ($P < 0.001$); T2MR was associated with early discontinuation, AdjOR 3.0 95% CI (1.7–5.6), $P < 0.001$. Proven candidemia after discontinuation of anidulafungin occurred in 3% of BDG and 2% of T2MR patients at a median of 8 and 21 days, respectively.
T2MR testing supports safe, early discontinuation of empiric antifungal therapy in ICU patients with suspected candidemia. Prospective studies to better define the role of T2MR in antifungal stewardship are warranted.

1. Introduction

Candidemia is an important cause of healthcare-associated infections accounting for approximately 6% in the United States and may be greater in high-risk patient populations (Lortholary et al., 2014; Magill et al., 2018). Prompt antifungal therapy and source control confer better outcomes for patients with invasive candidiasis (IC) (Pappas et al., 2016). However, prompt initiation of antifungal therapy can result in overuse and may lead to antifungal resistance and excess cost (Alexander et al., 2013; Fekkar et al. 2014; McCarty et al., 2018).

Traditional blood cultures are the gold standard for the diagnosis of candidemia (Pappas et al., 2016). Blood cultures take 2–3 days for results and may not detect up to 50% of IC (Nguyen et al., 2012). Non–culture-based tests to diagnose candidemia include the 1,3-β-D-glucan (BDG) assay that detects a component of the cell wall for some fungal pathogens, including *Candida* spp. (Pfaller and Castanheria, 2016). BDG is limited by false-positive results due to cross-reactivity with other organisms, certain medications, and physiologic changes (Pappas et al., 2016). The turnaround time (TAT) for BDG testing is approximately 8–12 h and is longer if samples are sent to a reference laboratory. Previous studies evaluated BDG-guided antifungal discontinuation in patients receiving echinocandin therapy for presumed IC (Nucci et al., 2016; Posteraro et al., 2016). In 21 patients with negative BDG results, anidulafungin was discontinued on day four of therapy without subsequent positive blood cultures for *Candida* for up to 30 days (Nucci et al., 2016). Similarly, in an observational study of ICU patients with risk factors for IC, negative BDG testing resulted in 72.9% reduction in initiating antifungal therapy (Posteraro et al., 2016). T2 Magnetic Resonance Candida Panel (T2MR) (T2Biosystems) detects *Candida* DNA via nanoparticle agglutination and subsequent changes in the nuclear magnetic resonance directly from whole blood (Langer and Weissleder, 2015). T2MR has a TAT of approximately 8 hs and has 97% sensitivity and 99% specificity (Mylonakis et al., 2015). A positive T2MR identifies the presence of 1 of the 3 following categories: *Candida albicans/tropicalis*, *Candida parapsilosis*, or *Candida glabrata/krusei*, which account for >90% of invasive candidiasis (Beyda et al., 2013; Clancy et al., 2018; Mylonakis et al., 2014; Pfaller and Diekema, 2007). In patient populations with 5% and 10% prevalence of candidemia, T2MR testing confers a negative predictive value (NPV) of 99.5% and 99%, respectively (Mylonakis E, et al., 2018). The high NPV of T2MR makes it an attractive adjunct to blood cultures in antifungal stewardship efforts, as it can rapidly rule out the most common organisms

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that cause candidemia and facilitate early discontinuation of empiric antifungal therapy.

The purpose of this study was to evaluate days of empiric echinocandin therapy (DOTs) in patients with suspected candidemia with negative BDG compared to negative T2MR.

2. Methods

2.1. Study design and setting

The present study was an IRB-approved, retrospective, quasi-experimental study conducted in the ICUs of a 4-hospital health system comprising a large urban, academic medical center (175 ICU beds), 2 community hospitals (42 ICU beds total), and a community teaching hospital (48 ICU beds). T2MR testing was implemented in November 2015 and replaced BDG as a rapid diagnostic test (RDT) to aid in diagnosis of candidemia. Anidulafungin was the formulary echinocandin for the health system, and use was restricted to approval by an infectious diseases consultation to continue therapy for more than 24 h during the entirety of the study period. Patients were manually screened for study inclusion, and data were abstracted from the medical record using a standardized case report form.

2.2. Patients groups and intervention

ICU patients during their first episode of presumed candidemia prompting initiation of empiric anidulafungin were eligible for study inclusion. Patients meeting the following criteria were included: age ≥ 18 years old, negative blood cultures, and a negative RDT (BDG or T2MR). Exclusion criteria included transplant patients, patients undergoing comfort measures only, noncandidemia fungal infections, patients with other indications for antifungal therapy (i.e., prophylaxis, esophageal perforation), and neutropenia. Patients in the BDG group were admitted between 1/1/2014 and 10/31/2015, before T2MR implementation, and underwent BDG testing, while the T2MR group was admitted after implementation between 1/1/2017 and 10/31/17.

A system-wide guideline outlined the standard of care for presumed IC during the entire study period.(See Fig. 1) Based on this guideline, patients were determined to have high risk of IC if they were on broad-spectrum antimicrobials for at least 72 h without clinical improvement and a "*Candida* score" ≥3 (León et al., 2006; Leroy et al., 2011). Patients meeting the above criteria at the discretion of the medical team would receive empiric anidulafungin therapy, 2 sets of blood cultures, an RDT, and an infectious disease consult. During the BDG time period, 2 BDG tests were ordered (24–48 h apart) in conjunction with blood cultures to evaluate need for the continuation of empiric antifungal therapy. BDG testing required the sample to be sent to a reference laboratory. Results were reported in the medical record as negative (<60 pg/mL), indeterminate (60–79 pg/mL), or positive (> 80 pg/mL). The institutional guideline defined a positive BDG as any single result >200 pg/mL or 2 results >80 pg/mL (Posteraro et al., 2011). Clinicians were encouraged to discontinue antifungal therapy for patients who did not meet the guideline definition of positive BDG. In the T2MR group, T2MR replaced BDG as the RDT to accompany blood cultures. T2MR testing was done in the hospital laboratory, and only 1 test was recommended. After a negative T2MR, clinicians were encouraged to discontinue antifungal therapy as candidemia is unlikely. During both time periods, the antimicrobial stewardship team reviewed BDG and T2MR results for patients receiving anidulafungin in TheraDoc (Premier, Charlotte, NC) clinical support system or the electronic medical record and intervened as appropriate.

Baseline demographics collected included age, sex, and comorbid conditions. Vasopressor use and an initial Sequential Organ Failure Assessment (SOFA) score were calculated using values temporally closest to the time of rapid diagnostic testing or anidulafugin initiation, whichever occurred first. A second SOFA score was calculated at the time the RDT results were reported to evaluate the change in patients' clinical status between test ordering and result. Risk factors for invasive candidiasis were obtained including the *Candida* score (León et al., 2006; Leroy et al., 2011). In some patients, multifocal colonization was unknown or presumed negative based on clinical cultures. Presence of a central venous catheter, immunosuppression therapy, prior antibiotic therapy, gastrointestinal surgery during index admission, and diagnosis of pancreatitis were also collected.

2.3. Outcomes

The primary efficacy endpoint was duration of empiric anidulafungin therapy (days). Secondary endpoints included TAT for the RDT, the number of subsequent RDTs and blood cultures, proportion of patients where antifungal therapy was restarted after index course, and in-hospital mortality. Development of subsequent candidemia

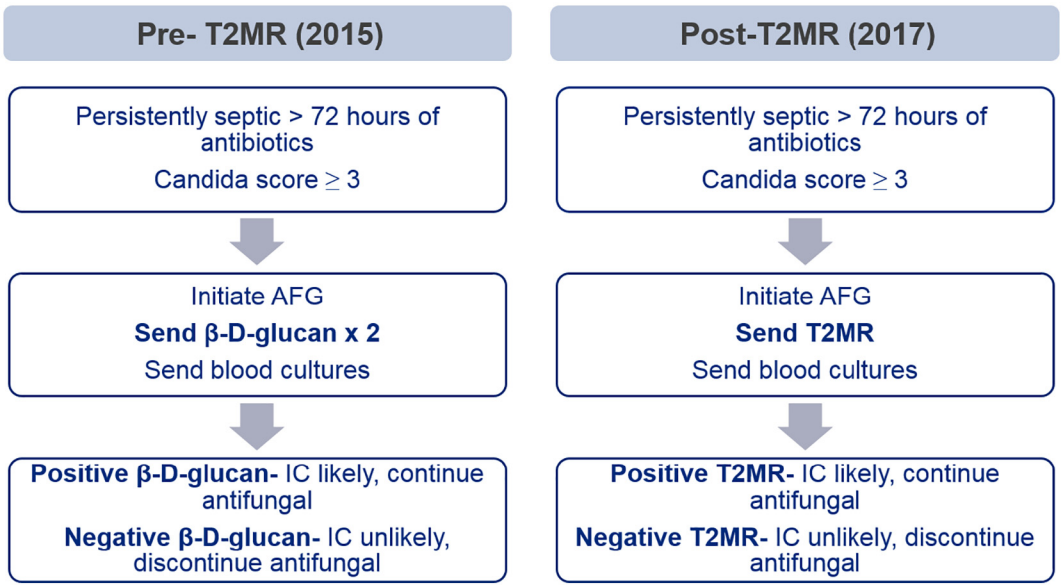

Fig. 1. Institutional guidelines for management of suspected or confirmed invasive candidiasis. T2MR = T2 Magnetic Resonance Candida Panel; AFG = anidulafungin; IC = invasive candidiasis.

was compared between study groups. Proven candidemia was defined as blood culture–confirmed candidemia, while probable candidemia was a positive RDT plus presence of risk factors for candidemia, and sepsis criteria. Factors associated with early discontinuation of empiric echinocandin therapy defined as 1 day of empiric therapy were evaluated. Linezolid days of therapy was the nonequivalent dependent variable and compared between the 2 study periods (Schweizer et al., 2016). Both anidulafugin and linezolid are restricted to infectious disease consult approval; thus, linezolid was chosen as a surrogate to represent patterns of restricted antimicrobial use in the ICU.

2.4. Statistical analysis

Results were reported as median [interquartile range (IQR)] for continuous data and number (percentage) for categorical data. The primary endpoint of duration of empiric anidulafungin therapy (days) was compared using the Mann–Whitney *U* test. Other continuous data following normal distribution were compared using the Student's *t* test, and categorical data used χ^2 or Fishers' exact using SPSS version 23 (IBM, Inc., Armonk, NY). Based on internal data and previous literature, the anticipated anidulafungin DOT with T2MR was 2 days and 5 days for BDG-guided therapy (estimated standard deviation of 7 days) (Posteraro et al., 2016; Wilson et al., 2017). Using an α of 0.05 and β of 0.2, a sample size estimation of 110 patients per group would be needed to detect a 60% reduction in duration of empiric antifungal therapy after accounting for nonparametric data distribution. Backward stepwise logistic multivariable regression was used to evaluate factors associated with early discontinuation of empiric anidulafungin and reported at unadjusted odds ratios (unadjOR) and 95% confidence intervals (95% CIs).

3. Results

During the study periods, 323 patients received anidulafungin with negative blood cultures and RDTs at the time of initiation. After screening for eligibility, 103 consecutive patients were included in each group. Patients treated at the urban academic medical center comprised of 80% of patients. Baseline characteristics are listed in Table 1 Significantly fewer patients in the BDG group were on vasopressors at baseline with 38% vs. 64% in the T2MR group, $P < 0.001$. The median initial SOFA score was significantly lower in the BDG arm vs. the T2MR arm: 9 (León et al., 2006; Mylonakis et al., 2015) vs. 12 (Lortholary et al., 2014; Pfaller and Castanheria, 2016), p < 0.001 (Table 1)

Both treatment groups had a similar distribution of invasive candidiasis risk factors. The median *Candida* score for both groups were 2 (Beyda et al., 2013; Clancy et al., 2013), with 40% of the BDG group having a *Candida* score ≥ 3 compared to 44% in the T2MR group (Table 1). Most patients were on antimicrobial therapy: 68% BDG vs. 75% in the T2MR group, $P = 0.355$. Test TAT was significantly shorter in the T2MR group compared to BDG: 0.4 (0.3, 0.8) days vs. 3.8 (2.3, 4.7). The T2MR result was indeterminate in 19% of the T2MR group, but all had a reportable result upon retesting.

Patients in the BDG group received a significantly longer duration of empiric anidulafungin with a median of 2 (Alexander et al., 2013; Fekker et al., 2014) vs. 1 days (Alexander et al., 2013; Beyda et al., 2013), $P < 0.001$ (Table 2). Linezolid utilization was similar between groups: 11.8 vs. 11.2 DOTs/1000 person-months. Antifungal therapy was restarted in 17% of the BDG group vs. 13% of the T2MR groups. Development of candidemia after discontinuation of the initial empiric therapy was 8% and 3% for BDG and T2MR, respectively. Blood culture–proven candidemia was only found in 3% (1 *C. albicans*; 1 *C. glabrata*; 1 *C. parapsilosis*) and 2% (1 *C. albicans*; 1 *C. tropicalis*) of each study arm. The median time to positive blood culture or RDT after discontinuation of anidulafungin was 11 days (4, 21). Inpatient mortality was significantly higher in the T2MR group, 60% vs. 43% ($P = 0.018$). However, development of invasive candidiasis was not associated with increased risk of mortality, and this was likely driven by underlying critical illness.

Table 1
Characteristics of patients treated with empiric echinocandin therapy in the ICU prior to negative BDG or T2MR.

Baseline characteristics *n* (%)	BDG $N = 103$	T2MR $N = 103$	*P* value
Female	53 (52)	43 (42)	0.163
Age, median (IQR)	61 (47-70)	59 (50-76)	
Underlying conditions			
Chronic liver disease	28 (27)	28 (27)	
Diabetes			
CKD	35 (34)	42 (41)	0.313
COPD	13 (13)	19 (18)	0.248
Active malignancy	19 (18)	22 (21)	0.601
Hemodialysis use	19 (18)	12 (12)	0.173
HIV infection	19 (18)	16 (25)	0.238
	4 (4)	2 (2)	0.407
On vasopressors at time of initiation	39 (38)	66 (64)	<0.001
Initial SOFA score, median (IQR)	9 (6-12)	12 (8-15)	< 0.001
Decrease in SOFA score	59 (58)	32 (31)	< 0.001
***Candida* risk factors**			
Candida score (total), median (IQR)	2 (2-3)	2 (2-3)	0.53
Candida score ≥ 3	41 (40)	45 (44)	0.669
Severe sepsis	91 (88)	101 (98)	0.006
Initial surgery	26 (25)	34 (33)	0.22
TPN	15 (14)	5 (5)	0.019
Multifocal colonization	19 (18)	9 (9)	0.042
CVC present at initiation	101 (98)	96 (93)	0.088
Immunosuppression therapy	9 (9)	5 (5)	0.268
Antibiotic therapy prior to initiation	70 (68)	77 (75)	0.355
GI surgery	18 (18)	13 (13)	0.33
>1 GI surgery	5 (5)	4 (4)	0.733
Diagnosis of pancreatitis	8 (8)	1(1)	0.017

Early discontinuation of therapy occurred in 100 of the 206 patients. In patients with early discontinuation, 62% of patients received T2MR testing. After controlling for receipt of vasopressors and multifocal *Candida* colonization, T2MR was associated with early discontinuation: AdjOR 3.1, 95% CI (1.7–5.6), $P < 0.001$.

4. Discussion

The present study is the first active comparison of 2 distinct RDT-based antifungal stewardship strategies. When compared to BDG and blood culture evaluation, T2MR and blood cultures were associated with a decrease in the median days of empiric echinocandin therapy in critically ill patients. T2MR testing was also the only independent predictor of early discontinuation of echinocandin therapy. The short TAT and high NPV make it a valuable test to rule out the most common

Table 2
Outcomes following negative BDG or T2MR.

Outcomes	BDG	T2MR	*P* value
Duration of empiric AFG therapy, median (IQR)	2 (1-5)	1 (1-2)	<0.001
Inpatient mortality, median (IQR)	44 (43)	61 (60)	0.018
ICU LOS, median (IQR)	13 (8-26)	15 (8-24)	0.711
Hospital LOS, median (IQR)	21 (12-31)	19 (11-30)	0.253
Discontinuation prior to RDT result, *n* (%)	46 (50)	9 (9)	< 0.001
Developed candidemia after discontinuation, n (%)	9 (9)	3 (3)	0.134
Probable	5 (5)	1 (1)	0.119
Proven	3 (3)	2 (2)	----
Time to positive, days, median (range)	8 (3-23)	21 (9-30)	----
Restart antifungals after index course	17 (17)	13 (13)	0.429
Subsequent RDTs sent after index	2 (1-3)	1 (1-2)	----

Abbreviations: AFG = anidulafungin; BDG = beta-D-glucan; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; RDT = rapid diagnostic test' T2MR = T2 magnetic resonance.

organisms implicated in candidemia. Overall, T2MR represents an important tool for antifungal stewardship in the ICU.

The use of T2MR in rapid identification of candidemia and association with providing timely antifungal therapy has been previously described (Wilson et al., 2017; Patch et al., 2018). There are limited data evaluating the clinical utility of negative T2MR results in the discontinuation of empiric antifungal therapy in patients deemed to be at risk for invasive *Candida* infections. Compared to historic data, T2MR implementation was associated with a reduction in micafungin usage (6.7 vs. 2.4 DOTs) without significant a difference in all-cause 30-day mortality (23% vs. 21%, respectively) (Patch et al., 2018).

Our BDG group also had shorter median durations of empiric therapy compared to previous studies (Nucci et al., 2016) likely due to active recommendations by the ID consult team to discontinue antifungal therapy in patients they deemed low risk. Although our study population had a high severity of illness, only 40% of subjects met *Candida* score criteria for high risk of IC. As a particular patient group's prevalence of candidemia decreases, the positive predictive value of T2MR decreases as well (Clancy et al., 2018). Testing lower-risk populations may increase the risk of false-positive results and unintentionally increase unnecessary antifungal use. Future antifungal stewardship efforts in our institution will emphasize risk stratification and limiting T2MR testing in patients with a relatively low pretest probability for candidemia.

Inpatient crude mortality was significantly higher in the T2MR group compared to BDG. Notably, the initial SOFA scores were significantly higher in the T2MR group compared to BDG: 12 (Lortholary et al., 2014; Pfaller and Castanheria, 2016) versus 9 (León et al., 2006; Mylonakis et al., 2015), which may account for the mortality discrepancy. The risk of early discontinuation in response to RDT is that patients may still go on to develop candidemia. T2MR testing includes the 5 most common species causing candidemia in the ICU setting, but other species may cause clinical candiemia (Beyda et al., 2013; Clancy et al., 2018; Mylonakis et al., 2014; Pfaller and Diekema, 2007). Unless clinical status improves, these patients still require an ongoing systematic approach to candimeia risk assessment. In our study, 3 patients in the T2MR group had subsequent proven or probable candidemia. All 3 patients had early discontinuation; however, the infection onset was 9, 21, and 30 days, representing new infections in patients at ongoing high risk. Therefore, clinicians should be relatively confident in the high NPV of T2MR (Mylonakis et al., 2014). Several limitations of this study must be noted. This study was unable to perform an unbiased assessment of guideline adherence as patients were identified using orders for anidulafungin. Cost minimization analysis was outside of the scope of this study, but both BDG and T2MR can be associated with significant acquisition cost. Another possible limitation is maturation bias. Linezolid DOTs served as the nonequivalent dependent variable used to evaluate consistency in the antimicrobial stewardship practice between the study groups. The similar usage between the 2 study periods suggests limited maturation in antimicrobial stewardship between the BDG and T2MR groups. Moreover, a multivariable analysis was used to account for confounding factors that predicted early discontinuation of empiric anidulafungin therapy. Another source of bias is the potential of misclassification stemming from the ambiguity of BDG results. Patients at the highest risk for misclassification are indeterminate or single low-level positive result which accounted for 14% of the BDG patients. This study included patients with BDG results that were in concordance with the system-wide, antimicrobial stewardship committee–approved guideline for evaluating and treating invasive candidiasis. By using this definition, it aligned with the standard of care during the study timeframe.

5. Conclusion

T2MR testing was associated with a shorter duration of empiric echinocandin therapy in patients with presumed candidemia when compared to BDG testing. T2MR is a useful tool in allowing prompt antifungal therapy while minimizing unnecessary exposure to antifungal agents. More research is needed to evaluate diagnostic stewardship strategies and optimize utilization of RDTs.

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