JAMS Journal of Antimicrobial Stewardship

Journal of Antimicrobial Stewardship

Original Research

T2 Magnetic Resonance Assay Improves Timely Management of Candidemia

Nicole M. Wilson (@NikkiVWs)[1], George Alangaden[2], Robert J. Tibbetts[2], Linoj P. Samuel[2], Susan L. Davis (@IDPharmProf)[1,3], Rachel M. Kenney[1]

[1]Department of Pharmacy Services, [2]Division of Infectious Diseases, Henry Ford Hospital, Detroit, MI, [3]Wayne State University, Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, MI, [4]Division of Microbiology, Pathology, and Laboratory Medicine, Henry Ford Health System, Detroit, MI

Background. The T2 magnetic resonance (T2MR) *Candida* species assay is a sensitive, direct from blood rapid diagnostic test to identify candidemia.

Methods. This IRB approved, single pre-post-test quasi-experiment was conducted in a four-hospital health-system with an antimicrobial stewardship program. T2MR was implemented in November 2015. The primary endpoint of time to appropriate antifungal therapy, time to candidemia detection, and patient outcomes were compared before and after T2MR.

Results. 161 patients with probable or proven candidemia were included: 87 patients pre-T2MR and 74 patients post-T2MR. The most common method of detection of candidemia was blood culture in the pre-group 49/87 (56%) and T2MR in the post-group 37/74 (50%). The median time to appropriate antifungal therapy was reduced from 39 hours to 22 hours post-T2MR, P=0.003. Among the subgroup of 37 patients diagnosed by T2MR, the median time to appropriate therapy was 5 hours. *Candida* eye involvement was diagnosed in 16/53 (30%) in the pre-T2MR group versus 6/49 (12%) of patients in the post-T2MR group (P=0.028). After adjusting for severe sepsis (adjusted OR 2.0, 95% CI [1.3-3.1], diagnosis by T2MR was independently associated with receipt of antifungal therapy within 12 hours (adjusted OR 5.8, 95% CI [2.5-13.6]). No significant differences in length of stay or mortality were detected.

Conclusion. This study suggests that T2MR is a valuable clinical tool to aid antifungal stewardship and to improve timely antifungal therapy for candidemia.

Key words. candida; candidemia; rapid diagnostics; T2MR; antimicrobial stewardship

Candida species are a common cause of nosocomial bloodstream infections, and are associated with significant morbidity and an estimated mortality rate between 30 and 50% [1,2,3]. Prompt administration of appropriate antifungal therapy is recognized as an important strategy to improve survival of candidemia [1, 4], but may be delayed due to limitations of traditional diagnostic methods. Blood cultures remain the gold standard for detection of candidemia; however, cultures may miss approximately 50% of episodes of invasive candidiasis and are limited by their slow time to identification [5].

Rapid diagnostic testing is an approach advocated for as a best practice in antimicrobial stewardship [6] and has important implications for patients with bloodstream infection. Rapid diagnostics combined with antimicrobial

Received 28 February 2017; editorial decision 22 March 2017; accepted 25 July 2017. Correspondence: R. Kenney, Henry Ford Hospital, Detroit, MI. (rkenney1@hfhs.org). Note: Nicole Wilson current affiliation: Department of Pharmacy Services, Olathe Medical Center, Olathe, KS. **Journal of Antimicrobial Stewardship™ 2017; 1(1):12-18.** DOI:

stewardship intervention have previously demonstrated improved antimicrobial management and reduced mortality for patients with bacteremia and candidemia [7]. The T2 magnetic resonance (T2MR) *Candida* species panel (T2 Candida® 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 in three clinically relevant groups – *Candida albicans/tropicalis*, *Candida glabrata/krusei*, and *Candida parapsilosis*. Results are obtained directly from a whole blood sample in approximately 3 to 5 hours with sensitivity and specificity of 91.1% and 99.4% [8].

The optimal role of the T2MR Candida species panel in clinical practice is unknown, as the clinical trial utilized mostly spiked specimens [8]. The T2MR *Candida* species panel for the detection of candidemia was implemented at our institution in November 2015. The purpose of this study was to compare the time to appropriate antifungal therapy in patients with candidemia before and after implementation of T2MR.

MATERIALS AND METHODS

Study design, setting, and selection of participants

This single pre-post-test quasi-experimental study was performed at a four-hospital health system comprised of 1789 total beds. The study received institutional board review approval with waiver of consent. Hospitalized adult patients with their first episode of proven or probable candidemia between April 1, 2015 and July 31, 2016 were eligible for inclusion. Proven candidemia was defined as at least one blood culture with any *Candida* species isolated or a positive T2MR Candida panel. Probable candidemia was defined as at least one serum 1,3-beta-D-glucan (BDG) assay $\geq$200 pg/mL. Patients were excluded if non-candida yeast was identified, if there was another indication for antifungal therapy other than a positive test or culture result, if they expired, or were hospice or comfort care prior to the time of the first actionable diagnostic result.

During the entire study, antifungal stewardship recommendations were in place. The institutional guideline defined presumed invasive candidiasis as a patient with fever or clinical deterioration while on broad spectrum antibiotics for at least 72 hours and a Candida score of 3 or greater [9]. The institutional guideline for invasive candidiasis recommended empiric echinocandin therapy for critically ill patients with presumed invasive candidiasis while awaiting the results of diagnostic tests. Empiric therapy with weight-based fluconazole dosing of 12mg/kg load, then 6mg/kg daily was recommended for non-critically ill patients with presumed candidiasis. The electronic medical record (EMR) contained an order panel for anidulafungin loading and maintenance doses, bundled with the suggested diagnostic tests for candidemia to facilitate guideline adherence. Institutional guidelines also recommended infectious diseases consultation and ophthalmology consultation for candidemia. Finally, guidelines suggested empiric echinocandin therapy for 3 to 5 days, then step down to azole antifungal according to presumed or microbiology confirmed susceptibility. Audit and feedback by the antimicrobial stewardship team in response to diagnostic results was routine Monday through Friday on day shift at all hospitals.

Blood cultures were performed using aerobic and anaerobic bottles on the VersaTrek (ThermoScientific Oakwood Village, Ohio). Subculture and Gram-stain were performed on positive specimens and the results were called to the medical team as a critical laboratory result. Candida susceptibility testing was available upon request. The serum BDG were sent out to MiraVista Diagnostics (Indianapolis, IN). Both of these methods remained unchanged throughout the entire study period. Results of all diagnostic tests for candidemia were provided in the electronic medical record.

Pre-intervention phase

The pre-T2MR intervention group included patients between April 1, 2015 and November 7, 2016. During the pre-intervention phase, the standard of care for candidemia diagnosis in the institutional guideline and EMR order panel included a serum BDG plus one set of blood cultures, and then repeated 24 to 48 hours later.

T2MR intervention phase

The post-intervention group included patients between November 8, 2015 and July 31 2016, after T2MR implementation. T2MR was performed in the centralized clinical microbiology laboratory during two shifts (7 am to 10 pm), 7 days per week during the post- intervention phase. In conjunction with T2MR implementation, the new standard of care for candidemia diagnosis in the institutional guideline and EMR order panel included a single T2MR assay plus one set of blood cultures, followed by a repeat set of blood cultures 24 to 48 hours later. The antimicrobial stewardship team performed education to

inform nurses, pharmacists, and prescribers about when the T2MR is indicated, how to obtain the blood specimen for T2MR, and implications of positives and negative results.

Study endpoints

The primary endpoint was the time to appropriate antifungal therapy. The time to appropriate antifungal therapy was defined as the difference between the draw time of the first candidemia diagnostic test obtained to the administration time of the first antifungal therapy that was presumed or documented to be active. Echinocandin therapy was considered appropriate in all cases. Fluconazole was defined as appropriate if administered according to the guideline weight-based dose and susceptibility was confirmed by blood culture or if *C. albicans*, *C. tropicalis* or *C. parapsilosis* were identified. For BDG diagnosis, fluconazole was defined as appropriate if administered according to the institutional guideline recommended weight-based dose. Secondary endpoints included receipt of early appropriate antifungal therapy, defined as antifungal administration within 12 hours of the draw time of the first candidemia diagnostic test obtained. Other secondary endpoints included time to detection of candidemia, ICU and hospital length of stay after the onset of candidemia, proportion of patients with *Candida* species eye involvement diagnosed by ophthalmology, and all-cause in hospital mortality. The time to detection of candidemia was defined as the difference from the draw time of the first candidemia diagnostic test obtained to the first positive result for candidemia. For blood cultures, the first positive result was defined as the time that yeast was reported on Gram-stain. Severe sepsis was defined as sepsis induced hypoperfusion or organ damage [10]. Length of stay was measured after candidemia onset, defined as the draw time of the first candidemia diagnostic test obtained.

Statistical analysis

Categorical variables were analyzed with Pearson Chi square or Fisher's exact test where appropriate; continuous variables were analyzed with the Mann-Whitney U. Bivariate and logistic regression analyses were performed to identify variables associated with early appropriate antifungal therapy. Variables included in the logistic regression were selected according to a *P*-value of 0.2 or less in bivariate analysis and clinical rationale. A subgroup analysis of patients diagnosed by T2MR was planned *a priori*. All analyses were performed using SPSS software version 21.0 (SPSS, IBM Inc. Chicago, Illinois).

RESULTS

Characteristics of study participants

A total of 161 patients were diagnosed with proven or probable candidemia, including 87 patients in the pre-T2MR group and 74 patients in the post-T2MR group. Patient characteristics are displayed in Table 1. The majority of patients were admitted to the ICU and met criteria for severe sepsis. The median (IQR) Candida score was 2 (0, 3) and 2 (1, 3), in the pre and post-T2MR groups, respectively, P=0.307. 24/87 (28%) of patients in the pre-T2MR group and 23/74 (31%) of patients in the post-T2MR group had a Candida score of at least 3 at the onset of candidemia, P=0.627.

Microbiology and candidemia management

Microbiology and treatment characteristics are presented in Table 2. The *Candida* species was definitively identified in 50 (57%) patients in the pre-T2MR group compared to 69 (93%) in the post T2MR group (P <0.001). *Candida* species outside of the scope of the T2MR panel were identified in 3 (3.4%) patients in the pre-group and 3 (4.1%) patients in the post-group.

No statistical differences in candidemia management were identified between groups. Antifungal therapy was initiated in 76/87 (87%) patients in the pre-group, and 70/74 (95%) in the post-group. Empiric antifungal therapy (prior to detection of candidemia) was received by 28/76 (37%) in the pre-T2MR group compared to 31/70 (44%) post-T2MR, P=0.360. Anidulafungin was the initial therapy in 63/76 (83%) of pre-T2MR patients and 59/70 (84%) of post T2MR patients, P=0.528. Infectious Diseases was consulted for management in 74/76 (97%) of patients in the pre- group and 67/70 (96%) of patients in the post-group, P=0.583. Central lines were removed or replaced in 63/70 (90%) and 49/59 (83%) of patients in the pre- and post-T2MR groups, respectively (P=0.245). Ophthalmology performed an eye exam in 53/76 (70%) and 49/70 (70%) of patients in the pre- and post-T2MR groups (P=0.972).

Overall, a reduction in the primary endpoint of time to appropriate therapy was identified in the post-T2MR group (39 hours pre-T2MR versus 22 hours post-T2MR, P=0.003). Receipt of early antifungal therapy within 12 hours was 19/76 (22%) before and 27/70 (37%) after T2MR implementation, P=0.078. After adjusting for

Table 1: Select characteristics of the study population

Characteristic	Pre-T2MR (n=87)	Post-T2MR (n=74)	*P*-value
Age, years	62 (52, 72)	62 (52, 69)	0.731
Male	52 (60)	39 (53)	0.367
ICU admission	66 (76)	57 (77)	0.862
Severe sepsis	46 (53)	46 (62)	0.235
Diabetes	24 (28)	29 (39)	0.118
Cancer	16 (18)	16 (22)	0.609
Transplant recipient	4 (5)	11 (15)	0.026
Central line present	70 (81)	59 (80)	0.908
Broad spectrum antimicrobials prior to candidemia	79 (91)	62 (84)	0.178
Gastrointestinal surgery in the previous 30 days	32 (37)	18 (24)	0.089
Total parenteral nutrition	16 (18)	8 (15)	0.550

Data presented as n (%) or median (25^{th} percentile-75^{th} percentile)

severe sepsis (adjusted OR 2.0, 95% CI [1.3-3.1], diagnosis by T2MR was independently associated with receipt of antifungal therapy within 12 hours (adjusted OR 5.8, 95% CI [2.5-13.6]), Hosmer-Lemeshow = 0.394. Among the subset of 37 patients diagnosed by T2MR, the time to detection and time to appropriate therapy were median (IQR) 11 (6, 23) hours and 5 (2, 20) hours, respectively.

Patient outcomes

No statistical difference was detected between groups for all cause in-hospital mortality: 29 (33%) pre-T2MR compared to 29 (39%) post-T2MR, *P*=0.441. No relationship between early antifungal therapy and survival was detected. 26/46 (56%) of patients who received early appropriate therapy survived compared with 66/100 (66%) of patients who received late therapy, *P*=0.270. Among survivors, 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, and median ICU length of stay after candidemia onset was 12 (4, 18) compared to 7 (4, 18) days, *P*=0.562. Ocular candidiasis was diagnosed in 16/53 (30%) in the pre-T2MR group versus 6/49 (12%) of patients in the post-T2MR group (*P*=0.028). Among the T2MR subgroup, 24/37 T2MRpatients had an eye exam performed, and ocular candida infection was diagnosed in 4/24 (16.6%) patients.

DISCUSSION

Compared to the historical standard using BDG and blood culture diagnosis, implementation of the T2MR assay with antifungal stewardship guidelines and intervention was associated with reduced time to detection and time to

Table 2: Microbiology, diagnosis, and treatment of candidemia

Variable	Pre-T2MR (n=87)	Post-T2MR (n=74)	*P*-value
Method of detection (first positive result)			<0.001
1,3 BDG	38 (44)	5 (7)	
Blood culture	49 (56)	32 (43)	
T2MR	0 (0)	37 (50)	
Candida species identified			<0.001
C. albicans/tropicalis	27 (31)	36 (48.6)	
C. glabrata/krusei	10 (11.5)	15 (20.3)	
C. parapsilosis	9 (10.3)	13 (17.6)	
other *Candida* species*	3 (3.4)	3 (4.1)	
multiple *Candida* species	1 (1.1)	2 (2.7)	
no species identification (BDG only)	37 (42.5)	5 (6.8)	
Time to detection, hours	45 (33, 76)	26 (11, 41)	<0.001
Time to detection by method, hours			Not tested
1,3 BDG	73 (50, 97)	111 (93, 115)	
Blood culture	39 (31, 46)	36 (25, 46)	
T2MR	-	11 (6,23)	
Time to appropriate therapy, hours (Pre-T2MR n= 76, Post-T2MR n= 70)	39 (12, 54)	22 (2, 43)	0.003
Time to appropriate therapy by method, hours			Not tested
BDG	5 (1, 75)	-	
Blood culture	41 (33, 52)	44 (27, 61)	
T2MR	-	5 (2,20)	
Initial echinocandin therapy	63/76 (83)	59/70 (84)	0.528

Data presented as n (%) or median (25th percentile-75th percentile)
*Other *Candida* species included *C. guilliermondii* (2), *C. kefyr, C. lusitaniae* (2), *C. utilis.*

appropriate antifungal therapy. We also identified a possible association with fewer patients experiencing *Candida* eye involvement. The importance of early antifungal therapy is established from prior literature [1,4,11]. In our study, severe sepsis and T2MR diagnosis were independently associated with early appropriate antifungal therapy. The median time to appropriate therapy was 22 hours among all patients in the T2MR phase, and 5 hours among the subgroup of 37 patients diagnosed by T2MR. Garey et al [1] previously

demonstrated that patients who received antifungal therapy less than 24 hours from candidemia onset had a 15.4% mortality rate versus a 41% mortality rate when therapy was delayed by more than 72 hours. Other studies confirm that early antifungal therapy after candidemia onset is an independent predictor of survival for critically ill patients in septic shock [4,11].

The observed association with T2MR diagnosis and *Candida* ocular involvement is a clinically relevant patient outcome improvement to consider. We hypothesize this outcome difference could relate to multiple factors: 1. The improved sensitivity of T2MR may detect lower inoculum candidemia that may be less likely to disseminate to the eye and 2. Improved timeliness of T2MR diagnosis resulted in more prompt antifungal therapy and prevents dissemination. Further study is needed to answer these specific questions.

Of note, the institutional guideline and others [12] advocate the use of the Candida score [9] as a simple, standardized approach to guide diagnostic testing and empiric therapy for candidemia. However, only 24/87 (28%) of patients in the pre-group and 23/74 (31%) of patients in the post-group had a Candida score ≥ 3. Additionally, a suboptimal number of patients, 37% pre-T2MR and 44% post-T2MR, received empiric antifungal therapy prior to the detection of candidemia. Our study demonstrates the clinical challenge of identifying patients at high risk for candidemia and supports that additional research is needed to refine the available risk factor and clinical prediction strategies for candidemia.

There are several limitations to this study. We utilized a quasi-experimental design because implementation of T2MR testing in select patient groups or locations would have been impractical, and potentially unethical. Maturation may be present in our study. Significant education regarding the ASP candidemia guideline, importance of early therapy for candidemia, and appropriate use and interpretation of T2MR results was provided to medical staff at the time of T2MR implementation. However, the ASP guideline advocated empiric antifungal therapy in patients with suspected candidemia both before and after T2MR implementation. We were unable to evaluate test performance, because blood cultures were not always collected at the same time as T2MR or BDG. Utilization of the BDG assay may decrease time to detection of probable candidemia but has limited sensitivity, specificity and multiple interfering substances [13]. Due to these known limitations of BDG, our institutional guideline in use for the pre-T2MR group suggested two serial measurements and a cutoff of 200 pg/mL for positivity, which is not consistent with the FDA labeling. Finally, this investigation was powered to examine time to appropriate therapy as the primary endpoint rather than mortality. Our definition of appropriate therapy may have been limited in select cases of BDG and T2MR diagnosis when susceptibility testing was unavailable. However, time to appropriate therapy for candidemia has been established as a surrogate outcome for mortality in previous studies [1,4] and most patients received initial therapy with an echinocandin. A notable strength of our study is the number of patients with candidemia, including 37 patients with a positive T2MR result. In contrast, the registration clinical trial of T2MR enrolled a total of 1801 patients with suspected candidemia, of whom only 6 had a candidemia detected [8].

In conclusion, early experience with the T2MR *Candida* species panel added to an antifungal stewardship strategy suggests improvements in the timeliness of antifungal therapy of patients with candidemia. ♦

Notes

Potential conflicts of interest. George Alangaden has received consulting fees from T2Biosystems and Astellas Pharmaceuticals. Susan Davis has received grant support from Merck, consulting fees from Allergan, the Medicines Company, and Zavante, and a speaker honorarium from Allergan. All other authors declare that they have no conflict of interest.

References

1. Garey KW, Rege M, Pai MP, Mingo DE, Suda KJ, Turpin RS, Bearden DT. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: A multi-institutional study. Clin Infect Dis 2006; 43:25-31.
2. Horn DL, Neofytos D, Anaissie EJ, Fishman JA, Steinbach WJ, Olyaei AJ, Marr KA, Pfaller MA, Chang CH, Webster KM. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis 2009; 48:1695-703.
3. Pfaller M, Neofytos D, Diekema D, Azie N, Meier-Kriesche HU, Quan SP, Horn D. Epidemiology and outcomes of candidemia in 3648 patients: data from the Prospective Antifungal Therapy (PATH Alliance)

registry, 2004 – 2008. Diagn Microbiol Infect Dis 2012; 74(4):323-31.
4. Patel GP, Simon D, Scheetz M, Crank CW, Lodise T, Patel N. The effect of time to antifungal therapy on mortality in candidemia associated septic shock. Am J Ther 2009; 16:508-11.
5. Clancy CJ, Nguyen MH. Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin Infect Dis 2013; 56:1284-92.
6. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, Srinivasan A, Dellit TH, Falck-Ytter YT, Fishman NO, Hamilton CW, Jenkins TC, Lipsett PA, Malani PN, May LS, Moran GJ, Neuhauser MM, Newland JG, Ohl CA, Samore MH, Seo SK, Trivedi KK. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016; 62:e51-77.
7. Huang AM, Newton D, Kunapuli A, Gandhi TN, Washer LL, Isip J, Collins CD, Nagel JL. Impact of rapid organism identification via matrix assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. Clin Inf Dis 2013; 57:1237-45.
8. Mylonakis E, Clancy CJ, Ostrosky-Ziechner L, Garey KW, Alangaden GJ, Vazquez JA, Groeger JS, Judson MA, Vinagre YM, Heard SO, Zervou FN, Zacharioudakis IM, Kontoyiannis DP, Pappas PG. T2 Magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: A clinical trial. Clin Infect Dis 2015; 60:892-9.
9. Leon C, Ruiz-Santana S, Saavedra P, Almirante B, Nolla-Salas J, Alvarez-Lerma F, Garnacho-Montero J, Leon MA, EPCAN Study Group. A bedside scoring system ("Candida score") for early antifungal treatment in non-neutropenic critically ill patients with Candida colonization. Crit Care Med 2006; 34:730-7.
10. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving Sepsis Campaign Guidelines Committee. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. Intensive Care Med 2013; 39:165-228.
11. Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to Candida infection: importance of empiric therapy and source control. Clin Infect Dis 2012; 54:1739-46.
12. Posteraro B, Tumbarello M, De Pascale G, Liberto E, Vallecoccia MS, De Carolis E, Di Gravio V, Trecarichi EM, Sanguinetti M, Antonelli M. (1,3)-β-d-Glucan-based antifungal treatment in critically ill adults at high risk of candidaemia: an observational study. J Antimicrob Chemother 2016; 71:2262-9.
13. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, Michalopoulos A, Rafailidis PI, Falagas ME. B-D-Glucan assay for diagnosis of invasive fungal infections: a meta-analysis. Clin Infect Dis 2011; 52:750-70.