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Short Communication

Clinical characteristics of *Candida tropicalis* fungaemia with reduced triazole susceptibility in Taiwan: a multicentre study

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ABSTRACT

Candida tropicalis is the second most common *Candida* species causing fungaemia in Taiwan, and decreased susceptibility to fluconazole has been reported. This study analysed the clinical characteristics of adult patients with *C. tropicalis* fungaemia and the antifungal susceptibilities of isolates at five tertiary hospitals in Taiwan (1 July 2011 to 30 June 2014). A standardised case record form was used retrospectively to collect demographic, clinical and microbiological characteristics, antifungal treatment and outcomes. MICs of non-duplicate isolates were determined using Sensititre™ YeastOne™ and were interpreted using cut-off values recommended by the CLSI. A total 248 patients were diagnosed over the study period; 30-day crude mortality was 52.0%. Multivariate analysis showed that high Charlson comorbidity index ≥4 (OR = 2.09, 95% CI 1.22–3.59; $P = 0.008$), neutropenia (OR = 4.61, 95% CI 1.42–15.00; $P = 0.011$) and treatment with an azole-based regimen (OR = 0.39, 95% CI 0.17–0.90; $P = 0.028$) were significantly associated with 30-day mortality. A total of 33.9% of isolates were non-susceptible to fluconazole (MIC_{50}, 2 mg/L; MIC_{90}, 16 mg/L; MIC range, 0.25 to >256 mg/L), whilst 56.9% to voriconazole (MIC_{50}, 0.25 mg/L; MIC_{90}, 1 mg/L; MIC range, 0.015 to >8 mg/L) according to CLSI clinical breakpoints. There was no significant correlation between overall mortality and MICs of fluconazole or voriconazole. This study showed high mortality in patients with *C. tropicalis* fungaemia, and azole-based antifungal treatment could improve outcomes regardless of fluconazole MICs of infecting isolates compared with patients without any treatment within 48 h.

1. Introduction

Candidaemia is one of the most common nosocomial infections and contributes significantly to morbidity and mortality. Although *Candida albicans* remains the most commonly identified species, the prevalence of non-*albicans Candida* spp. has increased in recent decades following extensive use of azoles and changing patient characteristics [1–3]. *Candida tropicalis* is one of the leading non-*albicans Candida* spp. causing candidaemia in Taiwan and is now emerging globally [1,2,4]. Despite effective treatment, high mortality rates continue to be reported in fungaemia caused by *C. tropicalis* [5,6]. *Candida tropicalis* fungaemia is often found in intensive care unit patients, especially in those with malignancies, receiving broad-spectrum antibiotics or undergoing prolonged catheterisation [5,7].

Antifungal susceptibility testing of *Candida* spp. is highly recommended for patients with candidaemia [8,9]. Advances in antifungal susceptibility testing techniques have prompted the Clinical and Laboratory Standard Institute (CLSI) to refine its standard methods, and species-specific epidemiological cut-off values (ECVs) have been established to detect potential emergence of

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resistant *Candida* isolates [8,10]. Revised species-specific clinical breakpoints (CBPs) have also been introduced to interpret triazole and echinocandin susceptibility of *Candida* isolates. Commercial methods including Etest, VITEK®2 and Sensititre™ YeastOne™ have been evaluated and found to be reliable [11].

Candida tropicalis isolates in Taiwan show reduced susceptibility to fluconazole and voriconazole but the clinical relevance of this remains undetermined [4]. In this study, the minimum inhibitory concentrations (MICs) of nine antifungal agents were determined using the Sensititre™ YeastOne™ colorimetric plate for *C. tropicalis* blood isolates taken from five medical centres in Taiwan between 2011 and 2014. Furthermore, clinical presentations were characterised, risk factors for acquiring isolates with reduced susceptibility to triazoles were identified, and the correlation between MICs and mortality was analysed.

2. Materials and methods

2.1. Hospital settings and definitions

Candida tropicalis blood isolates included for analysis were identified from laboratory records at five tertiary hospitals in Taiwan from 1 July 2011 to 30 June 2014. Only isolates from adult patients (aged >20 years) were included for further analysis. The five hospitals included Taipei Veterans General Hospital, Taipei ($n = 22$), China Medical University Hospital, Taichung ($n = 38$), Changhua Christian Hospital, Changhua ($n = 41$), Chi Mei Medical Center, Liouying Branch, Tainan ($n = 60$) and Kaohsiung Medical University Hospital, Kaohsiung ($n = 87$).

The study was approved by the Medical Ethics Committees of the five enrolled hospitals.

Candida isolates were identified to species level by morphological analysis on CHROMagar (Creative Life Science, Ltd., New Taipei, Taiwan) and by biochemical methods using API ID 32C system (bioMérieux, Marcy l'Étoile, France) or VITEK®2 system (bioMérieux) according to regulation from each hospital. A standardised case record form was used retrospectively to collect patient demographic, clinical and microbiological characteristics, concurrent antibiotic usage, concomitant bacteraemia, antifungal treatment and outcomes. Broad-spectrum antibiotic usage included exposure to third- and fourth-generation cephalosporins, piperacillin/tazobactam, carbapenems, fluoroquinolones, glycylcycline, glycopeptides and oxazolidinones. Catheter-associated bloodstream infection (CA-BSI) was defined as concurrent isolation of *C. tropicalis* from catheter tips by semiquantitative roll plate method. According to the CBPs proposed by the CLSI, adequate antifungal therapy for a susceptible isolate was defined as administration of the recommended dose of an antifungal drug within the first 48 h after blood culture collection.

2.2. Antifungal susceptibility testing

The antifungal susceptibility of non-duplicate blood isolates taken from 248 patients to nine antifungal agents was determined using the broth microdilution method with the Sensititre™ YeastOne™ system (Trek Diagnostic Systems, Ltd., East Grinstead, UK) in accordance with the manufacturer's instructions, conducted in a reference laboratory in Taipei Veterans General Hospital. *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019 were used as quality control isolates for each testing. The ranges of tested concentrations for the nine antifungal agents were as follows: fluconazole, 0.12–256 mg/L; itraconazole, 0.015–16 mg/L; voriconazole, 0.008–8 mg/L; posaconazole, 0.008–8 mg/L; caspofungin, 0.008–8 mg/L; micafungin, 0.008–8 mg/L; anidulafungin, 0.015–8 mg/L; 5-fluorocytosine, 0.06–64 mg/L; and amphotericin B, 0.12–8 mg/L [4,11,12]. Susceptibility to the nine antifungal agents was interpreted using CPBs, or using ECVs for agents without CBPs, according to CLSI recommendations [10]. Isolates that were intermediate, resistant or non-wild-type (WT) to more than one agent from two different classes of antifungal agents were considered to be multidrug-resistant (MDR) [13].

2.3. Statistical analysis

Continuous variables were expressed as the mean ± standard deviation. Categorical variables were compared using the χ^2 test. To identify independent factors that may influence mortality, a logistic regression model was performed to calculate the odds ratio (OR) and corresponding 95% confidence interval (CI). Survival analysis was performed with a Kaplan–Meier analysis and log-rank test. All statistical analyses were conducted using SAS® statistical software v.9.4 (SAS Institute, Cary, NC), and a P-value of <0.05 was used as the threshold for statistical significance.

3. Results

3.1. Patient characteristics

Detailed characteristics of the 248 patients with fungaemia are summarised in Table 1. Implantation of an intravascular device was common (71.0%), and 53 patients (21.4%) were identified as having a CA-BSI, mostly central venous catheter (CVC) or Port-A related ($n = 45$; 18.1%). A total of 230 patients (92.7%) received broad-spectrum antibiotics before fungaemia onset, and prior fluconazole usage was recorded in 11 patients (4.4%). Most of the patients (69.8%) were initially treated with fluconazole, 40 patients (16.1%) received echinocandins (5 caspofungin, 19 micafungin and 16 anidulafungin) and only 2 patients (0.8%) received amphotericin B treatment. The time period between fungaemia onset to antifungal treatment was available for 215 patients (86.7%); 71 patients (28.6%) received their treatment within the first 24 h, 39 (15.7%) between 24–48 h, 40 (16.1%) between 48–72 h and 65 (26.2%) >72 h after sepsis onset. Moreover, 44 patients (17.7%) received effective treatment within the first 24 h, 34 (13.7%) between 24–48 h, 34 (13.7%) between 48–72 h and none >72 h after sepsis onset. The 30-day all-cause mortality was 52%.

3.2. Antifungal susceptibility

The results of antifungal susceptibility testing for the 248 isolates are summarised in Table 2. A total of 164 isolates (66.1%) and 107 isolates (43.1%) were susceptible to fluconazole and voriconazole, respectively. Seventy isolates (28.2%) were found to be WT for posaconazole isolates. All three echinocandin agents tested showed a 97.6% susceptibility rate, suggesting that echinocandins remain effective against the tested isolates. A total of 245 isolates (98.8%) were found to be WT for 5-fluorocytosine, and all 248 isolates were found to be WT amphotericin B. Of the 84 isolates that were non-susceptible to fluconazole, including those that were susceptible-dose dependent (S-DD) or resistant, only 4 were susceptible to voriconazole and 5 were WT for posaconazole. Six isolates (2.4%) were considered to be MDR. Three isolates were non-susceptible to triazoles and echinocandins. The other three isolates that were considered to be non-WT for 5-fluorocytosine were also S-DD to fluconazole but remained susceptible to echinocandins. No clustering of MDR isolates in the same ward was observed.

3.3. Mortality analysis

Analysis of factors associated with 30-day crude mortality is summarised in Table 3 and Supplemental Table S1. Fluconazole MIC, adequate antifungal treatment within the first 48 h and

Table 1
Basic demographic and clinical characteristics[a] of *Candida tropicalis* fungaemia patients with different fluconazole minimum inhibitory concentrations (MICs).

Characteristic	Total ($n=248$)	Fluconazole MIC (mg/L) of:		
		≤2 ($n=164$)	4 ($n=43$)	≥8 ($n=41$)
Age (mean ± S.D.)	65.7 ± 17.3	65.4 ± 16.9	66.2 ± 19.5	66.4 ± 16.2
Male sex	173 (69.8)	115 (70.1)	27 (62.8)	31 (75.6)
CCI	3.9 ± 2.4	4 ± 2.5	3.8 ± 2.3	3.5 ± 2.3
Origin of infection				
Primary candidaemia	75 (30.2)	46 (28.0)	12 (27.9)	17 (41.5)
CA-BSI	53 (21.4)	32 (19.5)	10 (23.3)	11 (26.8)
UTI	41 (16.5)	31 (18.9)	3 (7.0)	7 (17.1)
Underlying conditions				
Solid cancer	116 (46.8)	77 (47.0)	21 (48.8)	18 (43.9)
Haematological malignancy	22 (8.9)	19 (11.6)	1 (2.3)	2 (4.9)
Neutropenia	21 (8.5)	16 (9.8)	3 (7.0)	2 (4.9)
Diabetes mellitus	92 (37.1)	66 (40.2)	12 (27.9)	14 (34.1)
ESRD with dialysis	23 (9.3)	11 (6.7)	8 (18.6)	4 (9.8)
Liver cirrhosis	27 (10.9)	18 (11.0)	2 (4.7)	7 (17.1)
COPD	23 (9.3)	17 (10.4)	4 (9.3)	2 (4.9)
Congestive heart failure	28 (11.3)	17 (10.4)	9 (20.9)	2 (4.9)
Risk factors				
Receiving chemotherapy	64 (25.8)	49 (29.9)	7 (16.3)	8 (19.5)
Receiving steroids	192 (77.4)	124 (75.6)	34 (79.1)	34 (82.9)
Recent total parenteral nutrition	47 (19.0)	30 (18.3)	10 (23.3)	7 (17.1)
Recent abdominal surgery	28 (11.3)	18 (11.0)	7 (16.3)	3 (7.3)
Presence of CVC	101 (40.7)	68 (41.5)	20 (46.5)	13 (31.7)
Presence of Port-A	83 (33.5)	58 (35.4)	12 (27.9)	13 (31.7)
Presence of Foley catheter	103 (41.5)	70 (42.7)	14 (32.6)	19 (46.3)
Presence of pigtail catheter	21 (8.5)	14 (8.5)	2 (4.7)	5 (12.2)
Prior exposure to broad-spectrum antibiotics	230 (92.7)	151 (92.1)	40 (93.0)	39 (95.1)
Concomitant bacteraemia	92 (37.1)	58 (35.4)	23 (53.5)	11 (26.8)
Antifungal treatment				
Azole-based regimen	173 (69.8)	117 (71.3)	28 (65.1)	28 (68.3)
Echinocandin-based regimen	40 (16.1)	23 (14.0)	10 (23.3)	7 (17.1)
Amphotericin B-based regimen	2 (0.8)	2 (1.2)	0 (0)	0 (0)
No use of antifungal agents	33 (13.3)	22 (13.4)	5 (11.6)	6 (14.6)
Appropriate antifungal therapy	112 (45.2)	94 (57.3)	15 (34.9)	3 (7.3)
Outcomes				
30-Day mortality	129 (52.0)	88 (53.7)	25 (58.1)	16 (39.0)
Early mortality (0–7 days)	66 (26.6)	45 (27.4)	13 (30.2)	8 (19.5)
Late mortality (8–30 days)	63 (25.4)	43 (26.2)	12 (27.9)	8 (19.5)

S.D., standard deviation; CCI, Charlson comorbidity index; CA-BSI, catheter-associated bloodstream infection; UTI, urinary tract infection; ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter.
[a] Data are *n* (%) unless otherwise stated.

Table 2
Minimum inhibitory concentration (MIC) distribution to nine antifungal agents for 248 *Candida tropicalis* isolates.

Antifungal agent	MIC (mg/L)			Susceptibility according to CBPs [*n* (%)]				Interpretation according to ECVs [*n* (%)]	
	Range	MIC_{50}	MIC_{90}	S	S-DD	I	R	WT	Non-WT
Fluconazole	0.25 to >256	2	16	164 (66.1)	43 (17.3)		41 (16.5)		
Voriconazole	0.015 to >8	0.25	1	107 (43.1)	109 (44.0)		32 (12.9)		
Itraconazole	0.06–1	0.25	0.5					237 (95.6)	11 (4.4)
Posaconazole	0.015–2	0.25	0.5					70 (28.2)	178 (71.8)
Caspofungin	0.015 to >8	0.06	0.25	242 (97.6)		2 (0.8)	4 (1.6)		
Micafungin	0.015–2	0.03	0.03	242 (97.6)		2 (0.8)	4 (1.6)		
Anidulafungin[a]	0.03–2	0.12	0.25	242 (97.6)		1 (0.4)	4 (1.6)		
5-Fluorocytosine	<0.06–64	0.06	0.12					245 (98.8)	3 (1.2)
Amphotericin B	0.12–2	0.5	1					248 (100.0)	0 (0.0)

$MIC_{50/90}$, MIC required to inhibit 50% and 90% of the isolates, respectively; CBP, clinical breakpoint; ECV, epidemiological cut-off value; S, susceptible; S-DD, susceptible-dose dependent; I, intermediate; R, resistant; WT, wild-type.
[a] Only 247 isolates were available for drug susceptibility testing to anidulafungin.

concomitant bacteraemia were not significantly associated with mortality. Timing of antifungal treatment after fungaemia onset also showed no association with mortality ($P=0.76$). Multivariate analysis showed that high Charlson comorbidity index (CCI ≥ 4) (OR = 2.09, 95% CI 1.22–3.59; $P=0.008$), neutropenia (OR = 4.61, 95% CI 1.42–15.00; $P=0.011$) and treatment with an azole-based regimen (OR = 0.39, 95% CI 0.17–0.90; $P=0.028$) were associated with 30-day survival. No significant differences were observed among patients infected by isolates with different MICs for fluconazole ($P=0.515$) or voriconazole ($P=0.365$) (Supplementary Figs S1 and S2).

4. Discussion

This retrospective study showed high mortality, which was unrelated to fluconazole MICs, in patients with *C. tropicalis* fungaemia. The mortality associated with *C. tropicalis* fungaemia has been reported to be higher than other non-*albicans* candidaemias

Table 3
Risk factors associated with 30-day crude mortality in patients with *Candida tropicalis* fungaemia.

Variable	*n* (%)		Univariate analysis		Multivariate analysis	
	Survival ($n = 119$)	Mortality ($n = 129$)	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
CCI ≥ 4	48 (40.3)	73 (56.6)	1.93 (1.16–3.20)	0.011	2.09 (1.22–3.59)	0.008
CA-BSI	32 (26.9)	21 (16.3)	0.53 (0.29–0.98)	0.043		
Neutropenia	4 (3.4)	17 (13.2)	4.36 (1.42–13.37)	0.010	4.61 (1.41–15.00)	0.011
Liver cirrhosis	5 (4.2)	22 (17.1)	4.69 (1.71–12.82)	0.003		
Presence of CVC	40 (33.6)	61 (47.3)	1.77 (1.06–2.96)	0.029		
Presence of Port-A	49 (41.2)	34 (26.4)	0.51 (0.30–0.87)	0.014		
Treatment with azole-based regimen	93 (78.2)	80 (62.0)	0.37 (0.13–0.83)	0.016	0.39 (0.17–0.90)	0.028

OR, odd ratio; CI, confidence interval; CCI, Charlson comorbidity index; CA-BSI, catheter-associated bloodstream infection; CVC, central venous catheter.

[5,14]. Bassetti et al. found *C. tropicalis* to have a higher fungaemia mortality rate (58.3%) compared with other *Candida* spp. [6]. However, unlike in the current study, isolates from their study remained susceptible (92.3%) to fluconazole [6]. A recent study from Spain showed a lower mortality rate (18.6%) for *C. tropicalis*, and no difference in mortality was found between *C. tropicalis* and other *Candida* spp. [15]. High fluconazole and voriconazole resistance rates (23.2% and 26.8%, respectively) as defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were also found in that study. However, the authors noted that neither initial appropriate antifungal therapy nor fluconazole MIC had any significant impact on outcomes [15], and the latter finding is consistent with the results of the current study as we also found no differences in mortality for each fluconazole MIC category. Patients in the Spanish study had a lower CCI (mean, 2), which could have resulted in lower mortality.

Previous studies have identified several risk factors associated with candidaemia mortality, including sepsis, steroid usage and liver cirrhosis [6]. Early treatment and removal of CVCs within 48 h have been found to improve outcomes in candidaemia patients [15,16]. In the current study, high CCI (≥4), neutropenia and treatment with an azole-based antifungal regimen were found to be significantly associated with mortality. These results are consistent with a recent study conducted on cancer patients [2]. Patients with underlying haematological malignancies, particularly leukaemia, were more likely to have *C. tropicalis* infections compared with other candidaemia species [15]. In the current study, neutropenia was independently associated with a greater risk of mortality in candidaemia patients. Compared with other non-antifungal treatments, azole-based therapy was associated with lower mortality. Other treatment regimens were not significantly associated with lower mortality compared with non-treatment, a possible reason being that fewer patients received echinocandins or amphotericin B in this study. The current Infectious Diseases Society of America (IDSA) guidelines recommend echinocandins as first-line agents for candidaemia [9]. However, echinocandins were approved for treating invasive candidiasis as second-line agents before 2008 in Taiwan, which may explain the relatively lower echinocandin usage despite guideline recommendation.

This study suggests that *C. tropicalis* isolates in Taiwan are showing emerging resistance to triazole. Fluconazole resistance in *C. tropicalis* isolates has been noted to be higher than in *C. albicans* [4]. A recent study conducted in 2013 on global isolates found that *C. tropicalis* had a 11.6% resistance rate to fluconazole [17]. More recently, in a Taiwanese study (TSARY) conducted in 2014 a higher rate of non-susceptible *C. tropicalis* blood isolates was found for fluconazole and voriconazole (12.8% and 8.5%, respectively), but only 47 *C. tropicalis* blood isolates were included in this study [18]. In their study on *C. tropicalis* isolates collected from sterile sites, Yang et al. reported an emerging trend of fluconazole resistance over the past decade in Taiwan [19]. The prevalence of isolates with fluconazole MICs ≥ 64 mg/L increased from 0% in 2002 to 19.5% in 2006 [19]. In another recent study, respective fluconazole and voriconazole non-susceptible rates were 13.6% and 21.4% for *C. tropicalis* blood isolates collected between 2009–2010 in Taiwan [4]. In addition, a significant proportion (62.2%) of the isolates were considered to be non-WT for posaconazole [4]. The current study showed an even higher triazole-non-susceptible rate. Certain strains (diploid sequence type 140) with high fluconazole MICs (≥64 mg/L) have become more prevalent in Taiwan [20]. We did not perform further typing of the 13 isolates with high fluconazole MICs (≥64 mg/L) and therefore further investigation of the genetic relatedness between these isolates is warranted.

This study also showed a low resistance rate to echinocandins, which is consistent with previous studies in Taiwan [4,7,19]. Echinocandins were introduced in Taiwan less than a decade ago and have not been used widely. Rare usage could be a reason that the efficacy of these agents in Taiwan remains intact. A small number of MDR isolates was found in this study. Increased mortality caused by MDR strains has been reported. Prospective susceptibility monitoring, molecular detection of mutations, and research on genetic relatedness are required to monitor the spread of MDR strains.

This study has several limitations. First, clinical practice procedures and patient characteristics differed for each medical centre. Policies regarding antifungal treatment and removal of CVCs or implantations in patients with fungaemia were different for each centre. Information about catheter removal in patients with CA-BSI was unavailable, thus its influence on survival could not be evaluated. Second, surveillance of deep-seated infection also differed between each hospital. Data regarding eyeground check-up and cardiac echo were not available in this study. Third, lack of mortality data for other *Candida* spp., particularly *C. albicans*, means that it was not possible to compare the mortality of *C. tropicalis* with other species. Fourth, although MDR strains occurred in different hospitals, genetic relatedness should be determined to exclude clonal spread.

In conclusion, this study showed high mortality in patients with *C. tropicalis* fungaemia, and azole-based antifungal treatment could improve outcomes regardless of fluconazole MICs of infecting isolates compared with patients without any treatment within 48 h. Close monitoring of azole non-susceptibility and the prevalence of MDR strains could provide important reference information for Taiwanese hospitals. However, given the retrospective design of this study, confounding cannot be ruled out and a standardised treatment protocol for candidaemia was not used. Future prospective studies are needed to determine the clinical significance of different triazole susceptibilities and antifungal therapy in patients with *C. tropicalis* fungaemia.

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Competing interests

None declared.

Ethical approval

This study was approved by the Medical Ethics Committees of the five enrolled hospitals [Taipei Veterans General Hospital, Taipei, 2014-11-009ACF; China Medical University Hospital, Taichung, CMUH104-REC1-032; Changhua Christian Hospital, Changhua, 150501; Chi Mei Medical Center, Liouying Branch, Tainan, 10303-L12; Kaohsiung Medical University Hospital, Kaohsiung, KMUH-IRB-20140276].

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.10.015.

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