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Effect of initial antifungal therapy on mortality among patients with bloodstream infections with different *Candida* species and resistance to antifungal agents: A multicentre observational study by the Turkish Fungal Infections Study Group

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ABSTRACT

This study aimed to describe the effect of initial antifungal therapy on patient mortality and to detail the current distribution and resistance patterns of *Candida* spp. among patients with candidaemia. A prospective observational study was performed among consecutive patients with candidaemia from 10 Turkish medical centres between January 2015 and November 2018. The primary outcome was 10-day mortality. Species were identified using MALDI-TOF/MS. A total of 342 patients with candidaemia were included, of which 175 (51.2%) were male and 68 (19.9%) were aged <18 years. The most common species were *Candida albicans* (47.4%), *Candida parapsilosis* (26.6%), *Candida tropicalis* (9.6%) and *Candida glabrata* (7.6%). Among all *Candida* spp., the 10-day case fatality rate (CFR) was 32.2%. The CFR was highest in patients with *C. albicans* (57.3%) and lowest in patients with *C. parapsilosis* (21.8%). The resistance rate to fluconazole was 13% in *C. parapsilosis*, with no significant effect on mortality. No resistance to echinocandins was detected. In the multivariate analysis, being in the ICU [OR = 2.1 (95% CI 1.32–3.57); $P = 0.002$], renal failure [OR = 2.4 (1.41–3.97); $P = 0.001$], total parenteral nutrition [OR = 2 (1.22–3.47); $P = 0.006$], *C. albicans* infection [OR = 1.7 (1.06–2.82); $P = 0.027$] and echinocandin as primary agent [OR = 0.6 (0.36–0.99); $P = 0.047$] were significantly associated with mortality. Candidaemia is a deadly infection. Fluconazole resistance is emerging, although it was not significantly related to mortality. Using an echinocandin as the primary agent could be life-saving.

1. Introduction

Candida spp. are the fourth and seventh most common cause of healthcare-associated bloodstream infections (BSIs) in the USA and Europe, respectively [1,2]. According to hospital-based studies, the global incidence of candidaemia varies from 0.3 to 5 per 1000 admissions [3]. The attributable mortality rate of candidaemia was reported as between 5–71% [4]. In critically ill patients, both patient co-morbidities and the infection itself contribute to mortality [5]. The risk of mortality can be reduced by early initiation of appropriate antifungal treatment [6]. It is known that one of the

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main risks for increased mortality in candidaemia is a delay in appropriate antifungal treatment until positive blood culture [7]. Despite the known risk factors, candidaemia remains associated not only with a high mortality rate but also prolonged hospital stays and increased hospital costs [8].

The distribution of *Candida* spp. causing candidaemia varies according to geographic location, patient population and antifungal stewardship policies. *Candida albicans* remains the most frequently isolated species in almost every centre globally, however some studies report an increasing rate of isolation of non-*albicans Candida* spp. [9]. In a single-centre study from France, the change in species distribution of candidaemia isolates over a decade was evaluated and no significant differences was found between 2000 and 2010 [10]. In the USA and Northern Europe, *Candida glabrata* is reported as the second most common causative agent of candidaemia, whereas *Candida parapsilosis* is the most commonly isolated species following *C. albicans* in Southern Europe and Latin America [11]. A study by Ding et al. found previous azole therapy [odds ratio (OR) = 3.359, 95% confidence interval (CI) 1.136–10.154; $P = 0.031$] and use of artificial surgical implants (OR = 37.519, 95% CI 2.5–562.998; $P = 0.009$) to be significant risk factors for infection with non-*albicans Candida* spp. [12]. In another multicentre study, the mortality rate was found to be significantly higher in infections by non-*albicans Candida* spp. than infections by *C. albicans* (65% vs. 53%; $P = 0.10$), and female sex (OR = 2.09, 95% CI 1.13–3.86) and increased duration of central venous catheter (CVC) use (OR = 1.16 per 5-day interval, 95% CI 1.05–1.28) were found to be an independent risk factors for non-*albicans* candidaemia [13].

According to several guidelines, fluconazole or echinocandins may be considered for initial treatment of *Candida* BSI [14,15]. The severity of underlying diseases and co-morbidities of the patient, the epidemiological distribution of the causative agents, and the resistance rates can directly effect the choice of the primary drug for therapy of candidaemia. This study aimed to describe the effect of initial antifungal therapy on mortality among patients with candidaemia and to detail the current distribution and resistance patterns of *Candida* spp. isolates.

2. Methods

2.1. Study design and population

A prospective observational study was performed among consecutive patients with candidaemia from 10 Turkish medical centres between January 2015 and November 2018. The design of the study fulfilled the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) criteria. An episode of candidaemia was defined as the isolation of a *Candida* sp. isolate from blood cultures. Patient cultures with two or more fungal species were excluded from the analysis. The primary outcome was 10-day mortality. Treatment success was defined as clinical and mycological response at the end of therapy. Demographic and clinical data [age, sex, being in the intensive care unit (ICU), operation within previous month, antibiotic use within previous month, presence of malignancy, neutropenia, renal failure, solid-organ transplantation, presence of a CVC, total parenteral nutrition, usage of mechanical ventilation, prior antifungal exposure and initial antifungal therapy] were recorded on a standardised case report form. Initial antifungal therapy was defined as the primary antifungal treatment, either empirical or targeted, given to the patient for ≥96 h. Patients receiving amphotericin B or voriconazole and patients who did not receive any treatment were excluded from the analysis of initial antifungal therapy.

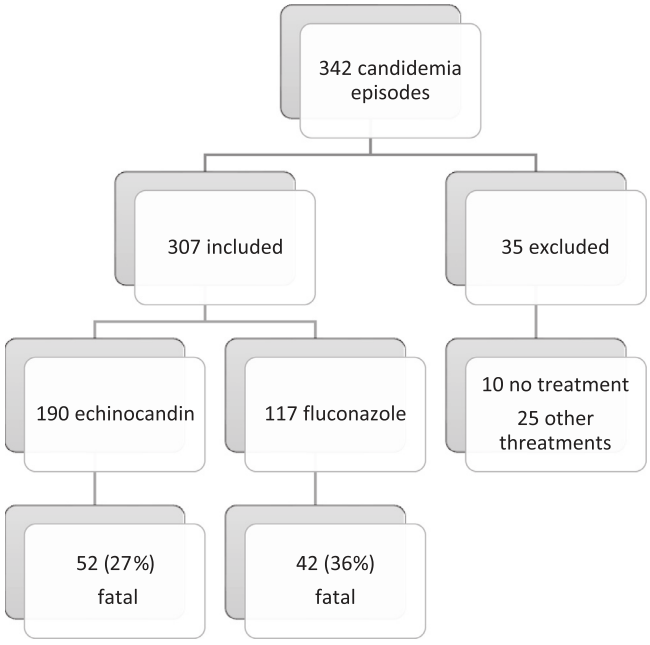

Fig. 1. Flowchart of candidaemia patients included in the study and initial antifungal therapy.

2.2. Mycological studies

For microbiological evaluation, all isolates were identified in the participating hospital laboratories and were confirmed by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (bioMérieux, Lyon, France) in the reference mycology laboratory (Mycology Laboratory, Koç University Hospital, Istanbul, Turkey). Antifungal susceptibility testing for fluconazole, voriconazole, posaconazole, caspofungin and amphotericin B was performed by the broth microdilution method according to Clinical and Laboratory Standards Institute (CLSI) guidelines [16]. Minimum inhibitory concentrations (MICs) were evaluated following incubation for 24 h and 48 h. For interpretation of antifungal susceptibility test results, if possible species-specific clinical breakpoints or epidemiological cut-off values were used as recommended by the CLSI [17,18].

2.3. Statistical data

Data were analysed using Stata Statistical Software: Release 14.2 (StataCorp LP, College Station, TX, USA). Continuous variables were compared by Student's *t*-test or Mann–Whitney *U*-test. Categorical variables were compared by χ^2 test. Statistical significance was determined using two-tailed tests, and a *P*-value of <0.05 was considered statistically significant. Variables that were found to have a significant effect on 10-day mortality in the univariate analysis were included in the multivariate model, and logistic regression was performed calculating the OR and corresponding 95% CI.

3. Results

A total of 342 patients with candidaemia were enrolled in the study, among which 35 patients were excluded (10 did not receive any antifungal therapy, 23 received amphotericin B and 2 received voriconazole). Among the 307 remaining patients, initial antifungal therapy was an echinocandin in 190 patients and fluconazole in 117 patients (Fig. 1).

Patients with *C. parapsilosis* were the youngest (mean age 42 years), whereas patients with *C. glabrata* infection were the old-

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Table 1
Predictors of 10-day mortality among patients with candidaemia in the univariate analysis[a].

Variable	Survived (n = 232)	Died (n = 110)	P-value
Age (years) (mean ± S.D.)	48 ± 27	51 ± 25	0.212
Female sex	114 (49.1)	53 (48.2)	0.869
Being in the ICU	74 (31.9)	62 (56.4)	<0.001
Operation within previous month	122 (52.6)	58 (52.7)	0.981
Antibiotic use in previous month	204 (87.9)	105 (95.5)	0.028
Malignancy	92 (39.7)	37 (33.6)	0.283
Renal failure	60 (25.9)	51 (46.4)	<0.001
Transplantation	17 (7.3)	6 (5.5)	0.518
CVC	188 (81.0)	98 (89.1)	0.060
Total parenteral nutrition	127 (54.7)	80 (72.7)	0.001
Mechanical ventilation	42 (18.1)	19 (17.3)	0.851
Candida albicans	99 (42.7)	63 (57.3)	0.012
Candida parapsilosis	67 (28.9)	24 (21.8)	0.167
Candida tropicalis	26 (11.2)	7 (6.4)	0.156
Candida glabrata	21 (9.1)	5 (4.5)	0.142
Echinocandin use as primary agent	138 (59.5)	52 (47.3)	0.034
Fluconazole use as primary agent	75 (32.3)	42 (38.2)	0.286
Fluconazole resistance	9 (3.9)	3 (2.7)	0.323

S.D., standard deviation; ICU, intensive care unit; CVC, central venous catheter.
[a] Data are n (%) unless otherwise stated.

Table 2
Predictors of 10-day mortality among patients with candidaemia in the multivariate analysis.

Variable	Unadjusted			Adjusted		
	OR	95% CI	P-value	OR	95% CI	P-value
Being in the ICU	2.7	1.72–4.39	<0.001	2.1	1.32–3.57	0.002
Antibiotic use within previous month	2.8	1.08–7.68	0.034	–	–	–
Renal failure	2.5	1.53–3.98	<0.001	2.4	1.41–3.97	0.001
Total parenteral nutrition	2.2	1.34–3.6	0.002	2	1.22–3.47	0.006
Candida albicans	1.8	1.13–2.84	0.012	1.7	1.06–2.82	0.027
Echinocandin use as primary agent	0.6	0.38–0.96	0.034	0.6	0.36–0.99	0.047

OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

est (mean age 57 years). Among the 342 included patients, 175 (51.2%) were male and 68 (19.9%) were aged <18 years. Among all the patients, 28 (8.2%) had previously received an antifungal drug (20 fluconazole, 5 echinocandin and 3 both fluconazole and an echinocandin). Among the 28 patients who had received previous antifungal treatment, 11 (39%) had *C. albicans* infection and 17 (61%) had non-*albicans Candida* infection. Among all *Candida* spp., the 10-day case fatality rate (CFR) was 32.2%. Independent predictors of mortality are shown in Table 1.

In the multivariate analysis, being in the ICU (OR = 2.1, 95% CI 1.32–3.57; P = 0.002), renal failure (OR = 2.4, 95% CI 1.41–3.97; P = 0.001), total parenteral nutrition (OR = 2, 95% CI 1.22–3.47; P = 0.006) and *C. albicans* infection (OR = 1.7, 95% CI 1.06–2.82; P = 0.027) were found to be significantly positively associated with 10-day mortality. In contrast, using an echinocandin as the primary agent was significantly negatively associated with 10-day mortality (OR = 0.6, 95% CI 0.36–0.99; P = 0.047) (Table 2).

The most common *Candida* spp. were *C. albicans* (47.4%), *C. parapsilosis* (26.6%), *Candida tropicalis* (9.6%) and *C. glabrata* (7.6%). Species-specific patient characteristics are presented in Table 3. The highest CFR was among patients with *C. albicans* (57.3%; P = 0.012) and the lowest was among patients with *C. parapsilosis* (21.8%; P = 0.167). The resistance rate to fluconazole was 13% in *C. parapsilosis* isolates. Among 12 patients with fluconazole-resistant *C. parapsilosis* isolates, three infections were fatal. The choice of initial antifungal therapy was fluconazole for 5 of 12 fluconazole-resistant *C. parapsilosis* infections before the positive blood culture and antifungal susceptibility test results were obtained. Among these five patients, one patient died who had received fluconazole for the first 7 days and caspofungin for the next 6 days. Fluconazole resistance has no significant effect on mortality (P = 0.167) compared with fluconazole-susceptible *C. parapsilosis* infections. No resistance to echinocandins was detected (Table 4).

4. Discussion

In this multicentre prospective observational study, initial echinocandin therapy was found to be associated with a better outcome (OR = 0.6, 95% CI 0.36–0.99; P = 0.047). Current guidelines from the Infectious Diseases Society of America (IDSA) recommend an echinocandin as the first-line therapy of candidaemia in clinically moderate and severe patients [14]. In a patient-level quantitative review of seven randomised trials, echinocandins were found to be associated with better survival rates than either triazoles or polyenes [19]. To date, there is only one randomised controlled study comparing fluconazole with an echinocandin for the treatment of *Candida* BSI, in which fluconazole was associated with lower success rates compared with anidulafungin [20]. In a recent large retrospective cohort analysis, initial echinocandin treatment was found to be associated with decreased hospital mortality compared with fluconazole (OR = 0.22, 95% CI 0.06–0.85; P = 0.028) [21].

On the other hand, some studies obtained discordant results regarding the superiority of empirical echinocandin treatment among patients with candidaemia. In a multicentre prospective cohort study from Spain, López-Cortés et al. found that empirical therapy with fluconazole was associated with a better prognosis (adjusted hazard ratio = 0.38, 95% CI 0.17–0.81; P = 0.01) but this association disappeared in the propensity score-based stratified and matched analyses, which could be the result of the control of confounding variables [22]. In another multicentre cohort study, no difference

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Table 3
Species-specific characteristics of patients with candidaemia[a].

Characteristic	*C. albicans* (n = 162)	Non-*albicans Candida* spp.				
		Total (n = 180)	*C. parapsilosis* (n = 91)	*C. tropicalis* (n = 33)	*C. glabrata* (n = 26)	Others[b] (n = 30)
10-day mortality	63 (38.9)	47 (26.1)	24 (26)	7 (21)	5 (19)	11 (37)
Age (years) (mean ± S.D.)	51.4 ± 26	46.4 ± 26	41.5 ± 28	46.2 ± 26	57.3 ± 21	52 ± 26
Female sex	85 (52.5)	82 (45.6)	35 (38)	14 (42)	17 (65)	16 (53)
Being in the ICU	67 (41.4)	69 (38.3)	48 (53)*	10 (30)	4 (15)	7 (23)
Operation within previous month	90 (55.6)	90 (50.0)	46 (51)	18 (55)	14 (54)	12 (40)
Antibiotic use within previous month	146 (90.1)	163 (90.6)	84 (92)	31 (94)	22 (85)	26 (87)
Malignancy	65 (40.1)	64 (35.6)	21 (23)	16 (48)	16 (62)**	11 (37)
Renal failure	56 (34.6)	55 (30.6)	33 (36)	8 (24)	4 (15)	10 (33)
Transplantation	8 (4.9)	15 (8.3)	5 (5)	2 (6)	2 (8)	6 (20)
CVC	134 (82.7)	152 (84.4)	78 (86)	30 (91)	21 (81)	23 (77)
Total parenteral nutrition	99 (61.1)	108 (60.0)	57 (63)	17 (52)	19 (73)	15 (50)
Mechanical ventilation	35 (21.6)	26 (14.4)	18 (20)	4 (12)	1 (4)	3 (10)
Diabetes mellitus	18 (11.1)	26 (14.4)	11 (12)	3 (9)	6 (23)	6 (20)
Echinocandin use as primary agent	86 (53.1)	104 (57.8)	45 (49)	21 (64)	17 (65)	21 (70)
Fluconazole use as primary agent	58 (35.8)	59 (32.8)	38 (42)	8 (24)	7 (27)	6 (20)

S.D., standard deviation; ICU, intensive care unit; CVC, central venous catheter.
[a] Data are n (%) unless otherwise stated.
[b] *C. krusei* (n = 9), *C. kefyr* (n = 9), *C. lusitaniae* (n = 5), *C. dubliniensis* (n=4) and *C. guilliermondii* (n = 3).
* P = 0.008.
** P = 0.009.

Table 4
Minimum inhibitory concentration (MIC) distribution of the isolates.

Species/antifungal agent	MIC (mg/L)			Susceptibility [n (%)]	
	MIC_{50}	MIC_{90}	Range	Resistant	Intermediate
Candida albicans (n = 162)					
Fluconazole	0.125	0.125	0.125–0.5	0	
Voriconazole	0.015	0.03	0.015–0.03	0	
Posaconazole	0.03	0.03	0.03–0.06	0	
Caspofungin	0.06	0.25	0.03–0.25	0	
Amphotericin B	1	1	0.5–1	0	
Candida parapsilosis (n = 91)					
Fluconazole	1	8	0.125–32	12 (13)	8 (9)
Voriconazole	0.015	0.5	0.015–0.5	0	9 (10)
Posaconazole	0.03	0.125	0.03–0.5	0	
Caspofungin	0.5	2	0.03–2	0	
Amphotericin B	1	2	0.5–2	0	
Candida glabrata (n = 26)					
Fluconazole	2	8	0.5–8	0	
Voriconazole	0.125	0.25	0.015–0.25	0	
Posaconazole	0.5	0.5	0.03–1	0	
Caspofungin	0.06	0.125	0.03–0.125	0	
Amphotericin B	2	2	1–2	0	
Candida tropicalis (n = 33)					
Fluconazole	0.5	1	0.125–2	0	
Voriconazole	0.03	0.06	0.015–0.125	0	
Posaconazole	0.03	0.06	0.03–0.125	0	
Caspofungin	0.125	0.25	0.03–0.25	0	
Amphotericin B	1	2	0.5–2	0	

$MIC_{50/90}$, MICs for 50% and 90% of the isolates, respectively.

in mortality between two drugs was found after adjustment for Acute Physiology and Chronic Health Evaluation (APACHE) II scores in patients with septic shock due to candidaemia [23].

The overall 10-day CFR in this study was 32.2% and was highest (57.3%; P = 0.012) among patients with *C. albicans* BSI (OR = 1.7, 95% CI 1.06–2.82; P = 0.027). *Candida parapsilosis* was the second most commonly isolated species, similar to previous reports from Turkey and Southern Europe [11,24]. In the current study, 12 (13%) of 91 *C. parapsilosis* isolates were found to be non-susceptible to fluconazole, which were obtained from patients in three different hospitals In a multicentre study from Turkey, the fluconazole resistance rate in *C. parapsilosis* was found be 7.7% [25]. In a recent global antifungal surveillance analysis, among 225 *C. parapsilosis* isolates from Europe, the fluconazole resistance rate was 15.1% and the majority of the non-susceptible isolates were obtained from three hospitals in Italy and harbouring the same resistance mechanism [26]. In the current study, high resistance to fluconazole in *C. parapsilosis* isolates was detected with no significant effect on patient outcomes (P = 0.167). Despite the higher MICs of echinocandins against *C. parapsilosis*, initial echinocandin treatment was not associated with a negative outcome in *C. parapsilosis* BSI [27]. These results could be explained by the low virulence of *C. parapsilosis*, but further investigations should be performed on the resistance mechanisms and clonal distribution of the *C. parapsilosis* isolates.

Strengths of this study were being a large prospective clinical cohort including *Candida* BSI. All of the samples were re-tested in the reference mycology laboratory using MALDI-TOF/MS. The ref-

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erence broth microdilution method was used for antifungal susceptibility testing. A limitation of the study was the lack of disease severity scores for the patients, but it is more likely to give echinocandins for severe patients and, despite this fact, patients who received echinocandins as initial therapy had better outcomes in the multivariate analysis.

In conclusion, candidaemia is one of the most fatal infections. Resistance to fluconazole is emerging, although in this study it was not significantly related to mortality. Using echinocandins as the primary agent was found to be beneficial.

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