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ORIGINAL ARTICLE

Change in species distribution and antifungal susceptibility of candidemias in an intensive care unit of a university hospital (10-year experience)

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Abstract

Candidemia is a nosocomial infection mostly found in critically ill patients. Our objectives were to evaluate the change in distribution and resistance profile of *Candida* spp. isolated from candidemic patients in our intensive care unit over two 5-year periods spanning 15 years and to evaluate the risk factors. Records from the microbiology laboratory were obtained, from January 2004 to December 2008 and from January 2013 to December 2017, retrospectively. Antifungal susceptibility was performed by E-test and evaluated according to EUCAST breakpoints. A total of 210 candidemia cases occurred; 238 *Candida* spp. were isolated in 197 patients (58.8% male; mean age, 59.2 ± 19.6 years). The most predominant risk factor was central venous catheter use. Species distribution rates were 32%, 28%, 17%, and 11% for *C. albicans* ($n = 76$), *C. parapsilosis* ($n = 67$), *C. glabrata* ($n = 40$), and *C. tropicalis* ($n = 27$), respectively. Resistance rate to anidulafungin was high in *C. parapsilosis* over both periods and increased to 73% in the second period. Fluconazole showed a remarkable decrease for susceptibility in *C. parapsilosis* (94 to 49%). The prevalence of MDR *C. parapsilosis* (6%/33%) and *C. glabrata* (0%/44%) increased in the second period. We observed a predominance of non-albicans *Candida* spp., with *C. parapsilosis* being the most frequent and *C. glabrata* infections presenting with the highest mortality. High level of echinocandin resistance in *C. parapsilosis* and increasing prevalences of MDR *C. parapsilosis* and *C. glabrata* seem emerging challenges in our institution.

Keywords Candida · Species · Candidemia · Susceptibility · E-test

Introduction

Candidemia is one of the three most frequently encountered nosocomial bloodstream infections [1, 2]. The incidence of candidemia was reported as 1.2 and 25 cases per 100,000 persons, 1.22 episodes per 1000 discharges in studies from Europe, United States, and Asia, respectively. [3–5].

Candidemia is a nosocomial infection found mostly in critically ill, immunosuppressed, and surgical patients; it leads to prolonged hospitalization and presents with high morbidity

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and mortality rates [6, 7]. Attributable mortality rate may reach 50% or higher in septic shock [8]. Use of broad-spectrum antibiotics and immunosuppressive drugs, prolonged hospitalization, intensive care unit (ICU) stay, history of intra-abdominal surgery, parenteral nutrition, hemodialysis, and use of central venous catheters (CVC) are among the important predisposing risk factors for candidemia [9, 10].

Prolonged hospital stay and hospital costs lead to significant economic burden. In a systematic review, mean cost per hospitalization associated with candidemia was demonstrated to range from $10,216 to $37,715 [11].

The incidence of candidemia has steadily increased over the recent years and the epidemiology of candidemia has changed over the decades, shifting from *C. albicans* to non-albican species. Although species distribution differs by geographic areas due to different underlying conditions, widespread therapeutic and prophylactic use of antifungal agents has led to a worldwide increase in prevalence of infections with non-albicans *Candida* species such as *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* [12–15]. Furthermore, extensive use of fluconazole may have led to selection of isolates that are resistant or less sensitive to fluconazole [16–18]. Increasing rates of acquired fluconazole resistance in non-albicans *Candida* spp. have been reported in both SENTRY study and population-based surveillance programs [15, 19–21].

Data regarding the incidence of candidemia is sparse in Turkey: incidence was reported as 1–1.5 per 1000 admissions in some studies [22–24]. There is only one multicenter study reporting in vitro resistance in candidemia isolates in Turkey [25]. Other reports evaluating candidemia cases are mostly from single centers and no prior study from Turkey evaluated candidemia cases by means of clinical aspects, species distribution, susceptibilities, and microbiological changes over time.

In this study, we aimed to evaluate the change in distribution and resistance profiles of *Candida* spp. isolated from blood cultures of candidemic patients followed up in the ICU of our hospital over two 5-year periods spanning 15 years and determine the underlying risk factors and outcome.

Material and methods

Documented candidemia in patients followed in the ICU of our university hospital over two 5-year periods (January 2004 to December 2008 and January 2013 to December 2017) were analyzed retrospectively.

Our university hospital has 1200 beds and is located at the center of Istanbul. Patients from all parts of our country may be referred to our center. Our 13-bed medical surgery intensive care unit admits 600–800 patients annually. In cases of candidemia, the first preferred regimen is fluconazole and it is re-evaluated and changed if necessary, according to the susceptibility results.

Patients and episodes

Records from the microbiology laboratory were evaluated to identify patients with positive peripheral blood cultures for *Candida* spp. from January 2004 to December 2008 and from January 2013 to December 2017, retrospectively, giving a gap of 5 years to be able to evaluate the evolution of resistance with time. Isolation of *Candida* spp. from at least one blood culture of a patient was defined as candidemia. Isolation of *Candida* spp. from the same patient was considered as a new candidemia episode if the isolation times were ≥ 1 month apart.

Clinical data were collected from the patients' available medical files and underlying risk factors were extracted for analysis. Presence of an underlying disease, intra-abdominal infection, sepsis, malignancies, CVC use, and recent surgery were the only accessible risk factors that could be analyzed.

A 30-day overall mortality (mortality attributed to all causes within 30 days after candidemia) was determined in eligible patients with available adequate data and compared at the level of species and antifungal drugs used for treatment.

Species identification

Blood cultures were monitored by an automated blood culture system (BacT/Alert; bioMerieux, France). Isolated *Candida* spp. were stored in cryoBank (Mast group, United Kingdom) at − 70 °C. Stored *Candida* spp. were subcultured onto Sabouraud dextrose agar (Oxoid, England) and incubated for at least 72 h at 30 °C. *Candida* spp. grown in cultures were evaluated after inoculation into CHROMagar (CHROMagar, Paris, France) and species identification was performed using the commercial identification system API 32C (bioMerieux, France).

Susceptibility testing

Antifungal susceptibility for amphotericin B, anidulafungin, fluconazole, voriconazole, and posaconazole was performed by E-test method (AB BIODISK, Sweden/bioMerieux, France) according to the manufacturer's instructions. Yeast cell suspensions were adjusted to 0.5 McFarland. Agar plates containing RPMI 1640 (with L-glutamine) medium supplemented with 2% glucose buffered with MOPS in a pH of 7.0 (Wisent Bioproducts, Canada) were used to perform E-test. The plates were incubated at 35 °C for 48 h and evaluated for minimal inhibitory concentration (MIC) results. MIC levels were determined as the lowest concentration at which the border of the elliptical zone of growth inhibition intersected the E-test strips. According to the manufacturer's

instructions, an 80% inhibition of growth was used as the endpoint when reading the MIC levels of azoles, whereas for amphotericin B, a complete inhibition of growth was required to determine the MIC endpoint. Interpretations of MIC levels were evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) Antifungal Clinical Breakpoints. Quality control was performed by testing the strains recommended by EUCAST: *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019 (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/AFST/Clinical_breakpoints/Antifungal_breakpoints_v_9.0_180212.pdf). *Candida* spp. that were multidrug resistant (MDR, defined as resistance to > 1 drug class) and extensively drug resistant (XDR, defined as resistance to three drug classes) were identified and compared in terms of rate between the two periods [26].

Statistical analysis

Data were analyzed using SPSS, version 25.0 (SPSS) for Windows. Chi-square test and analysis of variance (ANOVA) were used for evaluation of data. A p value < 0.05 was considered to be statistically significant.

Results

Over the two 5-year periods, a total of 210 candidemia cases were encountered and 238 *Candida* spp. were isolated in 197 patients. One hundred and sixteen (58.8%) of the patients were male and the mean age was 59.2 ± 19.63 years.

Risk factors

Patients' medical records were examined to evaluate the available risk factors. The most predominant risk factor was presence of CVC (87%), followed by underlying diseases (43%) and history of recent surgery (36%). Statistical analysis did not reveal significant relationship between any species and available underlying risk factors. No significant difference was observed when the underlying factors were compared between *C. albicans* and non-albicans *Candida* spp. or between *C. parapsilosis* and other *Candida* spp. Patient characteristics and underlying risk factors are demonstrated in Table 1.

Mortality

A 30-day overall mortality was determined in patients with available adequate data and compared at the level of species and antifungal drug used for treatment. In total, 100 patients were eligible for this analysis. Overall mortality was 64%, with 56%, 58%, 70%, and 94% mortality for *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. glabrata*, respectively. When compared at the species level, the rate of mortality was significantly higher in patients with *C. glabrata* infections ($p = 0.045$). Thirty-day overall mortality rates and relationship between antifungal susceptibility and antifungal treatment are demonstrated in Table 2.

Epidemiology

Non-albicans *Candida* spp. were predominant with a rate of 68% within the entire study period. Overall species distribution was 32%, 28%, 17%, and 11% for *C. albicans*, *C. parapsilosis*, *C. glabrata*, and *C. tropicalis*, respectively.

Over the first 5-year period, 100 candidemia episodes were identified in 100 patients and 124 *Candida* spp. were isolated. The most frequent species were *C. albicans* (29%), followed by *C. parapsilosis* (24%), *C. glabrata* (18%), *C. tropicalis* (11%), and *C. dubliniensis* (6%). Non-albicans *Candida* spp. constituted 71% of the isolates. Twenty-three episodes (18.5%) involved mixed candidemia with *C. glabrata* in 15 (65.2%), *C. albicans* in 14 (60.8%), and *C. parapsilosis* in 9 (39.1%). The distribution of the *Candida* spp. in the first 5-year period is demonstrated in Table 3.

Over the second 5-year period, 110 candidemia episodes were identified in 97 patients and 114 *Candida* spp. were isolated. Two episodes of candidemia were encountered in nine patients and four episodes of candidemia were detected in one patient. The most frequent species were *C. albicans* (35.1%), followed by *C. parapsilosis* (28.9%), *C. glabrata* (15.8%), and *C. tropicalis* (11.4%). Non-albicans *Candida* spp. constituted approximately 64.9% of the isolates. Five episodes (4.5%) were accepted as mixed candidemia with *C. albicans* and *C. glabrata* involved in 3 (30%) of the episodes. The distribution of the *Candida* spp. in the second period is demonstrated in Table 3.

Antifungal susceptibility

Over the first 5-year period, susceptibility to amphotericin B was 100% among all *Candida* spp. All of *C. albicans* and almost all of the non-albicans *Candida* spp. were susceptible to anidulafungin. On the other hand, only 56% of *C. parapsilosis* were intermediately susceptible to anidulafungin. Fluconazole susceptibility rate was 94% for *C. albicans* and *C. parapsilosis* and 100% for *C. tropicalis*. Susceptibility rates of *Candida* spp. to major antifungals in the first 5-year period are demonstrated in Table 4.

In the second 5-year period, amphotericin B susceptibility remained high at 95% for *C. albicans*, while it decreased to 79%, 72%, and 85% for *C. parapsilosis*, *C. glabrata*, and *C. tropicalis*, respectively. Susceptibility rates of all *Candida* spp. to anidulafungin were approximately 85%, except for *C. parapsilosis*, which showed 3% susceptibility and 24%

Table 1 Characteristics and risk factors in candidemia cases

	Candidemia, n (%)								
Risk factors	*C. albicans* (*n* = 58)	*C. parapsilosis* (*n* = 54)	*C. tropicalis* (*n* = 21)	*C. glabrata* (*n* = 25)	*C. dubliniensis* (*n* = 6)	Mixed *Candida* spp. (*n* = 28)	Others (*n* = 18)	Total (*n* = 210)	*p*
Central venous catheter	51 (88)	50 (93)	20 (95)	19 (76)	5 (83)	22 (79)	16 (89)	183 (87)	> 0.05
Underlying diseases	29 (50)	18 (33)	8 (38)	8 (32)	3 (50)	14 (50)	10 (56)	90 (43)	> 0.05
Malignancies	17 (30)	13 (24)	6 (29)	7 (36)	2 (33)	7 (25)	5 (28)	57 (27)	
Others (DM, CRI, immuno-suppressive diseases)	12 (21)	5 (9)	2 (10)	1(4)	1 (16)	7 (25)	5 (28)	33 (16)	
Recent surgery	25 (43)	24 (44)	9 (43)	12 (48)	1 (17)	5 (18)		76 (36)	
Sepsis	23 (40)	18 (33)	3 (14)	13 (52)	3 (50)	10 (36)	2 (11)	72 (34)	
Intra-abdominal infection	19 (33)	21 (39)	6 (29)	5 (20)	3 (50)	11 (39)	4 (22)	69 (33)	

DM diabetes mellitus, *CRI* chronic renal insufficiency

intermediate susceptibility. Fluconazole susceptibility remained high for *C. albicans* and *C. tropicalis* (93% and 92%, respectively), but showed a remarkable decrease to 49% for *C. parapsilosis* (MIC_{50} = 4 μg/mL and MIC_{90} = 256 μg/mL). Susceptibility rates of *Candida* spp. to major antifungals in the second 5-year period are demonstrated in Table 4.

Ranges of MIC and MIC_{50} and MIC_{90} levels of the *Candida* spp. are demonstrated in Table 5.

Resistance to more than one drug was detected in *C. parapsilosis* (15/67 22%), *C. glabrata* (8/40; 20%), and *C. albicans* (1/76; 1.3%) over 10 years and 79% were classified as MDR. Over the first 5-year period, only two *C. parapsilosis* isolates (2/34; 6%) were determined to be resistant to azole and echinocandin class of drugs. On the other hand, over the second 5 years, 11 of 33 *C. parapsilosis* isolates (33%) were resistant to azole and echinocandins, one was resistant to azole and amphotericin B, and one was resistant to amphotericin B and echinocandins. Five isolates (15%) were resistant to all three drug classes and were classified as XDR. Eight isolates of *C. glabrata* (8/18; 44%) were defined as MDR: five were resistant to azole and amphotericin B, and three were resistant to amphotericin B and echinocandins.

Table 2 Thirty-day overall mortality

	Overall mortality *n* (%)	*p*
C. albicans (*n* = 43)	24 (56)	NS
C. parapsilosis (*n* = 31)	18 (58)	NS
C. glabrata (*n* = 16)	15 (94)	0.045
C. tropicalis (*n* = 10)	7 (70)	NS
Total (*n* = 100)	64(64)	

Discussion

Candidemia remains an important cause of morbidity and mortality, especially in hospitalized and critically ill patients [6, 7]. The distribution of *Candida* species has changed in recent years with a trend of increasing rate of non-albicans *Candida* spp. [12–15, 27, 28] while Asian studies revealed that *C. albicans* is still predominant [5, 29]. Although current study also revealed a predominance of non-albicans *Candida* spp. (68%), *C. albicans* is leading one, with a rate of 32%, followed by *C. parapsilosis* (28%), and *C. glabrata* and *C. tropicalis*, similar to the other reports from Turkey [22, 24].

When compared over the two 5-year periods, the distribution of the species was almost stable: non-albicans *Candida* spp. constituted 71% of the isolates in the first period, while it decreased to 64.9% in the second period. Although statistically insignificant, the frequency of *C. albicans* and *C. parapsilosis* increased from 29% to 35% and 24% to 29%, respectively. It may be due to the fact that more patients with intra-abdominal surgery were recruited in the second period.

Table 3 Distribution of *Candida* spp. in the intensive care unit

	2004–2008	2013–2017	
Candida spp. *n*=	124 (%)	*n* = 114 (%)	Total *n* = 238
C. albicans	36 (29)	40 (35)	76 (32)
C. parapsilosis	34 (24)	33 (29)	67 (28)
C. glabrata	22 (18)	18 (16)	40 (17)
C. tropicalis	14 (11)	13 (11)	27 (11)
C. dubliniensis	7 (6)	1	8 (3)
C. lusitaniae	3 (2)	-	3 (1)
C. krusei	2 (2)	2 (2)	4 (2)
Others	6 (5)	7 (6)	13 (5)

Table 4 Susceptibility rates of *Candida* spp. to major antifungals

	2004–2008				2013–2017		
Candida spp. ($n = 113$)	S *n* (%)	I *n* (%)	R *n* (%)	($n = 104$)	S *n* (%)	I *n* (%)	R *n* (%)
C. albicans ($n = 36$)				($n = 40$)			
AMB	36 (100)				38 (95)		2 (5)
FCZ	34 (94)	1 (3)	1 (3)		37 (93)		3 (7)
VOR	32 (88)	2 (6)	2 (6)		35 (88)	3 (7)	2 (5)
PSC	32 (88)		4 (12)		34 (85)		6 (15)
AND	36 (100)				35 (88)		5 (12)
C. parapsilosis ($n = 34$)				($n = 33$)			
AMB	34 (100)				26 (79)		7 (21)
FCZ	32 (94)	2(6)			16 (49)	1 (2)	16 (49)
VOR	33 (97)		1 (3)		17 (52)	1 (3)	15 (45)
PSC	32 (94)		2(6)		16 (48)		17 (52)
AND		19 (56)	15 (44)		1 (3)	8 (24)	24 (73)
C. glabrata ($n = 22$)				($n = 18$)			
AMB	22 (100)				13 (72)		5 (28)
FCZ		21(95)	1 (5)			17 (94)	1 (6)
VOR	IE				IE		
PSC	IE				IE		
AND	22 (100)				15 (83)		3 (17)
C. tropicalis ($n = 14$)				($n = 13$)			
AMB	14 (100)				11 (85)		2 (15)
FCZ	14 (100)				12 (92)	1 (8)	
VOR	14 (100)				12 (92)	1 (8)	
PSC	14 (100)				6 (46)		7 (54)
AND	13 (93)		1 (7)		11 (85)		2 (15)
C. dubliniensis ($n = 7$)							
AMB	IE						
FCZ	IE						
VOR	7 (100)						
PSC	7 (100)						
AND	IE						

AMB amphotericin B, *FCZ* fluconazole, *VOR* voriconazole, *PSC* posaconazole, *AND* anidulafungin, *IE* insufficient evidence, *S* susceptible, *R* resistant, *I* intermediate

Among non-albicans species, *C. parapsilosis* was the most prominent in Latin America, India, South Africa, and Asia [5, 13, 15, 30, 31]. It is also frequently encountered in some Mediterranean countries including Turkey [32] with isolation rates ranging from 6 to 66% [33, 34]. The prevalence of different *Candida* spp. may vary due to patient-related or -unrelated factors. *C. parapsilosis* is more common in neonatal or surgical ICUs; CVC, total parenteral nutrition, recent surgery, use of echinocandins, and poor infection control are among important risk factors [6, 35–37]. Recent fluconazole therapy, older age, gastrointestinal surgery, and intravenous drug use are the prevalent risk factors for *C. glabrata* infections [10, 35]. The most predominant risk factor was use of CVC in our study, although the risk factors were comparable among *Candida* spp. in our study. This may be due to the small number of cases and similar characteristics of the patients. Prior gastrointestinal surgery, antifungal use, and CVC were reported as significant risk factors for non-albicans candidemia [38, 39]. Although statistically insignificant, ICU stay, CVC use, recent surgery, and poor infection control may have led to the predominance of *C. parapsilosis* among non-albicans species.

The incidence rate of candidemia cases due to mixed species was reported in the range of 2–6% [7, 40]. In our study, this rate was 13.3%, higher than the other studies. Although this higher rate could not be attributed to any risk factor by

Table 5 MIC range, MIC_{50} and MIC_{90} levels of the *Candida* spp.

2004–2008				2013–2017			
MIC (μg/mL)				MIC(μg/mL)			
Candida spp.	MIC range	MIC_{50}	MIC_{90}		MIC range	MIC_{50}	MIC_{90}
(*n* = 106)				(*n* = 104)			
C. albicans (*n* = 36)				(*n* = 40)			
AMB	0.002–0.5	0.25	0.38		0.094–3	0.5	0.75
FCZ	0.004–> 256	0.19	0.75		0.064–32	0.19	1.5
VOR	0.002–> 32	0.008	0.064		0.003–> 32	0.016	0.094
PSC	0.002–> 32	0.023	0.064		0.012–0.19	0.047	0.094
AND	0.002–0.008	0.002	0.064		< 0.002–4	0.002	0.064
C. parapsilosis (*n* = 34)				(*n* = 33)			
AMB	0.006–0.5		0.38		0.064–3	0.38	1.5
FCZ	0.064–3		0.38		0.125–256	4	256
VOR	0.003–0.047		0.094		0.001–8	0.125	3
PSC	0.004–0.25		0.064		0.023–0.94	0.094	0.19
AND	1–> 32	4	12		0.002–> 32	> 32	> 32
C. glabrata (*n* = 22)				(*n* = 18)			
AMB	0.006–0.	0.38	0.5		0.094–3	0.75	1.5
FCZ	1.5–> 256	12	24		0.5–48	4	12
VOR	0.002–4	0.25	2		0.032–1	0.125	0.5
PSC	0.002–> 32	12	> 32		0.047–> 32	0.5	1.5
AND	0.002–0.016	0.002	0.016		0.002–> 32	0.006	0.019
C. tropicalis (*n* = 14)				(*n* = 13)			
AMB	0.125–0.5	0.19	0.25		0.047–3	0.5	1
FCZ	0.125–0.5	0.25	0.5		0.125–3	0.38	1
VOR	0.006–0.047	0.016	0.032		0.008–0.19	0.023	0.094
PSC	0.004–0.064	0.012	0.047		0.003–0.5	0.094	0.125
AND	0.002–2	0.004	0.016		0.002–1	0.008	0.125

AMB amphotericin B, *FCZ* fluconazole, *VOR* voriconazole, *PSC* posaconazole, *AND* anidulafungin, *IE* insufficient evidence, *S* susceptible, *R* resistant, *I* intermediate

statistical analysis, recent intra-abdominal surgery might be the contributing factor.

Overall mortality of candidemia may reach 50% or even exceed 60% in treated patients [8, 41]. In a review of randomized trials, increased mortality was seen with *C. tropicalis* infections, while *C. parapsilosis* infections were associated with lower mortality [42]. In our study, overall mortality was 64%. Mortality rate was higher for *C. glabrata* and lower for *C. parapsilosis* and *C. albicans* infections.

Due to their broad-spectrum activity against *Candida* species, the echinocandins are preferred extensively for the treatment of candidemia. The highest echinocandin MICs are found for *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, and *C. guilliermondii* [15, 43]. In the current study, almost all *Candida* spp. (except *C. parapsilosis*) were susceptible to anidulafungin in the first period but the resistance rate was high in *C. parapsilosis* (44%) and even increased to 73% in the second period.

In the SENTRY program, resistance to echinocandins was uncommon among all *Candida* spp. [15]. On the other hand, 51 isolates were reported to have MIC values of 4 μg/mL to anidulafungin from Europe, Latin and North America [44]. Similarly, 22 years of candidemia study from Norway revealed that none of *C. parapsilosis* isolates were susceptible with intermediate susceptibility of 89% (28.3% with MIC > 4 μg/mL), similar to our results [45]. These discrepancies may be due to the difference in the analysis of susceptibilities between Clinical Laboratory Standards Institute (CLSI) referred in SENTRY and EUCAST in Norwegian and our study [26, 46]. A study from Israel evaluated 899 candidemia cases using the E-test for antifungal susceptibility and interpreted the results according to CLSI breakpoints. None of the *C. parapsilosis* isolates were resistant to caspofungin. Since we have used EUCAST breakpoints, this might have led to an overestimation of resistance in our study [47].

C. parapsilosis species complex and *C. guilliermondii* have higher MIC values to echinocandins, but since glucan synthesis is still inhibited at therapeutic levels, treatment with echinocandins is generally effective [48–51]. *C. parapsilosis* sensu stricto is reported to be more resistant to anidulafungin, and Borghi et al. reported 34 *C. parapsilosis* sensu stricto strains having MIC values of 4 μg/mL from Italy [50, 52, 53]. Since a subclassification has not been performed, *C. parapsilosis* sensu stricto might have predominated and this might have also led to higher MIC values to anidulafungin in our strains. Although a clonal analysis has not been performed, another hypothesis for this high resistance rate might be a single resistant *C. parapsilosis* clone circulating in our unit.

Susceptibility rate of *Candida* spp., except for *C. glabrata* to fluconazole, voriconazole, and posaconazole, was high in the first period. Because of *C. albicans* ranked the first and *C. parapsilosis* the second in our unit, fluconazole was prescribed more frequently empirically. In case of determination of azole resistance, echinocandins or amphotericin B (especially in *C. parapsilosis* infections) were preferred for antifungal treatment. Susceptibility rate to fluconazole and voriconazole remained high for *C. albicans* and *C. tropicalis*, but only half of *C. parapsilosis* were susceptible in the second period. Since fluconazole is recommended as the first-line therapy for *C. parapsilosis* infections and resistance to echinocandins was noted in our center, fluconazole was prescribed very intensely [8]. As a consequence, susceptibility rate to fluconazole might have significantly decreased in *C. parapsilosis*. Decreased susceptibility of *C. parapsilosis* to other azoles in our study may be related to cross-resistance, which has been described also in previous studies [15].

In the second period, although susceptibility to amphotericin B remained high in *C. albicans*, it decreased in the non-albicans group (72%–85%). Since *C. parapsilosis* and *C. glabrata* predominated in non-albicans spp., amphotericin B was frequently used empirically besides fluconazole. This might have led to the decrease in rate of susceptibility. Multidrug resistance is uncommon and usually involves acquired resistance in species with intrinsic resistance. It is mostly encountered in *C. glabrata and C. auris.* Antifungal use, subtherapeutic drug levels, and poor infection control are among the risk factors [27]. Resistance to more than one drug class was detected predominantly in *C. parapsilosis* and *C. glabrata* in our study. We think that this high rate of multidrug resistance might be due to poor infection control.

Lastly, we have compared our results with the results of the first multicenter study reporting resistance rates according to CLSI breakpoints in 1991 candidemia cases in our country [25]. MIC_{90} levels are similar in terms of resistance in most *Candida* spp., except for *C. albicans* and *C. parapsilosis*: MIC_{90} levels for fluconazole and anidulafungin in *C. parapsilosis* were higher in our study. These discrepancies may be due to the E-test method used in our study and due to a probably endemic *C. parapsilosis* isolate circulating in our unit.

There are some limitations to our study. First, this is a retrospective and mainly laboratory-based study. Since the medical records were incomplete in certain parameters such as previous hospitalization, total parenteral nutrition, previous antibiotic, antifungal, and corticosteroid use for an important number of patients, these parameters could not be evaluated. Second, we have used the E-test, which is an alternative method for antifungal susceptibility. EUCAST and CLSI recommend broth microdilution as the reference method, but as this method is labor-intensive and expensive, the E-test method is preferred for being more practical and easier to perform [26, 46, 54, 55]. The agreement rates of the E-test with the reference method are usually favorable [55]. However, microdilution broth test was suggested to be more convenient for non-albicans *Candida* spp., in particular for the isolates with high MIC values against azoles [56]. Morace et al. demonstrated that the E-test provides valuable results with the exception of *C. glabrata* for azoles and *C. parapsilosis* for echinocandins. [57]. Thus, the use of E-test in our study might explain the high resistance rates of *C. parapsilosis* to anidulafungin. On the other hand, Lovero et al. found 95.6–97.8% agreement for *C. parapsilosis* when compared the EUCAST and E-test method for echinocandins and favored the use of commercial methods [58].

In conclusion, although there is a predominance of non-albicans *Candida* spp. in our institution, *C. albicans* remained the most commonly encountered *Candida* species. Among non-albicans *Candida* spp., *C. parapsilosis* ranked first followed by *C. glabrata*. Predominant risk factors were presence of an underlying disease, use of CVC, and history of recent surgery. Mortality rate was higher in patients infected with *C. glabrata*. High level of echinocandin resistance and MDR/XDR among *C. parapsilosis* and *C. glabrata* isolates is an important issue in our unit. Distribution and antifungal susceptibilities of *Candida* spp. differ throughout years. Every center should follow their change in species and susceptibility profile closely and direct empirical antifungal therapies based on the local resistance profile.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

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