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Changing Trends of *Candida* Species and Antifungal Susceptibility Profile of *Candida* Bloodstream Isolates: A 5-Year Retrospective Survey

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Abstract

Background: *Candida* species have emerged as one of the most common causes of bloodstream infections (BSIs). There are limited data on the distribution of *Candida* spp. and susceptibility by year.
Objectives: In this study, we analyzed changes in the distribution of *Candida* spp. and their antifungal susceptibility profiles from blood cultures.
Methods: Records from January 2016 to December 2020 were obtained from the microbiology laboratory in Istanbul. Antifungal susceptibility tests were performed using the VITEK 2 compact system and evaluated according to EUCAST breakpoints. A total of 241 unique candidemia episodes were included in this study.
Results: *Candida albicans* was the predominant pathogen (n = 95, 39.42%), followed by *C. parapsilosis* (n = 82, 34.02%), *C. glabrata* (n = 18, 7.47%), *C. tropicalis* (n = 17, 7.05%), *C. krusei* (n = 15, 6.22%), and other *Candida* spp. (n = 14, 5.79%). There was no statistically significant difference in the percentage of episodes of *Candida* spp. After data analysis, a tendency to shift from *C. albicans* to *C. parapsilosis* was observed in the period analyzed in this study. *Candida albicans* was the most common species in intensive care units (ICUs), hematology and hemopoietic stem cell transplantation units, and surgical clinics, with *C. parapsilosis* predominant in medical clinics. In general, micafungin susceptibility was the highest, and fluconazole was the lowest. There was reduced sensitivity to fluconazole and voriconazole for *C. albicans* and *C. parapsilosis* over 5 years.
Conclusions: Detecting changes in the distribution of *Candida* spp. and antifungal susceptibility over time will lead to the selection of appropriate empirical therapy and monitor phenomena of antifungal resistance. Empirical treatment with antifungal agents is associated with high costs, toxicities, and risk of antifungal resistance. Therefore, it is mandatory to determine and monitor *Candida* spp. and antifungal susceptibility testing to select appropriate antifungal agents.

Keywords: Antifungal Drugs, *Candida albicans*, Drug Susceptibility, Non-albicans *Candida* Species

1. Background

In recent years, *Candida* species has emerged as one of the most common causes of bloodstream infections (BSIs) (1-5). Candidemia, known as *Candida* BSI, is mostly associated with intra-abdominal surgical procedures, long-term and broad-spectrum antibiotics, intravenous devices, immunosuppressive drugs, and total parenteral nutrition (6, 7). Candidemia is usually diagnosed using blood cultures; however, blood culture positivity can be detected in nearly half of invasive *Candida* infections (8). In this limited diagnosis, the true epidemiology of candidemia is unclear and may vary. The distribution of *Candida* spp. that causes candidemia varies according to different geographical areas and even hospital units. This difference in the distribution of *Candida* spp. is due to predisposing conditions in patients, hospital-related factors, and antifungal drug exposure (9, 10).

The incidence of candidemia has been changing in most regions of the world with the emergence of non-*albicans Candida* (NAC) species (2, 7). This change and, especially, the increasing use of azole antifungal agents have brought forth antifungal resistance and treatment difficulty. There are limited data on the incidence of candidemia in Turkey and was reported 1.23 to 13.3 episodes/1000 admissions, respectively (11, 12). Furthermore, there are limited data about the distribution of *Candida* spp. and susceptibility by year.

2. Objectives

In this study, we aimed to analyze changes in the distribution of *Candida* spp. and their antifungal susceptibility

profiles from blood cultures during the 2016 - 2020 period at a tertiary care center in Istanbul, Turkey.

3. Methods

This single-center retrospective study was performed on positive blood cultures for *Candida* spp. between January 2016 and December 2020 in a tertiary care center with a capacity of 500 beds in Istanbul, Turkey. This medical center has 4 main intensive care units (ICUs, including neonatal, pediatric, coronary, and cardiovascular surgical care units), 6 surgery departments, and adult and pediatric hematology-oncology departments [including a hematopoietic stem cell transplantation (HSCT) unit].

Candidemia was defined as the first positive culture for *Candida* growth on blood culture. Only the initial episode from each patient was submitted for evaluation. Blood cultures were monitored by BacT/Alert 3D automated blood culture system (bioMérieux, France), and positive ones were subcultured on Sabouraud dextrose agar (bioMérieux, France) and blood agar plates (bioMérieux, France). Suspected colonies of yeasts were identified, and their antifungal susceptibility tests were performed by the VITEK 2 compact system (bioMérieux, France) using VITEK 2 YST-ID and YST-YS07 cards. We used the VITEK 2 system that concluded an excellent quantitative and qualitative agreement with CLSI and EUCAST broth microdilution reference methods, albeit this is not a comparison study (13, 14). The results of antifungal susceptibility tests were properly evaluated in accordance with the European Committee on Antimicrobial Susceptibility Testing (15). Fluconazole, voriconazole, amphotericin B, caspofungin, and micafungin antifungal susceptibility results were evaluated. Minimal inhibitory concentrations (MIC50 and MIC90) and MIC geometric mean (MIC GM) assessment were evaluated when at least 10 *Candida* spp. were detected.

3.1. Statistical Analysis

Statistical analyses were performed using SPSS version 15.0 (SPSS, Chicago, IL, USA). Categorical variables were reported as numbers and percentages, while numerical variables were reported as mean $\pm$ SD, minimum and maximum. The analyses were performed using the chi-square test. P values < 0.05 were considered statistically significant.

4. Results

Of the initial 360 incidences of *Candida* BSI, 241 were evaluated. A total of 5 *Candida* spp., including 3 *C.famata*, 1 *C. guilliermondii*, and 1 *C. dubliniensis*, were isolated. Susceptibility tests were not performed, and the remaining 236 *Candida* samples were analyzed on the BacT/ALERT 3D system. During the observation period, a total of 11 different *Candida* spp. were found. *Candida albicans* was the predominant pathogen (n = 95, 39.42%), followed by *C. parapsilosis* (n = 82, 34.02%), *C. glabrata* (n = 18, 7.47%), *C. tropicalis* (n = 17, 7.05%), *C. krusei* (n = 15, 6.22%), and other *Candida* spp. (n = 14, 5.79%). While the ratio of *C. albicans* decreased from 54.5 to 28.8% between 2016 and 2019, the percentage of it increased to 38,9% in 2020. The ratio of *C. parapsilosis* tended to increase from 20.6 to 38.9% from 2016 to 2020. There was no statistically significant difference between the percentages of incidents of *Candida* spp. The distribution of *Candida* spp. is shown in Table 1.

The incidents represent 124 ICU patients (51.25%), 53 pediatric ICU patients (22.08%), 30 patients (12.5%) from the hematology unit, 23 patients (9.58%) from the internal medicine unit, and 11 patients (4.58%) from surgical units. The distribution of *Candida* spp., by hospital unit, is demonstrated in Table 2. *Candida parapsilosis* was significantly more common in the pediatric ICU ($P < 0.05$). *Candida albicans* was the most common species in the ICU and hematology and surgical clinics, and *C. parapsilosis* was predominant in internal medicine clinics ($P > 0.05$). Over 5 years, susceptibility to amphotericin B, fluconazole, voriconazole, caspofungin, and micafungin were determined against the 5 most isolated *Candida* spp.

Micafungin susceptibility was the highest with a 97.4% ratio, and fluconazole was the lowest with a 66.1% ratio in 236 isolates. Antifungal susceptibility results and MIC values are shown in Table 3. We found that amphotericin B, caspofungin, and micafungin MIC50 and MIC90 values were low for many *Candida* spp., while these values were high for *C. krusei*. Reduced sensitivities to fluconazole and voriconazole for *C. albicans* and *C. parapsilosis* were found. None of the *C. glabrata* isolates were sensitive to fluconazole. Over the years, the change in susceptibility ratio was statistically significant for fluconazole toward *C. albicans*, as well as for voriconazole toward both *C. albicans* ($P < 0.005$) and *C. parapsilosis*. Besides, the evaluation of different distribution, caspofungin, and fluconazole sensitivities was statistically significant for all *Candida* spp (Table 4 and Figure 1).

5. Discussion

Incidences of candidemia and the distribution of *Candida* spp. vary geographically and among different populations, age groups, study periods, types of hospitals, and even hospital units. The distribution of *Candida* spp. was shifted from *C. albicans* to NAC species (3, 5, 16-22). When risk factors between *C. albicans* and NAC BSI were

Table 1. Distribution of *Candida* Species Over the Years [a]

Candida Species	Total	2016	2017	2018	2019	2020	P Value [b]
Candida albicans	95 (39.42)	18 (54.5)	18 (40.9)	28 (41.2)	17 (28.8)	14 (38.9)	0.195
C. parapsilosis	82 (34.02)	7 (20.6)	13 (29.5)	26 (38.2)	22 (37.3)	14 (38.9)	0.364
C. glabrata	18 (7.47)	3 (9.1)	3 (6.8)	3 (4.4)	7 (11.9)	2 (5.6)	0.596
C. tropicalis	17 (7.05)	1 (3.0)	4 (9.1)	5 (7.4)	5 (8.5)	2 (5.6)	0.875
C. krusei	15 (6.22)	3 (9.1)	1 (2.3)	3 (4.4)	5 (8.5)	3 (8.3)	0.549
C. lusitaniae	4 (1.66)	1 (3.0)	1 (2.3)	1 (1.5)	1 (1.7)	0 (0.0)	0.909
C. kefyr	4 (1.66)	1 (3.0)	2 (4.5)	1 (1.5)	0 (0.0)	0 (0.0)	0.337
C. famata	3 (1.24)	0 (0.0)	1 (2.3)	1 (1.5)	0 (0.0)	1 (2.8)	0.688
C. rugosa	1 (0.41)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.473
C. dubliniensis	1 (0.41)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0.707
C. guilliermondii	1 (0.41)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0.707
Total	241 (100)	34 (14.1)	44 (18.3)	68 (28.3)	59 (24.5)	36 (14.9)	

[a] Values are expressed as No. (%).
[b] $P < 0.05$ is statistically significant.

Table 2. Distribution of *Candida* Species According to Different Hospital Units [a]

Candida Species	Total	ICU	Adult and Pediatric Hematology and Transplantation	Pediatric ICU	Surgical	Internal Medicine	P Value [b]
Candida albicans	95 (39.42)	50 (40.3)	13 (43.3)	17 (32.1)	6 (54.5)	9 (39.1)	0.647
C. parapsilosis	82 (34.02)	42 (33.9)	4 (13.3)	25 (47.2)	1 (9.1)	10 (43.5)	0.008
C. glabrata	18 (7.47)	8 (6.5)	4 (13.3)	3 (5.7)	3 (27.3)	0 (0.0)	0.055
C. tropicalis	17 (7.05)	9 (7.3)	3 (10.0)	2 (3.8)	0 (0.0)	3 (13.0)	0.518
C. krusei	15 (6.22)	6 (4.8)	4 (13.3)	4 (7.5)	1 (9.1)	0 (0.0)	0.240
Others [c]	14 (5.81)	9 (7.3)	2 (6.7)	2 (3.8)	0 (0.0)	1 (4.3)	0.919
Total	241 (100)	124 (51.25)	30 (12.5)	53 (22.08)	11 (4.58)	23 (9.58)	

[a] Values are expressed as No. (%).
[b] $P < 0.05$ is statistically significant.
[c] Other *Candida* species are *C. lusitaniae*, *C. kefyr*, *C. famata*, *C. rugosa*, *C. dubliniensis*, and *C. guilliermondii*.

compared, older age and underlying cardiovascular diseases were risk factors for *C. albicans*, while cancer and chemotherapy were risk factors for NAC (23). Although some researchers have reported no change in the distribution of species over time (24, 25), recent studies from Kuwait (3), Lebanon (17), Italy (18), Israel (19), India (20), Saudi Arabia (21), and China (22) have indicated a predominance of NAC species compared to *C. albicans*. In this study, the increase in the prevalence of NAC species can be interpreted as the improvement of diagnostic methods and the treatment of cancer patients in our hospital, which has increased in recent years.

Candida albicans, as the most frequently isolated species worldwide (1, 3, 5-7, 11, 16, 18-20, 22, 24-28), was also the leading species isolated in this study (39.4%), followed by *C. parapsilosis*, *C. glabrata*, and *C. tropicalis* (34, 7.4, and 7%, respectively). According to the studies conducted in Turkey, the most frequent species were *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. glabrata* (7, 11, 27, 29, 30), which is in line with other studies in the literature (6, 16, 17, 21, 22, 24, 26). *Candida parapsilosis* was reportedly the most frequent species in some studies (27, 31, 32), whereas *C. glabrata* was the leading species in the studies of Israel et al. (19) and Aldardeer et al. (33). The prevalence of isolated *Candida* spp. varies among specific age groups. Although Cleveland et al. (4) reported a significant decline in infants and pediatric patients due to the increased use of azoles as prophylaxis in neonatal ICUs, non-compliance with precautionary infection control and increased risk factors (such as diabetes mellitus, ICU admissions, and immunosuppressive treatments) indicated that the prevalence of candidemia in pediatric patients is still high. While *C. glabrata* was com-

Table 3. Antifungal Susceptibilities to 5 Antifungal Agents for Various *Candida* Species

Candida Species and Antifungal Agent	Minimum Inhibitory Concentration [a]				*In vitro* Susceptibility; No. (%)		
	Range (mg/L)	50%	90%	GM	S	DDS	R
Candida albicans **(n = 95)**							
AB	≤ 0.25 - 1	0.50	1	0.49	95 (100)	0	0
CAS	≤ 0.25 - 1	≤ 0.12	≤ 0.25	0.17	95 (100)	0	0
FLZ	≤ 0.5 - 32	≤ 0.5	16	1.15	77 (81)	4 (4.2)	14 (14.8)
MCF	≤ 0.06 - 0.5	≤ 0.06	≤ 0.06	0.06	95 (100)	0	0
VRC	≤ 0.12 - ≥8	≤ 0.12	1	0.98	75 (79)	2 (2.1)	18 (18.9)
C. parapsilosis **(n = 82)**							
AB	≤ 0.25 - 8	0.50	1	0.35	76 (92.7)	0	6 (7.3)
CAS	≤ 0.25 - 2	≤ 0.12	≤ 0.25	0.71	82 (100)	0	0
FLZ	≤ 0.5 - 32	1.00	8.00	1.78	55 (67.1)	9 (10.9)	18 (21)
MCF	≤ 0.06 - 2	0.50	1.00	0.54	80 (97.6)	0	2 (2.4)
VRC	≤ 0.12 - 2	≤ 0.12	0.50	0.17	63 (76.8)	16 (19.5)	3 (3.7)
C. glabrata **(n = 18)**							
AB	≤ 0.25 - 8	0.50	1.00	0.56	17 (94.4)	0	1 (5.6)
CAS	≤ 0.25 - 0.5	≤ 0.12	0.25	0.23	10 (55.6)	0	8 (44.4)
FLZ	2 - 16	4.00	8.00	4.76	0	17 (94.4)	1 (5.6)
MCF	≤ 0.06	≤ 0.06	≤ 0.06	0.06	18 (100)	0	0
VRC	IE	IE	IE	IE	IE	IE	IE
C. tropicalis **(n = 17)**							
AB	≤ 0.2 - 0.5	≤ 0.25	0.50	0.28	17 (100)	0	0
CAS	≤ 0.12 - 0.25	≤ 0.12	≤ 0.12	0.13	17 (100)	0	0
FLZ	≤ 1 - 16	1	2	1.38	15 (88.2)	0	2 (11.8)
MCF	≤ 0.06	≤ 0.06	≤ 0.06	1.11	17 (100)	0	0
VRC	≤ 0.12 - 0.25	≤ 0.12	≤ 0.12	0.12	16 (94.1)	0	1 (5.9)
C. krusei **(n = 15)**							
AB	≤ 0.25 - 4	0.50	4	0.78	11 (73.4)	0	4 (226.6)
CAS	≤ 0.12 - ≥ 8	≤ 0.12	≥8	0.70	8 (53.3)	0	7 (46.7)
FLZ	1 - 32	8	32	6.6	0	0	15 (100)
MCF	≤ 0.06 - ≥ 8	0.12	≥8	1.4	12 (80)	0	3 (20)
VRC	≤ 0.12 - 0.25	≤ 0.12	≤ 0.12	0.13	15 (100)	0	0
C. kefyr **(n = 4)**							
AB	1 - 2	*	*	*	2 (50)	0	2 (50)
CAS	≤ 0.12 - ≤ 0.25	*	*	*	4 (100)	0	0
FLZ	≤ 0.5 - 2	*	*	*	4 (100)	0	0
MCF	0.12	*	*	*	4 (100)	0	0
VRC	≤ 0.12	*	*	*	4 (100)	0	0
C. lusitaniae **(n = 4)**							
AB	0.5	*	*	*	4 (100)	0	0
CAS	≤ 0.25 - 4	*	*	*	3 (75)	0	1 (25)
FLZ	≤ 0.5 - ≤ 1	*	*	*	4 (100)	0	0
MCF	0.12 - 1	*	*	*	4 (100)	0	0
VRC	≤ 0.12	*	*	*	4 (100)	0	0
C. rugosa **(n = 1)**							
AB	0.5	*	*	*	1 (100)	0	0
CAS	1	*	*	*	1 (100)	0	0
FLZ	4	*	*	*	1 (100)	0	0
MCF	0.12	*	*	*	1 (100)	0	0
VRC	≤ 0.12	*	*	*	1 (100)	0	0

Abbreviations: IE, insufficient evidence; S, susceptible; R, resistant; DDS, dose-dependent susceptible; AMB, amphotericin B; CAS, caspofungin; FCZ, fluconazole; MCF, micafungin; VOR, voriconazole; MIC, minimum inhibitory concentration; GM, geometric mean.

[a] * MIC50, MIC90, and GM values were not performed because the number is smaller than 10.

Table 4. Susceptibility Rates for *Candida* Species Over the Years [a]

Candida Species and Years	AMB	CAS	FLU	MCF	VRC
C. albicans **(n = 95)**					
2016	18 (100)	18 (100)	9 (50)	18 (100)	10 (55.6)
2017	18 (100)	18 (100)	11 (61.1)	18 (100)	13 (72.2)
2018	28 (100)	28 (100)	26 (92.9)	28 (100)	25 (89.3)
2019	17 (100)	17 (100)	16 (94.1)	16 (94.1)	16 (94.1)
2020	14 (100)	14 (100)	14 (100)	14 (100)	11 (78.6)
P value	-	-	< 0.001	0.482	0.034
C. parapsilosis **(n = 82)**					
2016	7 (100)	7 (100)	6 (85.7)	6 (85.7)	7 (100)
2017	12 (92.3)	13 (100)	8 (61.5)	13 (100)	11 (84.6)
2018	25 (96.2)	26 (100)	20 (76.9)	26 (100)	23 (88.5)
2019	20 (90.9)	22 (100)	13 (59.1)	21 (95.5)	12 (54.5)
2020	13 (92.8)	14 (100)	8 (57.1)	14 (100)	10 (71.4)
P value	0.913	-	0.477	0.166	0.034
C. glabrata **(n = 18)**					
2016	3 (100)	3 (100)	0	3 (100)	0
2017	3 (100)	3 (100)	0	3 (100)	0
2018	3 (100)	1 (33.3)	0	3 (100)	0
2019	6 (85.7)	2 (28.6)	0	7 (100)	0
2020	2 (100)	1 (50)	0	2 (100)	0
P value	1.000	0.125	-	-	-
C. tropicalis **(n = 17)**					
2016	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)
2017	4 (100)	4 (100)	3 (75)	4 (100)	3 (75)
2018	5 (100)	5 (100)	5 (100)	5 (100)	5 (100)
2019	5 (100)	5 (100)	4 (80)	5 (100)	5 (100)
2020	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)
P value	-	-	0.787	-	0.378
C. krusei **(n = 15)**					
2016	2 (66.7)	2 (66.7)	0	2 (66.7)	3 (100)
2017	0	1 (100)	0	1 (100)	1 (100)
2018	1 (33.3)	0	0	2 (66.7)	3 (100)
2019	5 (100)	1 (20)	0	4 (80)	5 (100)
2020	3 (100)	3 (100)	0	3 (100)	3 (100)
P value	0.093	0.105	-	1.000	1.000
All species (n = 236)					
2016	32 (94.1)	33 (94.1)	18 (59.9)	32 (94.1)	23 (74.2)
2017	40 (93)	43 (100)	26 (60.5)	43 (100)	30 (81.1)
2018	64 (95.5)	62 (92.5)	53 (79.1)	66 (98.5)	58 (87.9)
2019	54 (94.7)	48 (84.2)	34 (59.6)	54 (96.4)	39 (78)
2020	34 (97.1)	34 (97.1)	24 (68.6)	35 (100)	26 (78.8)
Total	224 (94.9)	221 (93.6)	155 (65.7)	230 (97.4)	176 (81.1)
P value	1.000	0.035	0.048	0.305	0.074

Abbreviations: AMB, amphotericin B; CAS, caspofungin; FCZ, fluconazole; MCF, micafungin; VOR, voriconazole.
[a] Values are expressed as No. (%).

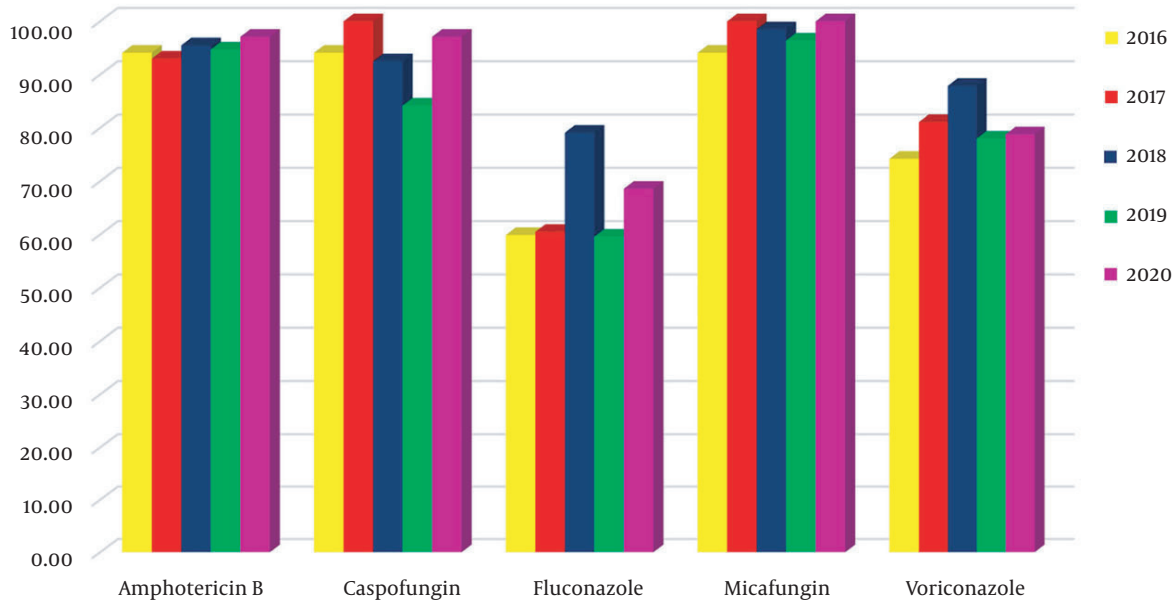

Figure 1. Antifungal susceptibility percentages to all *Candida* isolates per year

monly observed in elderly patients (1), *C. parapsilosis* was found mainly in children and neonates (1, 18, 21). In contrast with the study conducted by Aslan et al. (34), who reported that 42.2% of the pediatric ICU patients had *C. albicans*, *C. parapsilosis* was the most common species in our pediatric ICU patients.

The distribution of *Candida* spp. differs among various departments. Li et al. (5) observed that *C. albicans* was detected in 51.4% and *C. tropicalis* in 8.6% of the surgical patients in their facility, whereas *C. tropicalis* accounted for 27.3% of all cases. Similarly, Israel et al. (19) reported that the leading species was *C. tropicalis* in hematology-oncology patients and one-third of candidemias occurred in ICUs. Caggiano et al. (18) indicated that *C. parapsilosis* was most frequently detected in adult and pediatric hematology-oncology patients, and 31.2% of the patients with candidemia were in ICUs, predominantly in the neonatal ICU. In our study, 1.25% of patients were in the ICU and commonly had *C. albicans*, similar to the rate reported by Ergon et al. in Turkey (25). According to the period analyzed in this study, when the overall prevalence of *Candida* spp. was evaluated, it was observed that the prevalence of *C. albicans* (the predominant species) decreased gradually and equalized with *C. parapsilosis* in 2020. Khan et al. (3) stated that *C. albicans* was the most frequently isolated species during the period 2006 - 2012 in Kuwait and decreased with an increase in the prevalence of *C. parapsilosis*, in contrast with the results of Mete et al. (12), who mentioned no significant change in the distribution of the species over time.

The frequency of *C. albicans*, which had a decreasing trend until 2019, increased again during the COVID-19 pandemic. However, the increase in the frequency of *C. parapsilosis* in NAC species continued. It has been shown that the use of broad-spectrum antibiotics, the presence or prolonged use of central venous catheters, and immunosuppressive treatments increase fungal infections in the COVID-19 period (35, 36).

Likewise, advanced age and cardiovascular diseases are important risk factors for hospitalization in COVID 19, and immunosuppressive treatments used in the treatment of COVID 19 explain the increase in the frequency of *C. albicans* that we detected during the pandemic period (37, 38). The prevalence of *C. krusei* has been reported to be increasing in recent years (2). In this study, 6.22% of our patients had *C. krusei* candidemia, and no statistically significant differences were noted by year. These epidemiological differences may be related to geographical features, as well as the fact that patients in these studies belong to different risk factors, such as malignancy, exposure to antifungal agents, previous antibiotic use, and the presence of a central venous catheter (9, 10).

Reduced susceptibility to fluconazole has been reported for *C. glabrata* (1), *C. parapsilosis* (12), *C. tropicalis* (16), and *C. albicans* (17, 20), whereas high susceptibility to fluconazole has been reported for *C. albicans* (5, 7, 16, 19, 21, 24,

26, 28), *C. parapsilosis* (7, 21, 24, 26), and *C. glabrata* (7, 28). High susceptibility rates have been reported for voriconazole in *Candida* isolates (2, 26, 28). In this study, *C. parapsilosis* and *C. glabrata* presented a decrease in susceptibility to fluconazole, whereas *C. albicans* showed an increased susceptibility. It is known that long-term use of fluconazole plays a role in the development of fluconazole resistance in *Candida* spp. (39). However, in our hospital, a change from fluconazole to echinocandins had begun in the empirical treatment of candidemia, according to the 2016 Infectious Diseases Society of America (IDSA) guidelines (40). In the current study, an increase in fluconazole and voriconazole sensitivity in *C. albicans* was interpreted as a result of using echinocandin rather than fluconazole in the empirical treatment option.

Candida parapsilosis has emerged as an important nosocomial pathogen (41). In the current study, the sensitivity of fluconazole decreased by 55% in *C. parapsilosis* (which is the second most common yeast pathogen in BSI), suggesting that it may be associated with clonal outbreaks of fluconazole-resistant *C. parapsilosis*. Decreased fluconazole sensitivity and increased echinocandin resistance in *C. glabrata* over the years can be explained by the co-resistance of *C. glabrata* to fluconazole and echinocandins. This is due to the increased use of echinocandin and fluconazole (42). Although all *Candida* spp. had high susceptibility to amphotericin B (6, 12, 17, 28, 34), *C. glabrata* had the highest resistance rate among *Candida* spp. (3, 20, 22, 28). In addition, *C. krusei* had reduced susceptibility to amphotericin B, and these isolates were also multi-drug resistant (MDR).

Although echinocandin resistance was as low as reported in the literature (2, 4, 20, 24), Israel et al. (19) reported increased resistance to caspofungin in *C. glabrata* (33.6%) and *C. krusei* (67%). In contrast, all *C. glabrata* and most *C. krusei* isolates were susceptible to another echinocandin derivative, micafungin. In all candidemia episodes, micafungin susceptibility showed a higher ratio compared to caspofungin, and this was associated with the use of caspofungin as the emprical echinocandin. MDR (resistance to 2 or more classes of antifungal agents) has been reported to be high in *C. parapsilosis* (33%) and *C. glabrata* (44%) by Cleveland et al. (4). In the study conducted by Mete et al. (12) in Turkey, 79% of the patients had MDR, of whom 22% were with *C. parapsilosis*, 20% with *C. glabrata*, and 1.3% with *C. albicans* over 10 years. Despite those statistics, in these data, 48.5% of the patients had MDR, of whom 19.1% were with *C. parapsilosis*, 13.5% with *C. albicans*, 5.3% with *C. glabrata*, 7.9% with *C. krusei*, and 1.1% with *C. tropicalis* over 5 years.

5.1. Conclusions

The mortality rate of invasive candidiasis remains high despite new antifungal drugs and recent advances in antifungal therapies. Early diagnosis and initiation of appropriate antifungal treatment may be delayed because of complex, relatively slow, and insensitive fungal culture. Empirical treatment with antifungal agents is associated with high costs, toxicities, and risk of antifungal resistance. Therefore, it is mandatory to determine and monitor *Candida* spp. and antifungal susceptibility testing for the selection of appropriate antifungal agents as empiric treatment of suspected infection.

Footnotes

Authors' Contribution: Study concept and design, ACY and DA; Acquisition of data, ACY; Analysis and interpretation of data, ACY; Drafting of the manuscript, ACY; Critical revision of the manuscript for important intellectual content, DA; Statistical analysis, ACY; Administrative, technical, and material support, ACY; Study supervision, ACY.

Conflict of Interests: There is no conflict of interest.

Data Reproducibility: The data presented in this study are openly available in one of the repositories or will be available on request from the corresponding author by this journal representative at any time during submission or after publication. Otherwise, all consequences of possible withdrawal or future retraction will be with the corresponding author.

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References

1. Lindberg E, Hammarstrom H, Ataollahy N, Kondori N. Species distribution and antifungal drug susceptibilities of yeasts isolated from the blood samples of patients with candidemia. *Sci Rep*. 2019;**9**(1):3838. doi: 10.1038/s41598-019-40280-8. [PubMed: 30846717]. [PubMed Central: PMC6405987].
2. Seyoum E, Bitew A, Mihret A. Distribution of Candida albicans and non-albicans Candida species isolated in different clinical samples and their in vitro antifungal suscetibity profile in Ethiopia. *BMC Infect Dis*. 2020;**20**(1):231. doi: 10.1186/s12879-020-4883-5. [PubMed: 32188422]. [PubMed Central: PMC7081544].
3. Khan Z, Ahmad S, Al-Sweih N, Mokaddas E, Al-Banwan K, Alfouzan W, et al. Changing trends in epidemiology and antifungal susceptibility patterns of six bloodstream Candida species isolates over a 12-year period in Kuwait. *PLoS One*. 2019;**14**(5). e0216250. doi: 10.1371/journal.pone.0216250. [PubMed: 31042770]. [PubMed Central: PMC6494055].
4. Cleveland AA, Farley MM, Harrison LH, Stein B, Hollick R, Lockhart SR, et al. Changes in incidence and antifungal drug resistance in candidemia: results from population-based laboratory surveillance in Atlanta and Baltimore, 2008-2011. *Clin Infect Dis*. 2012;**55**(10):1352–61. doi: 10.1093/cid/cis697. [PubMed: 22893576]. [PubMed Central: PMC4698872].

5. Li Y, Du M, Chen LA, Liu Y, Liang Z. Nosocomial bloodstream infection due to Candida spp. in China: species distribution, clinical features, and outcomes. *Mycopathologia*. 2016;**181**(7-8):485–95. doi: 10.1007/s11046-016-9997-3. [PubMed: 26994763].
6. Xiao Z, Wang Q, Zhu F, An Y. Epidemiology, species distribution, antifungal susceptibility and mortality risk factors of candidemia among critically ill patients: a retrospective study from 2011 to 2017 in a teaching hospital in China. *Antimicrob Resist Infect Control*. 2019;**8**:89. doi: 10.1186/s13756-019-0534-2. [PubMed: 31161036]. [PubMed Central: PMC6542075].
7. Kılınçel Ö, Akar N, Karamurat ZD, Çalışkan E, Öksüz Ş, Öztürk CE, et al. [Distribution and antifungal susceptibility of Candida species isolated from blood cultures]. *Turk Mikrobiyol Cem Derg*. 2018;**48**(4):256–63. Turkish. doi: 10.5222/tmcd.2018.256.
8. 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**(9):1284–92. doi: 10.1093/cid/cit006. [PubMed: 23315320].
9. Guinea J. Global trends in the distribution of Candida species causing candidemia. *Clin Microbiol Infect*. 2014;**20**:5–10. doi: 10.1111/1469-0691.12539.
10. Lortholary O, Desnos-Ollivier M, Sitbon K, Fontanet A, Bretagne S, Dromer F, et al. Recent exposure to caspofungin or fluconazole influences the epidemiology of candidemia: a prospective multicenter study involving 2,441 patients. *Antimicrob Agents Chemother*. 2011;**55**(2):532–8. doi: 10.1128/AAC.01128-10. [PubMed: 21078946]. [PubMed Central: PMC3028765].
11. Yesilkaya A, Azap O, Aydin M, Akcil Ok M. Epidemiology, species distribution, clinical characteristics and mortality of candidaemia in a tertiary care university hospital in Turkey, 2007-2014. *Mycoses*. 2017;**60**(7):433–9. doi: 10.1111/myc.12618. [PubMed: 28338249].
12. Mete B, Zerdali EY, Aygun G, Saltoglu N, Balkan ,I, Karaali R, et al. Change in species distribution and antifungal susceptibility of candidemias in an intensive care unit of a university hospital (10-year experience). *Eur J Clin Microbiol Infect Dis*. 2021;**40**(2):325–33. doi: 10.1007/s10096-020-03994-6. [PubMed: 32935158].
13. Meurman O, Koskensalo A, Rantakokko-Jalava K. Evaluation of Vitek 2 for identification of yeasts in the clinical laboratory. *Clin Microbiol Infect*. 2006;**12**(6):591–3. doi: 10.1111/j.1469-0691.2006.01409.x. [PubMed: 16700713].
14. Melhem MS, Bertoletti A, Lucca HR, Silva RB, Meneghin FA, Szeszs MW. Use of the VITEK 2 system to identify and test the antifungal susceptibility of clinically relevant yeast species. *Braz J Microbiol*. 2013;**44**(4):1257–66. doi: 10.1590/S1517-83822014005000018. [PubMed: 24688520]. [PubMed Central: PMC3958196].
15. The European Committee on Antimicrobial Susceptibility Testing. *Clinical breakpoints for fungi (Candida and Aspergillus species)*. Switzerland: The European Committee on Antimicrobial Susceptibility Testing; 2019, [cited 1st of Jan 2016]. Available from: https://www.eucast.org/astoffungi/clinicalbreakpointsforantifungals/.
16. Tan TY, Hsu LY, Alejandria MM, Chaiwarith R, Chinniah T, Chayakulkeeree M, et al. Antifungal susceptibility of invasive Candida bloodstream isolates from the Asia-Pacific region. *Med Mycol*. 2016;**54**(5):471–7. doi: 10.1093/mmy/myv114. [PubMed: 26868904].
17. Araj GF, Asmar RG, Avedissian AZ. Candida profiles and antifungal resistance evolution over a decade in Lebanon. *J Infect Dev Ctries*. 2015;**9**(9):997–1003. doi: 10.3855/jidc.6550. [PubMed: 26409741].
18. Caggiano G, Coretti C, Bartolomeo N, Lovero G, De Giglio O, Montagna MT. Candida bloodstream infections in italy: changing epidemiology during 16 years of surveillance. *Biomed Res Int*. 2015;**2015**:256580. doi: 10.1155/2015/256580. [PubMed: 26064890]. [PubMed Central: PMC4439500].
19. Israel S, Amit S, Israel A, Livneh A, Nir-Paz R, Korem M. The Epidemiology and Susceptibility of Candidemia in Jerusalem, Israel. *Front Cell Infect Microbiol*. 2019;**9**:352. doi: 10.3389/fcimb.2019.00352. [PubMed: 31681629]. [PubMed Central: PMC6801307].
20. Bhattacharjee P. Epidemiology and antifungal susceptibility of Candida species in a tertiary care hospital, Kolkata, India. *Curr Med Mycol*. 2016;**2**(2):20–7. doi: 10.18869/acadpub.cmm.2.2.5. [PubMed: 28681016]. [PubMed Central: PMC5490301].
21. Al-Musawi TS, Alkhalifa WA, Alasaker NA, Rahman JU, Alnimr AM. A seven-year surveillance of Candida bloodstream infection at a university hospital in KSA. *J Taibah Univ Med Sci*. 2021;**16**(2):184–90. doi: 10.1016/j.jtumed.2020.12.002. [PubMed: 33897322]. [PubMed Central: PMC8046963].
22. Lin S, Chen R, Zhu S, Wang H, Wang L, Zou J, et al. Candidemia in adults at a tertiary hospital in China: clinical characteristics, species distribution, resistance, and outcomes. *Mycopathologia*. 2018;**183**(4):679–89. doi: 10.1007/s11046-018-0258-5. [PubMed: 29572768].
23. Shigemura K, Osawa K, Jikimoto T, Yoshida H, Hayama B, Ohji G, et al. Comparison of the clinical risk factors between Candida albicans and Candida non-albicans species for bloodstream infection. *J Antibiot (Tokyo)*. 2014;**67**(4):311–4. doi: 10.1038/ja.2013.141. [PubMed: 24424346].
24. Lyon GM, Karatela S, Sunay S, Adiri Y, Candida Surveillance Study I. Antifungal susceptibility testing of Candida isolates from the Candida surveillance study. *J Clin Microbiol*. 2010;**48**(4):1270–5. doi: 10.1128/JCM.02363-09. [PubMed: 20129963]. [PubMed Central: PMC2849617].
25. Ergon MC, Doluca Dereli M, Ener B, Atalay MA, Koc AN, Cerikcioglu N, et al. [Distribution of yeast species isolated from blood cultures for a six year period in Turkey: A multi centre study]. *Mikrobiyol Bul*. 2020;**54**(4):638–46. Turkish. doi: 10.5578/mb.69837. [PubMed: 33107293].
26. Canela HMS, Cardoso B, Vitali LH, Coelho HC, Martinez R, Ferreira M. Prevalence, virulence factors and antifungal susceptibility of Candida spp. isolated from bloodstream infections in a tertiary care hospital in Brazil. *Mycoses*. 2018;**61**(1):11–21. doi: 10.1111/myc.12695. [PubMed: 28940753].
27. Dagi HT, Findik D, Senkeles C, Arslan U. Identification and antifungal susceptibility of Candida species isolated from bloodstream infections in Konya, Turkey. *Ann Clin Microbiol Antimicrob*. 2016;**15**(1):36. doi: 10.1186/s12941-016-0153-1. [PubMed: 27245756]. [PubMed Central: PMC4888423].
28. Mokaddas EM, Al-Sweih NA, Khan ZU. Species distribution and antifungal susceptibility of Candida bloodstream isolates in Kuwait: a 10-year study. *J Med Microbiol*. 2007;**56**(Pt 2):255–9. doi: 10.1099/jmm.0.46817-0. [PubMed: 17244809].
29. Alp S, Arikan-Akdagli S, Gulmez D, Ascioglu S, Uzun O, Akova M. Epidemiology of candidaemia in a tertiary care university hospital: 10-year experience with 381 candidaemia episodes between 2001 and 2010. *Mycoses*. 2015;**58**(8):498–505. doi: 10.1111/myc.12349. [PubMed: 26155849].
30. Kazak E, Akin H, Ener B, Sigirli D, Ozkan O, Gurcuoglu E, et al. An investigation of Candida species isolated from blood cultures during 17 years in a university hospital. *Mycoses*. 2014;**57**(10):623–9. doi: 10.1111/myc.12209. [PubMed: 24934185].
31. Muderris T, Kaya S, Ormen B, Aksoy Gokmen A, Varer Akpinar C, Yurtsever Gul S. Mortality and risk factor analysis for Candida blood stream infection: A three-year retrospective study. *J Mycol Med*. 2020;**30**(3):101008. doi: 10.1016/j.mycmed.2020.101008. [PubMed: 32651136].
32. Zhang W, Song X, Wu H, Zheng R. Epidemiology, species distribution, and predictive factors for mortality of candidemia in adult surgical patients. *BMC Infect Dis*. 2020;**20**(1):506. doi: 10.1186/s12879-020-05238-6. [PubMed: 32660641]. [PubMed Central: PMC7359486].
33. Aldardeer NF, Albar H, Al-Attas M, Eldali A, Qutub M, Hassanien A, et al. Antifungal resistance in patients with Candidaemia: a retrospective cohort study. *BMC Infect Dis*. 2020;**20**(1):55. doi: 10.1186/s12879-019-4710-z. [PubMed: 31952505]. [PubMed Central: PMC6969401].
34. Aslan N, Yildizdas D, Alabaz D, Horoz OO, Yontem A, Kocabas E. Invasive Candida infections in a pediatric intensive care unit in turkey: evaluation of an 11-year period. *J Pediatr Intensive Care*. 2020;**9**(1):21–

6. doi: 10.1055/s-0039-1695061. [PubMed: 31984153]. [PubMed Central: PMC6978178].
35. Casalini G, Giacomelli A, Ridolfo A, Gervasoni C, Antinori S. Invasive fungal infections complicating COVID-19: A narrative review. *J Fungi (Basel)*. 2021;**7**(11). doi: 10.3390/jof7110921. [PubMed: 34829210]. [PubMed Central: PMC8620819].
36. Seagle EE, Jackson BR, Lockhart SR, Georgacopoulos O, Nunnally NS, Roland J, et al. The landscape of candidemia during the COVID-19 pandemic. *Clin Infect Dis*. 2021. doi: 10.1093/cid/ciab562. [PubMed: 34145450].
37. Ko JY, Danielson ML, Town M, Derado G, Greenlund KJ, Kirley PD, et al. Risk factors for coronavirus disease 2019 (COVID-19)-associated hospitalization: COVID-19-associated hospitalization surveillance network and behavioral risk factor surveillance system. *Clin Infect Dis*. 2021;**72**(11):e695–703. doi: 10.1093/cid/ciaa1419. [PubMed: 32945846]. [PubMed Central: PMC7543371].
38. Vahey GM, McDonald E, Marshall K, Martin SW, Chun H, Herlihy R, et al. Risk factors for hospitalization among persons with COVID-19-Colorado. *PLoS One*. 2021;**16**(9). e0256917. doi: 10.1371/journal.pone.0256917. [PubMed: 34473791]. [PubMed Central: PMC8412293].
39. Spampinato C, Leonardi D. Candida infections, causes, targets, and resistance mechanisms: traditional and alternative antifungal agents. *Biomed Res Int*. 2013;**2013**:204237. doi: 10.1155/2013/204237. [PubMed: 23878798]. [PubMed Central: PMC3708393].
40. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of America. *Clin Infect Dis*. 2016;**62**(4):e1–50. doi: 10.1093/cid/civ933. [PubMed: 26679628]. [PubMed Central: PMC4725385].
41. Yamin DH, Husin A, Harun A. Risk factors of Candida parapsilosis catheter-related bloodstream infection. *Front Public Health*. 2021;**9**:631865. doi: 10.3389/fpubh.2021.631865. [PubMed: 34458217]. [PubMed Central: PMC8387826].
42. Pristov KE, Ghannoum MA. Resistance of Candida to azoles and echinocandins worldwide. *Clin Microbiol Infect*. 2019;**25**(7):792–8. doi: 10.1016/j.cmi.2019.03.028. [PubMed: 30965100].