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Original Article

Investigation of the distribution and antifungal susceptibility of *Candida* species isolated from clinical specimens in central part of Turkey

Burak Ezer[1], Selin Ugrakli[2], Enes Kasapoglu[3]

[1] *Beyhekim Training and Research Hospital, Medical Microbiology, Konya, Turkey*
[2] *Necmettin Erbakan University Medicine Faculty, Medical Microbiology, Konya, Turkey*
[3] *Cumra District Health Directorate, Public Health, Konya, Turkey*

Abstract

Introduction: This study aimed to examine the distribution and antifungal susceptibility of *Candida* species in a university hospital and investigate the association of *Candida* species with age, gender, and clinical specimens.

Methodology: A total of 939 samples isolated *Candida* spp. from various clinical samples between 01.01.2019-06.08.2024 were included in the study. Between 01.01.2019-29.04.2022, *Candida* species and antifungal susceptibilities were determined using Vitek2 automated system. Between 30.04.2022-06.08.2024, *Candida* species were detected using the Phoenix automated system and MALDITOF-MS, and antifungal susceptibilities were determined by the gold standard method of broth microdilution.

Results: *Candida albicans* was detected in 511 (54.4%) and non-albicans candida species (NAC) in 428 (45.6%) of the samples with *Candida* spp. growth. The most frequently detected species were *C. albicans* in 511 (54.4%) samples, *C. parapsilosis* in 215 (22.9%) samples, and *C. glabrata* in 85 (9.1%) samples. The MIC values of all antifungals were statistically significantly higher in NAC species than in *C. albicans* ($p < 0.001$). *C. tropicalis* was isolated most frequently in CSF, *C. albicans* was isolated most frequently in ocular corneal fluid, *C. tropicalis* was isolated most frequently in pleural fluid and *C. albicans* was isolated in all vaginal discharge samples. The higher MIC values of caspofungin, micafungin, and anidulafungin in *C. parapsilosis* isolates were statistically significant compared to *C. albicans* and *C. glabrata* ($p < 0.001$).

Conclusions: Investigating the distribution and antifungal susceptibility of *Candida* species is vital to initiate appropriate and early empirical antifungal therapy. Each center should determine its species distribution and closely monitor antifungal resistance changes.

Key words: *Candida*; antifungal; resistance.

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Introduction

Candida species are found as normal flora members in mucosa, skin, gastrointestinal tract and vagina. In addition to being a member of normal flora, their most important feature is their ability to cause opportunistic infections. *Candida* species, which were generally observed in immunosuppressive patients in the past, are now reported with increasing rates in various patient groups [1]. The most important risk factors for *Candida* infections include blood transfusion, antibiotic and steroid use, urethral catheter, total parenteral nutrition, and invasive procedures [2]. In recent years, there have been significant changes in the incidence and antifungal resistance status of *Candida* species with the pandemic effect [3]. Although *Candida albicans* is the most common *Candida* species, a significant increase in the incidence of non-albicans Candida (NAC) species has also been reported [4]. NAC species show resistance to azole group antifungals more frequently than *Candida albicans* species [5]. The increase in the incidence of *Candida* infections worldwide, especially with the pandemic, the increase in the frequency of NAC species, and changes in antifungal susceptibility patterns have increased the importance of determining the distribution of *Candida* species in relevant centers and performing accurate antifungal susceptibility tests for appropriate empirical antifungal treatment [6]. Epidemiologic data on the distribution of isolated *Candida* species and their antifungal susceptibilities are necessary to prevent nosocomial infections and to apply effective treatment.

This study aimed to investigate the distribution of *Candida* species and antifungal susceptibility profiles in a university hospital located in the central region of Turkey.

Methodology

BD BACTEC Plus Aerobic/F was used as a blood culture device. Blood culture samples giving a positive signal were simultaneously inoculated onto sheep blood

agar, Eosin Methylene Blue (EMB), and Sabouraud Dextrose Agar (SDA). After incubation at 25-30 °C and 36-37 °C, the media were checked every day.

A total of 939 samples isolated *Candida* spp. from various clinical specimens between 01.01.2019 and 06.08.2024 were included in the study. Between 01.01.2019 and 29.04.2022, *Candida* species and antifungal susceptibilities were determined using Vitek2 (bioMérieux, MarcyL'Etoile, France) automated system. Between 30.04.2022-06.08.2024, *Candida* species were detected using the Phoenix automated system (Becton Dickinson, M50, USA) and MALDITOF-MS (bioMérieux, MarcyL'Etoile, France), and antifungal susceptibilities were determined by the broth microdilution method (MICRONAUT-AM Antifungal Agents MIC, Bruker, Germany). Susceptibilities to amphotericin B, caspofungin, fluconazole, flucytosine, micafungin, and voriconazole were investigated jointly by both Vitek-2 and broth microdilution methods. Antifungal resistance was reported according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) version 9 and Clinical and Laboratory Standards Institute (CLSI) M38 criteria. The minimum inhibitory concentration (MIC) value for each antifungal was determined. CLSI criteria were taken into account for antifungals that do not have breakpoints according to EUCAST criteria. Amphotericin B susceptibility status reporting is reported according to EUCAST version 9, and MIC values of 1 and below are reported as susceptible, and values of 2 and above are reported as resistant.

Table 1. Characteristics of clinical specimens with *Candida* spp. growth included in the study.

Feature	n	%
Gender		
Male	524	55.8
Female	415	44.2
Material		
Abscess	15	1.6
BOF	32	3.4
Sputum	9	1.0
CSF	1	0.1
Drainage	14	1.5
Corneal Fluid	1	0.1
Urine	244	26.0
Blood	536	57.1
Catheter	30	3.2
Peritoneal Fluid	3	0.3
Pleural Fluid	1	0.1
Vaginal Discharge	4	0.4
Wound	49	5.2
***Candida* types**		
Albicans	511	54.4
Non-Albicans	428	45.6
***Candida* subtypes**		
C. albicans	511	54.4
C. auris	1	0.1
C. crusei	6	0.6
C. dubliniensis	3	0.3
C. glabrata	85	9.1
C. guilliermondii	7	0.7
C. kefyr	25	2.7
C. lipolytica	2	0.2
C. lusitaniae	7	0.7
C. orthopsilosis	1	0.1
C. parapsilosis	215	22.9
C. pelliculosa	2	0.2
C. sake	1	0.1
C. tropicalis	72	7.7
C. zeylanoides	1	0.1

Statistical Analysis

The data obtained from the study were transferred to the computer and analyzed with the SPSS (Statistical Package for Social Sciences) 21.0 package program. In descriptive analyses, frequency data were presented as numbers (n) and percentages (%), while numerical data were presented using the median (Q1 (1st quartile)-Q3 (3rd quartile)). The conformity of the numerical data to normal distribution was examined by visual (histogram) and analytical methods (Kolmogorov-Smirnov test). The Mann-Whitney U test was used to compare the numerical variables that were found to not comply with normal distribution in two independent groups. Statistical significance level was accepted as $p < 0.05$ for all tests.

Results

A total of 939 patients, 524 males (55.8%) and 415 females (44.2%), were included in the study. The median age of the patients was 62.00 years (30.00-72.00). The most common clinical specimen types in which *Candida* spp. growth was detected were blood samples with 536 (57.1%) samples, urine with 244 (26.0%) samples, and bronchoalveolar lavage fluid (BOF) with 32 (3.4%) samples. Of the organisms grown, 511 (54.4%) were *Candida albicans* and 428 (45.6%) were NAC. The most frequently detected species were *C. albicans* in 511 (54.4%) samples, *C. parapsilosis* in 215 (22.9%) samples, and *C. glabrata* in 85 (9.1%) samples (Table 1).

The most common agents detected in men were *C. albicans* in 278 (53.1%) samples, *C. parapsilosis* in 134 (25.6%) samples, and *C. tropicalis* in 48 (9.2%) samples. The most frequently detected agents in women were *C. albicans,* detected in 233 (56.1%) samples, *C. parapsilosis,* detected in 81 (19.5%) samples, and *C. glabrata,* detected in 47 (11.3%) samples.

The MIC values for amphotericin B, caspofungin, fluconazole, flucytosine, micafungin, anidulafungin, itraconazole, posaconazole and voriconazole were significantly higher in NAC species than in *C. albicans*

Table 2. Comparison of MIC values of *Candida* species isolated from clinical samples.

	Albicans	Non-Albicans	*p*
Amphotericin B	0.125 (0.062-0.150)	0.250 (0.125-0.250)	< 0.001
Caspofungin	0.031 (0.030-0.062)	0.120 (0.060-0.250)	< 0.001
Fluconazole	0.500 (0.250-1.000)	4.000 (1.000-8.000)	< 0.001
Flucytosine	0.062 (0.062-0.062)	64.00 (47.00-80.00)	< 0.001
Micafungin	0.007 (0.001-0.015)	0.060 (0.015-0.125)	< 0.001
Anidulafungin	0.010 (0.001-0.015)	0.060 (0.015-0.250)	< 0.001
Itraconazole	0.031 (0.031-0.031)	0.060 (0.031-0.250)	< 0.001
Posaconazole	0.007 (0.007-0.015)	0.032 (0.015-0.125)	< 0.001
Voriconazole	0.007 (0.007-0.015)	0.060 (0.016-0.250)	< 0.001

($p < 0.001$).

Comparison of MIC values of *Candid*a species isolated from clinical specimens is presented in Table 2.

According to the antifungal susceptibility profile determined with VITEK-2, caspofungin and micafungin susceptibility were statistically higher than NAC species *(*$p < 0.001$). According to the antifungal profile determined by the microdilution method, azole group antifungals were found to be more susceptible to *C. albicans* species, which was statistically significant ($p < 0.001$).

The antifungal resistance of *Candida albicans* and NAC species is given in Tables 3 and 4.

Of the samples included in the study, 367 (39.1%) were in 2021, 263 (28.0%) in 2022, 209 (22.3%) in 2023, and 100 (10.6%) in 2024.

A statistically significant difference was found between *C. albicans*, *C. glabrata,* and C. *parapsilosis* ($p = 0.006$). It was determined that this difference was due to the higher incidence of *C. albicans* in 2021.

The distribution of *Candida* species isolated according to years is given in Table 5.

C. albicans was more common in abscess (73.3%), BOF (65.6%), sputum (88.9%), ocular corneal fluid (100.0%), urine (65.6%), catheter (60.0%), vaginal

Table 3. Antifungal resistance profiles of *Candida albicans* and Non-albicans *Candida* strains with VITEK2 automated system.

Feature	Albicans	Non-Albicans	*p*
	n (%)	n (%)	
Amphotericin B			
Sensitive	219 (100.0)	226 (98.7)	0.2492
Resistant	0 (0.0)	3 (1.3)	
Caspofungin			
Sensitive	155 (70.8)	82 (36.9)	
Resistant	64 (29.2)	22 (9.9)	**< 0.001**[1]
Medium	0 (0.0)	118 (53.2)	
Anidulafungin			
Sensitive	182 (86.3)	106 (47.5)	
Resistant	29 (13.7)	12 (5.4)	**< 0.001**[1]
Medium	0 (0.0)	105 (47.1)	
Micafungin			
Sensitive	184 (84.4)	54 (30.9)	
Resistant	34 (15.6)	7 (4.0)	**< 0.001**[1]
Medium	0 (0.0)	114 (65.1)	
Flucytosine			
Sensitive	180 (100.0)	218 (98.2)	
Resistant	0 (0.0)	2 (0.9)	0.2542
Medium	0 (0.0)	2 (0.9)	
Fluconazole			
Sensitive	205 (93.6)	100 (44.8)	
Resistant	9 (4.1)	34 (15.2)	**< 0.001**[1]
Medium	5 (2.3)	89 (39.9)	
Itraconazole			
Sensitive	198 (93.0)	131 (79.9)	**< 0.001**[1]
Resistant	15 (7.0)	33 (20.1)	
Posaconazole			
Sensitive	200 (94.8)	139 (84.8)	**< 0.002**[1]
Resistant	12 (5.7)	25 (15.2)	
Voriconazole			
Sensitive	202 (92.7)	130 (76.9)	
Resistant	9 (4.1)	28 (16.6)	**< 0.001**[1]
Medium	7 (3.2)	11 (6.5)	

[1]: Pearson chi-square test was performed; [2]: Fisher's exact chi-square test was performed.

Table 4. Antifungal resistance profiles of *Candida albicans* and Non-albicans *Candida* strains with broth microdilution method.

Feature	Albicans	Non-Albicans	*p*
	n (%)	n (%)	
Amphotericin B			
Sensitive	219 (100.0)	226 (98.7)	0.2492
Resistant	0 (0.0)	3 (1.3)	
Caspofungin			
Sensitive	155 (70.8)	82 (36.9)	
Resistant	64 (29.2)	22 (9.9)	**< 0.001**[1]
Medium	0 (0.0)	118 (53.2)	
Anidulafungin			
Sensitive	182 (86.3)	106 (47.5)	
Resistant	29 (13.7)	12 (5.4)	**< 0.001**[1]
Medium	0 (0.0)	105 (47.1)	
Micafungin			
Sensitive	184 (84.4)	54 (30.9)	
Resistant	34 (15.6)	7 (4.0)	**< 0.001**[1]
Medium	0 (0.0)	114 (65.1)	
Flucytosine			
Sensitive	180 (100.0)	218 (98.2)	
Resistant	0 (0.0)	2 (0.9)	0.2542
Medium	0 (0.0)	2 (0.9)	
Fluconazole			
Sensitive	205 (93.6)	100 (44.8)	
Resistant	9 (4.1)	34 (15.2)	**< 0.001**[1]
Medium	5 (2.3)	89 (39.9)	
Itraconazole			
Sensitive	198 (93.0)	131 (79.9)	**< 0.001**[1]
Resistant	15 (7.0)	33 (20.1)	
Posaconazole			
Sensitive	200 (94.8)	139 (84.8)	**< 0.002**[1]
Resistant	12 (5.7)	25 (15.2)	
Voriconazole			
Sensitive	202 (92.7)	130 (76.9)	
Resistant	9 (4.1)	28 (16.6)	**< 0.001**[1]
Medium	7 (3.2)	11 (6.5)	

[1]: Pearson chi-square test was performed; [2]: Fisher's exact chi-square test was performed.

Table 5. Distribution of isolated *Candida* species by year.

Pathogens	2021	2022	2023	2024
	n (%)	n (%)	n (%)	n (%)
C. albicans	228 (62.1)	135 (51.3)	104 (49.8)	44 (44.0)
C. auris	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
C. crusei	0 (0.0)	2 (0.8)	4 (1.9)	0 (0.0)
C. dubliniensis	2 (0.5)	1 (0.4)	0 (0.0)	0 (0.0)
C. glabrata	24 (6.5)	25 (9.5)	21 (10.0)	15 (15.0)
C. guilliermondii	1 (0.3)	3 (1.1)	3 (1.4)	0 (0.0)
C. kefyr	17 (4.6)	1 (0.4)	4 (1.9)	3 (3.0)
C. lipolytica	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
C. lusitaniae	1 (0.3)	3 (1.1)	2 (1.0)	1 (1.0)
C. orthopsilosis	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
C. parapsilosis	70 (19.1)	66 (25.1)	55 (26.3)	24 (24.0)
C. pelliculosa	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)
C. sake	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
C. tropicalis	22 (6.0)	26 (9.9)	14 (6.7)	10 (10.0)
C. zeylanoides	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

discharge (100.0%) and wound (73.5%) samples. NAC species were more common in CSF (100.0%), drainage (64.3%), blood (54.1%), peritoneal fluid (66.7%), and pleural fluid (100.0%) samples (Table 6).

C. tropicalis was the most frequently isolated strain in CSF, *C. albicans* was the most frequently isolated strain in corneal fluid, *C. tropicalis* was the most frequently isolated strain in pleural fluid, and *C. albicans* was the most frequently isolated strain in all vaginal discharge samples. The lower MIC values of amphotericin B and flucytosine in *C. albicans* isolates compared to *C. glabrata* and *C. parapsilosis* were statistically significant ($p < 0.001$).

The high MIC values of caspofungin, micafungin, and anidulafungin in *C. parapsilosis* isolates were statistically significant compared to *C. albicans* and *C. glabrata* ($p < 0.001$).

The MIC values of all azole group antifungals in *C. glabrata* isolates were significantly higher than *C. albicans* and *C. parapsilosis* ($p < 0.001$) (Table 7).

Discussion

Significant rises in invasive nosocomial *Candida* cases have been reported. Especially serious increases are observed in infections caused by NAC species [7-10]. In this study, although the *C. albicans* species were detected more frequently (54.4%), NAC species were also detected at a high rate (45.6%). In the literature, the most common *Candida* species that can cause various infections in humans are reported as *C. albicans*, *C. parapsilosis*, *C. tropicalis, C. glabrata,* and *C. krusei*, respectively [10,11]. Similar to the literature, the most frequently isolated species in our study were *C. albicans* (54.4%), *C. parapsilosis* (22.9%), and *C. glabrata* (9.1%), respectively. Inappropriate use of empirical antifungal therapy has been blamed for the recent shift from *C. albicans*-type infections to NAC-type infections. It has been shown that fluconazole usage increases the risk of *C. glabrata* and *C. krusei* infections, while caspofungin use increases the risk of *C. parapsilosis*, *C. glabrata,* and *C. krusei* infections [12,13]. Similar to the literature, it was determined that infections caused by *Candida albicans* species, which

Table 6. Distribution of clinical samples from which *Candida* species were isolated.

Sample	Albicans, n (%)	Non-albicans, n (%)
Abscess	11 (73.3)	4 (26.7)
BOF	21 (65.6)	11 (34.4)
Sputum	8 (88.9)	1 (11.1)
CSF	0 (0.0)	1 (100.0)
Drainage	5 (35.7)	9 (64.3)
Corneal Fluid	1 (100.0)	0 (0.0)
Urine	160 (65.6)	84 (34.4)
Blood	246 (45.9)	290 (%54.1)
Catheter	18 (60.0)	12 (40.0)
Peritoneal Fluid	1 (33.3)	2 (66.7)
Pleural Fluid	0 (0.0)	1 (100.0)
Vaginal Discharge	4 (100.0)	0 (0.0)
Wound	36 (73.5)	13 (26.5)

Table 7. Comparison of MIC values of *C.albicans*. *C.glabrata* and *C.parapsilosis* species.

	***C. albicans* Median (Q1-Q3)**	***C. glabrata* Median (Q1-Q3)**	***C. parapsilosis* Median (Q1-Q3)**	***p***
Amphotericin B	0.125 (0.062-0.150)	0.250 (0.125-0.250)	0.250 (0.125-0.250)	< 0.001
Caspofungin	0.031 (0.030-0.062)	0.062 (0.031-0.062)	0.125 (0.062-0.250)	< 0.001
Fluconazole	0.500 (0.250-1.000)	8.000 (4.000-10.000)	2.000 (1.000-16.000)	< 0.001
Flucytosine	0.062 (0.062-0.062)	0.093 (0.062-0.125)	0.125 (0.062-0.125)	< 0.001
Micafungin	0.007 (0.001-0.015)	0.015 (0.001-0.015)	0.125 (0.06-0.125)	< 0.001
Anidulafungin	0.010 (0.001-0.015)	0.015 (0.015-0.032)	0.250 (0.060-0.500)	< 0.001
Itraconazole	0.031 (0.031-0.031)	0.250 (0.064-2.000)	0.031 (0.031-0.062)	< 0.001
Posaconazole	0.007 (0.007-0.015)	0.250 (0.125-0.500)	0.015 (0.007-0.060)	< 0.001
Voriconazole	0.007 (0.007-0.015)	0.125 (0.062-0.250)	0.031 (0.015-0.250)	< 0.001

were 62.1% in 2021, decreased to 44.0% in 2024 in our center due to inappropriate steroid and antifungal treatments used during the pandemic period. In a study conducted in Egypt, it was reported that fluconazole resistance was detected at a higher rate in NAC species than in *C. albicans* species [14]. In another study in the literature, fluconazole resistance rates of NAC species isolated in pediatric patient groups were found to be higher [15]. In our study, MIC values of all antifungals were found to be statistically significantly ($p < 0.001$) higher in NAC species, and azole group antifungal resistance was found to be higher in NAC species compared to *C. albicans* species. When the studies in the literature were examined, amphotericin B resistance was either not detected or reported for a few strains [16-18]. In the present study, amphotericin B resistance was detected in only 9 isolates, in accordance with the literature. In a study conducted in Iran, caspofungin resistance was found only in *Candida albicans* species (17.4%) [19]. In our study, the EUCAST recommendations were taken into consideration during the period when antifungal susceptibility was investigated with the broth microdilution method. Since the number of samples reported as intermediate susceptibility in NAC species for echinocandin-derived antifungals was quite high and could not be included in the resistant category, echinocandin resistance was detected more in *C. albicans* species compared to NAC species. In the period when antifungal susceptibility was investigated with VITEK2, echinocandin resistance was detected higher rate in NAC species as expected. One of the limitations of our study is that echinocandin resistances were not confirmed by molecular methods.

Candida albicans has been reported as the most common agent (63.4%) in vulvovaginal candidiasis cases [20]. In our findings, *Candida albicans* was isolated in all vaginal discharges. In many studies in the literature, similar to our study, *Candida albicans* was reported to be the most common causative agent in blood cultures [21]. *Candida auris* was first reported in Japan in 2009 and has rapidly spread all over the world and has become an important public health problem. Since *Candida auris*, which is held responsible for outbreaks in intensive care units, is resistant to many antifungals, especially fluconazole, necessary precautions should be taken. In the literature, it is recommended to use MALDITOF-MS or molecular methods to make the correct diagnosis of *Candida auris* [22,23]. In our hospital, *Candida auris* was detected in only one isolate using MALDITOF-MS in 2024, and the increase in cases was prevented by taking effective measures to prevent nosocomial infections.

In the literature, it is reported that increased resistance is observed in *C. glabrata* isolates against azole group antifungals, especially fluconazole, and that they are generally sensitive to caspofungin, micafungin, and anidulafungin [24,25]. In our study, the MIC values of azole group antifungals in *C. glabrata* isolates were statistically higher and significant ($p < 0.001$) than those of *C. albicans* and *C. parapsilosis* species, and the MIC values of echinocandin-type antifungals were lower than those of *C. parasilosis* species, supporting the literature data.

Conclusions

In conclusion, it is vital to follow *Candida* species that differ according to geographical regions and antifungal resistance profiles that change with the pandemic period in order to start appropriate empirical treatment. Each center should take the necessary precautions against resistant *Candida* species such as *Candida auris*, which can cause outbreaks in intensive care units and have a highly mortal course, by determining the change in their species distribution over the years.

Authors' contributions

BE: Writing the article and collecting samples, interpreting data and analysis; SU: Final check of the written article and determination of the topic, interpreting analysis; EK: Making statistical evaluations, interpreting data and analysis

Corresponding author

Dr. Burak Ezer, MD
Beyhekim Training and Research Hospital,
Medical Microbiology,
Konya, Turkey
Tel: +(90)536 952 44 32
Email: dr.burakezer@gmail.com

Conflict of interests

No conflict of interests is declared.

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