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ORIGINAL ARTICLE

Increase in Antifungal Resistance Due to Variability in *Candida* Species: Experience from the Central Mycology Laboratory

Deniz Turan[1], Sebahat Aksaray[2]

[1]Department of Medical Microbiology, University of Health Sciences Türkiye, Haydarpasa Numune Training and Research Hospital, Istanbul, Türkiye
[2]Department of Medical Microbiology, University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, Istanbul, Türkiye

Abstract

Introduction: Invasive candidiasis is a significant fungal infection associated with healthcare, with *Candida albicans* being the most commonly isolated species. *Candida auris* and other resistant species have become a global concern due to their potential for multi-drug resistance and causing outbreaks in hospitals. This study aims to validate the antifungal resistance of *Candida* species sent to the ISLAB-2 Central Mycology Laboratory for identification and antifungal susceptibility testing (AFST) using the Vitek-2 automated system (bioMérieux, France) by conducting further tests with the Sensititre YeastOone (SYO).

Methods: The study included 65 *Candida* spp. isolates that showed antifungal resistance and were sent to the ISLAB-2 Central Mycology Laboratory for identification and AFST between May 18, 2022, and August 14, 2023. *Candida* species with unexpected resistance profiles were further tested for antifungal susceptibility using SYO.

Results: Among the species, the highest resistance was found in *C. auris*, with resistance rates for fluconazole, amphotericin B, anidulafungin, micafungin, and caspofungin being 97.1%, 94.3%, 17.1%, 20%, and 25.7%, respectively. Resistance rates in other species were generally lower, except for *Candida parapsilosis*, which had a fluconazole resistance rate of 92.6%.

Discussion and Conclusion: The presence of antifungal resistance, including in multidrug-resistant *Candida* species, complicates the treatment of invasive fungal diseases with high mortality and morbidity rates. Rapid and accurate species identification is critically important for initiating appropriate antifungal treatment in the early stages. Taking necessary precautions for colonization and infection, especially in intensive care units, can prevent the spread of multidrug-resistant *Candida* species.

Keywords: Antifungal resistance; *Candida auris; Candida species*; Health-care-associated infections; Multi-drug resistance.

Correspondence: Deniz Turan, M.D. Department of Medical Microbiology, University of Health Sciences, Haydarpasa Numune Training and Research Hospital, İstanbul, Türkiye
Phone: +90 216 542 32 32 **E-mail:** dennizturan@hotmail.com
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Invasive *Candida* infections are health-care-associated fungal infections that develop primarily in the presence of underlying predisposing factors or immunocompromised patients[1]. The most frequently isolated species from clinical specimens is *Candida albicans*. However, the epidemiology of *Candida* infections has changed in recent years, and the incidence of non-*albicans Candida* species has increased[2]. The most clinically significant non-*albicans Candida* species include *Candida glabrata, Candida tropicalis*, as well as *Candida parapsilosis*, and *Candida auris*, which have attracted attention in recent years with their multi-drug resistance and the hospital outbreaks they have caused[3,4]. The said change in the epidemiology of *Candida* infections is caused by the increase in the patient population in the risk group and the emergence of antifungal resistance due to the selective pressure caused by the increased use of antifungal drugs (in prophylactic and empirical therapies or agriculture)[5]. In consequence, our currently limited antifungal treatment options are further reduced by drug–drug interactions, toxicity, and limitations in routes of administration[5].

Invasive candidiasis is infections associated with high morbidity and mortality rates. Initiation of appropriate antimicrobial therapy in the early period will affect the prognosis positively[6]. The aim of antifungal susceptibility testing (AFST), which is applied in clinical microbiology laboratories and is becoming increasingly important, is to guide the treatment of patients, detect antifungal drug resistance, and reliably obtain the minimum inhibitory concentration (MIC) values to be used to guide epidemiological studies[7].

In this context, this study was carried out to conduct the AFST of *Candida* species, which were sent to the ISLAB-2 Central Mycology Laboratory for identification and AFST and found to have antifungal resistance with the Vitek-2 (bioMérieux, France) automated system through the routinely applied method, with the Sensititre YeastOne (SYO) method and to verify their antifungal resistance.

Materials and Methods

Between May 18, 2022, and August 14, 2023, a total of 6306 *Candida* species were isolated from various clinical specimens sent to ISLAB 2 Central Mycology Laboratories for identification and AFST. MALDI-TOF MS (Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry, bioMérieux, France) was used to identify the *Candida* species.

The antifungal susceptibility of isolates was tested with Vitek-2 (bioMérieux, France) through the routinely applied method. A total of 356 *Candida* spp. were found to be resistant. Among the *Candida* species with unexpected resistance profiles, randomly selected 65 *Candida* spp. (35 *C. auris*, 14 *C. parapsilosis*, 6 *C. glabrata*, 4 *C. albicans*, 3 *C. krusei*, 2 *C. tropicalis*, and 1 *C. guilliermondii*) was conducted with the SYO (Thermo Fisher Scientific, Waltham, MA, USA) colorimetric microdilution method containing amphotericin B, flucytosine, fluconazole, voriconazole, itraconazole, posaconazole, anidulafungin, micafungin, and caspofungin. Analysis of the isolates according to the sample types revealed that there were 24 blood, 20 urine, 12 catheters, 3 tracheal aspirates, 3 wounds, and 1 each of peritoneal fluid, pleural fluid, and biopsy. A single sample from each patient was included in the study. AFST and reading and interpretation of the results were performed per the manufacturer's instructions. *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 standard strains were used for quality control.

Evaluation of the Results

The MIC values obtained after incubation were evaluated according to the species-specific clinical breakpoints (CBPs) specified in the CLSI-M60 (Clinical and Laboratory Standards Institute Performance Standards for AFST of Yeasts) guidelines[8]. For non-*albicans Candida* species and antifungal agents for which CBPs are not specified in these guidelines, the results were evaluated based on the respective epidemiological cutoff values (ECVs)[9]. The isolates are categorized as susceptible or resistant according to CBP and as wild type (WT; no detectable phenotypic resistance) or non-WT (containing more likely mechanisms of resistance) according to ECV[10]. Only MIC values were reported for the species with no CBP and ECV values. In the case of *C. auris* spp., Centers for Disease Control and Prevention (CDC) MIC results were evaluated in line with recommendations[11].

Results

Of the 65 *Candida* isolates included in the study, 32 (49.2%) were isolated from female patients' samples and 33 (50.8%) from male patients' samples. The mean age of the patients

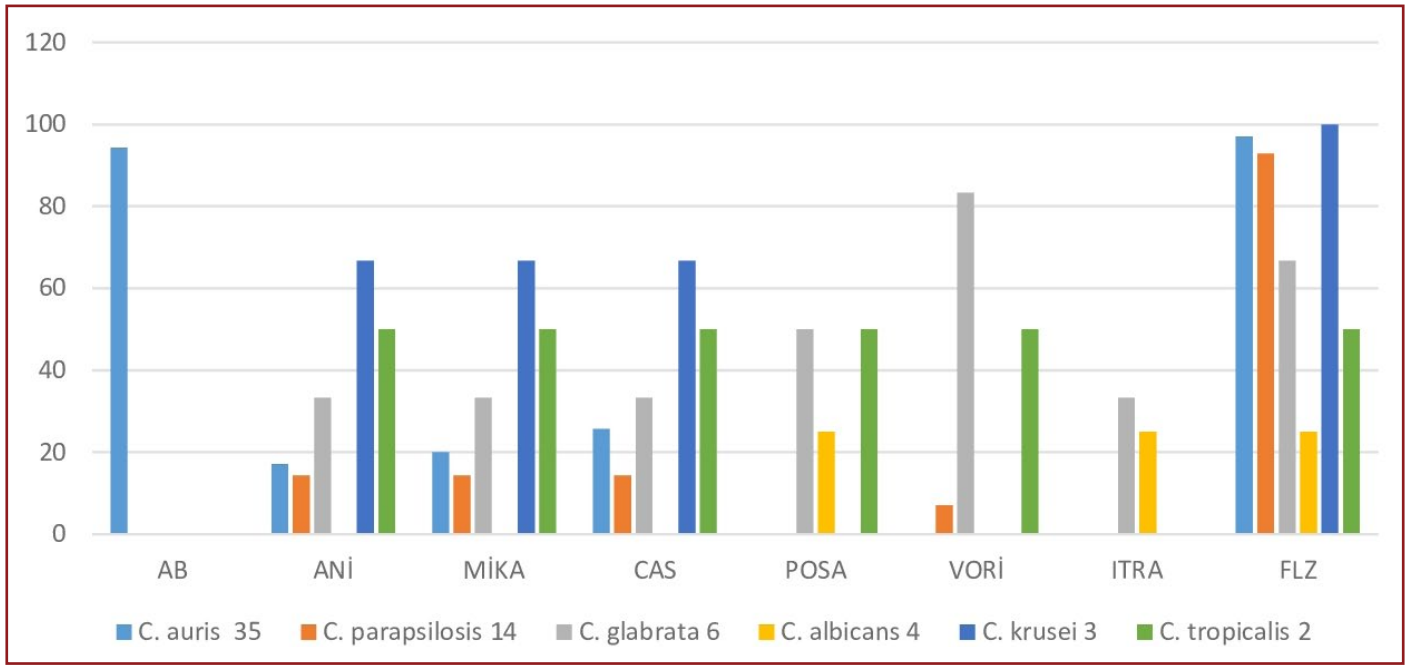

Figure 1. Resistance rates of Candida species for each antifungal drug.

AB: Amfoterisin B; ANI: Anidulafungin; MICA: Micafungin; CAS: Caspofungin; POS: Posaconazole; VOR: Voriconazole; ITRA: Itraconazole; FLZ: Fluconazole.

was 54.7 (min. 0 and max. 94) years. It was determined that 47 (72.3%) samples were sent from intensive care units (ICUs), 14 (21.5%) from the hospital services, and 4 (6.2%) from the palliative care patients.

Analysis of the 65 *Candida* isolates according to their species revealed that 35 (53.8%) were *C. auris*, 14 (21.5%) *C. parapsilosis*, 6 (9.2%) *C. glabrata*, 4 (6.3%) *C. albicans*, 3 (4.6%) *C. krusei*, 2 (3.1%) *C. tropicalis*, and 1 (1.5%) *C. guilliermondii*.

C. auris has attracted attention in recent years due to its multidrug resistance and the hospital outbreaks it has caused. In our study, 35 *C. auris* isolates were evaluated. Analysis of these isolates according to the sample types revealed that 16 were isolated from urine, 7 from blood, 6 from catheter, 2 from tracheal aspirate, 2 from wound, and 1 from pleural fluid. The rate of 35 *C. auris* isolates found to be resistant to fluconazole, amphotericin B, anidulafungin, micafungin, and caspofungin was 97.1%, 94.3%, 17.1%, 20%, and 25.7%, respectively. The rate of 14 *C. parapsilosis* isolates found to be resistant to fluconazole and voriconazole was 92.6% and 7.1%, respectively. In addition, 14.3% of *C. parapsilosis* isolates were found to be resistant to each anidulafungin, micafungin, and caspofungin from the echinocandin group. The rate of 6 *C. glabrata* isolates found to be resistant to fluconazole was 66.7%, and 33.3% of *C. glabrata* isolates were found to be resistant to each of anidulafungin, micafungin, and caspofungin from the echinocandin group. The rate of 4 *C. albicans* isolates found to be resistant to fluconazole was 25%, and the rate of 3 *C. krusei* isolates found to be resistant to each of anidulafungin, micafungin, and caspofungin from the echinocandin group was 66.7%. The rate of 2 *C. tropicalis* isolates found to be resistant to fluconazole and voriconazole and each of anidulafungin, micafungin, and caspofungin from the echinocandin group was 50%. The reason why the resistance rates are so high may be because we worked with a limited number of isolates in terms of test (SYO) cost. In addition, because the isolates included in the study were selected from the population found to be resistant by the first method and some species contained a small number of isolates, the percentage values in the resistance data appear to be high. MIC ranges and MIC50-MIC90 values for the antifungal drug of *Candida* spp. for which AFSTs were performed are shown in Table 1, and the rates of *Candida* spp. isolates found to be resistant to antifungal drugs are shown in Figure 1.

Discussion

Candida species are among the most common fungal pathogens causing invasive infections worldwide[12]. In the "priority pathogens" list published by the World Health

Table 1. MIC (µg/mL) of Candida isolates isolated from clinical samples and resistance/non-wild type (non-WT)

Yeast species (n)	Antifungal drug	MIC range	MIC_{50}	MIC_{90}	GM	Resistance status/ non-WT (%)			
						S	DDS/I	R	Non-WT
Candida auris (35)									
	AB	1–4	2	4	2.21	5.7		94.3	
	ANI	0.12–8	0.12	4	0.27	82.9		17.1	
	MICA	0.06–8	0.12	8	0.23	80		20	
	CAS	0.12–8	0.12	8	0.23	74.3		25.7	
	FC	0.06–0.12	0.06	0.06	0.06				
	POS	0.008–8	0.03	0.25	0.03				
	VOR	0.06–8	0.25	1	0.30				
	ITRA	0.03–16	0.12	0.25	0.10				
	FLZ	16–256	128	256	64	2.9		97.1	
Candida parapsilosis (14)									
	AB	0.12–0.5	0.5	0.5	0.39				
	ANI	0.5–8	1	1	0.79	85.7		14.3	
	MICA	0.5–8	1	1	0.84	85.7		14.3	
	CAS	0.25–8	1	1	0.67	85.7		14.3	
	FC	0.06–0.06	0.06	0.06	0.06				
	POS	0.008–0.06	0.03	0.06	0.03				
	VOR	0.06–1	0.25	0.5	0.32	14.3	78.6	7.1	
	ITRA	0.015–0.12	0.06	0.12	0.06				
	FLZ	1–128	16	16	12.49	7.1		92.9	
Candida glabrata (6)									
	AB	0.25–1							
	ANI	0.03–2				66.7		33.3	
	MICA	0.008–2				66.7		33.3	
	CAS	0.12–8				66.7		33.3	
	FC	0.06–0.12							
	POS	0.03–8							50
	VOR	0.25–8							83.3
	ITRA	0.06–16							33.3
	FLZ	16–256					33.3	66.7	
Candida albicans (4)									
	AB	0.25–0.5							
	ANI	0.03–0.25				100			
	MICA	0.008–0.25				100			
	CAS	0.03–0.5				100			
	FC	0.06–0.12							
	POS	0.008–2							25
	VOR	0.008–0.5				75	25		
	ITRA	0.03–1							25
	FLZ	0.12–16				75		25	
Candida krusei (3)									
	AB	0.5–2							
	ANI	0.12–4				33.3		66.7	
	MICA	0.06–8				33.3		66.7	
	CAS	0.06–4				33.3		66.7	
	FC	0.06–8							

Table 1. CONT.

Yeast species (n)	Antifungal drug	MIC range	MIC_{50}	MIC_{90}	GM	Resistance status/ non-WT (%)			
						S	DDS/I	R	Non-WT
	POS	0.008–0.5							
	VOR	0.06–0.5							
	ITRA	0.03–1							
	FLZ	16–64						100	
Candida tropicalis (2)									
	AB	0.25–0.5							
	ANI	0.06–2						50	
	MICA	0.015–2						50	
	CAS	0.06–4						50	
	FC	0.06–0.06							
	POS	0.25–0.5							50
	VOR	0.12–4						50	
	ITRA	0.25–0.5							
	FLZ	1–64						50	

MIC: Minimum inhibitory concentration; AB: Amfoterisin B; ANI: Anidulafungin; MICA: Micafungin; CAS: Caspofungin; POS: Posaconazole; VOR: Voriconazole; ITRA: Itraconazole; FLZ: Fluconazole.

Organization for the 1st time in October 2022, 19 fungal species threatening public health were emphasized, especially multi-drug-resistant (MDR) *C. auris*, azole-resistant *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. glabrata* species were noted in the category of critical and high-priority pathogens[13]. The epidemiology of fungal infections has shifted toward non-*albicans Candida* species, increasing antifungal resistance. The role of AFST in clinical laboratories has also increased as emerging new fungal pathogens require more frequent susceptibility testing as part of antifungal management. The CLSI and the European Committee on Antimicrobial Susceptibility Testing were established to standardize the technical aspects of in vitro antimicrobial susceptibility testing and develop the related CBPs. However, reference methods' labor-intensive and technical training requirements have increased the need for reliable, cost-effective, and easy-to-perform commercial testing strategies[7].

In our study, the MIC values of fluconazole and amphotericin B to inhibit growth in *C. auris* isolates were found to be high, whereas the MIC values of echinocandins were found to be relatively low. On the other hand, the rate of *C. parapsilosis* isolates, the second most isolated species from candidemia samples in this study, found to be resistant to fluconazole and voriconazole was 92.6% and 7.1%, respectively. In addition, 14.3% of *C. parapsilosis* isolates were found to be resistant to each anidulafungin, micafungin, and caspofungin from the echinocandin group.

The frequency of different *Candida* species in clinical isolates and, thus, the expected susceptibility results vary according to geographical location and patient characteristics[14]. *C. auris*, which frequently features a MDR phenotype and came to the fore with the hospital outbreaks it has caused on a global scale in recent years, has been increasingly reported worldwide[12]. Mulet Bayona et al.[15] reported a hospital outbreak in Spain that involved 550 patients in the 4 years between 2017 and 2021, triggered by an increase in the number of patients admitted to ICUs due to coronavirus disease 2019 (COVID-19). While most of the isolates investigated in the said study were found to be resistant to fluconazole, the rates of isolates found to be resistant to echinocandin and amphotericin B were only 2.8% and 0.6%, respectively. Similarly, in a study conducted in Qatar,[16] *C. auris* cases associated with COVID-19 were reported as part of an uninterrupted clonal epidemic during the pandemic. The molecular analysis of resistance revealed known mutations in several genes responsible for echinocandin and azole resistance. They reported that all isolates were resistant to fluconazole (MIC ≥32 mg/L), MIC values of amphotericin B ranged from 1 to 4 mg/L, and resistance to echinocandins were low (5%). The use of mechanical ventilation and other invasive procedures, the selective pressure of intense antimicrobials and antifungals, and the reuse of personal protective equipment and

medical supplies without an effective disinfectant treatment due to their unavailability facilitate the selection and spread of *C. auris* among patients in ICUs. As a matter of fact, outbreaks of *C. auris* colonization/infection have been reported in COVID-19 ICUs in the USA, India, Mexico, Italy, Lebanon, and Brazil.

In contrast to the widely reported high resistance rates of *C. auris* against fluconazole, amphotericin B, and anidulafungin, Nobrega de Almedia et al.[17] found low MICs of these antifungal agents for *C. auris* in all 45 isolates they investigated. They attributed this finding to the fact that there was not yet long-term antifungal exposure in the hospital setting and not enough time to induce resistance. They also assumed that the ERG11 and FKS1 mutations responsible for resistance did not develop in these isolates.

In our country, Erturk Şengel et al.[18] investigated antifungal drug resistance with the SYO method in patients with *C. auris* candidemia in the COVID-19 ICU in 2021. They determined that all patients were resistant to fluconazole and amphotericin B and sensitive to anidulafungin and micafungin. In addition, as a result of phylogenetic analysis, they found that the strains were similar to strains from the South Asian class (Clad I). In another study[19] conducted in our country, antifungal susceptibility was studied with the liquid microdilution method in three cases with *C. auris*. Consequently, it was found that the MIC values of fluconazole were high, whereas the MIC values of other antifungal drugs were low. In our center, the first *C. auris* isolate was detected at the end of 2020 in the pandemic hospital, where COVID-19 patients were followed intensively.

C. parapsilosis is the second-most isolated species from candidemia samples in Latin America, several Asian, European, and African countries, as well as in our center. Newborns, patients on total parenteral nutrition, and patients with central venous catheters are at risk for *C. parapsilosis*-induced candidemias[20]. In a multicenter study conducted in southern Africa within the scope of the SENTRY study investigating antifungal resistance, it was determined that more than 50% of *C. parapsilosis* had fluconazole resistance and 44% of them also developed cross-resistance to voriconazole[20,21]. In the same study, resistance rates were found to be quite low in Latin America and Asia-Pacific countries. Therefore, it was concluded that, as in the distribution of species, antifungal-resistant strains might differ according to geographical regions[20,21].

Fluconazole-resistant *C. parapsilosis* isolates cause severe clonal candidemia outbreaks in many countries. *C. parapsilosis* infections can be spread by health-care workers, and isolates from outbreaks may be more lethal than sporadic isolates. In a study based in Izmir, Turkey,[22] it was demonstrated that fluconazole was ineffective against *C. parapsilosis* isolates and that *C. parapsilosis* isolates carrying Y132F in the resistance gene Erg11 were associated with a higher estimated mortality rate. In a study conducted in our country in which the effect of the first antifungal treatment on patient mortality and the presence of resistance in *Candida* spp. were investigated, Doğan et al.[23] found that *C. parapsilosis* was not resistant to echinocandins and was resistant to fluconazole at a rate of 13%, but this resistance did not have a significant effect on mortality. In comparison, in this study, the rate of *C. parapsilosis* isolates found to be resistant to fluconazole and voriconazole was 92.6% and 7.1%, respectively. In addition, 14.3% of *C. parapsilosis* isolates were found to be resistant to each anidulafungin, micafungin, and caspofungin from the echinocandin group. The very high resistance rate of *C. parapsilosis* to fluconazole may be attributed to the fact that only resistant isolates were investigated in this study.

The results of the multicenter SENTRY study,[21] a worldwide study of antifungal resistance to fluconazole and echinocandins in *Candida* species over 20 years from 1997 to 2016, revealed that the incidence of *C. albicans* decreased in all geographical regions, the incidence of *C. glabrata* and *C. parapsilosis* increased, and the incidence of *C. parapsilosis* and *C. tropicalis* increased in Latin America. In addition, *C. auris* was detected in 6 isolates. The highest resistance rates to fluconazole were found in *C. glabrata* strains (10.6%) in North American countries and *C. tropicalis* strains (9.2%) in Asia-Pacific countries. Resistance rate to echinocandin was 3.5% in *C. glabrata* and 0.1% in *C. albicans* and *C. parapsilosis*. The highest resistance rate to micafungin was found in *C. glabrata* (2.8%), followed by *C. tropicalis* (1.3%) in North American countries.

In a study conducted between 2018 and 2020 investigating the distribution of fungal agents and the effect of the COVID-19 pandemic on antifungal resistance, Pfaller et al.[24] found that fluconazole resistance in *C. glabrata*, which was 5.8% between 2018 and 2019, decreased to 2% in 2020. On the other hand, they found that fluconazole resistance in *C. parapsilosis* and *C. tropicalis*, which were 9.8% and 0.7%, respectively, during the period between 2018 and 2019, increased in 2020, along with resistance to voriconazole. They also found that resistance to echinocandin varied between species. In parallel, in our center, an increase in resistance to fluconazole was observed in both *C. parapsilosis* and *C. auris* species after the COVID-19 pandemic.

The limitation of this study is that AFDT with SYO cannot be applied to all isolates in terms of cost-effectiveness. This may have led to higher than expected resistance rates.

Conclusion

The presence of antifungal resistance, including in multidrug-resistant *Candida* species, complicates the treatment of invasive fungal diseases with high mortality and morbidity rates. Rapid and accurate species identification is critically important for initiating appropriate antifungal treatment in the early stages. Taking necessary precautions for colonization and infection, especially in ICUs, can prevent the spread of multi-drug-resistant *Candida* species.

Ethics Committee Approval: This study has been approved by the Clinical Studies Ethics Board of University of Health Sciences, Haydarpasa Numune Training and Research Hospital (Decision Number: HNEAH-KAEK 2023/156/4258). The study has been conducted in accordance with the Helsinki guidelines.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: None declared.

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