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DISTRIBUTION OF *CANDIDA* SPECIES ISOLATED FROM DIFFERENT CLINICAL SPECIMENS AND THEIR ANTIFUNGAL SUSCEPTIBILITY PROFILE: A 5 YEAR RETROSPECTIVE ANALYSIS

FARKLI KLİNİK ÖRNEKLERDEN İZOLE EDİLEN CANDIDA TÜRLERİNİN DAĞILIMI VE ANTİFUNGAL DUYARLILIK PROFİLLERİ: 5 YILLIK RETROSPEKTİF ANALİZ

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Abstract

Objective: In this study it was aimed to evaluate the distribution of *Candida* species and their antifungal susceptibility profiles in Kocaeli University Hospital, Kocaeli, Turkey.

Methods: A retrospective study on the distribution of *Candida* species and antifungal susceptibility profile were conducted from January 2017 to December 2021 in our laboratory. Different clinical samples collected were cultured on Sabouraud dextrose agar and incubated for an appropriate time. *Candida spp.* were identification by MALDI-TOF MS. And their antifungal susceptibility profile were determined by the VITEK 2 Compact system (BioMérieux, France).

Results: Totally 1667 clinical samples isolated from 1046 patients were included in this study. Of Clinical samples, 83.4% were from adults (≥ 18years) and 16.6% from pediatric group (< 18 years). Among all isolates, 1072 (64.3%) were *C. albicans* and 596 (35.7%) were non albicans *Candida* (NAC) species. *C. albicans* was mostly isolated from adults, whereas *C. parapsilosis* was mostly isolated from pediatric group. Regardless of *Candida* species identified, 88.7% were susceptible and 9.3% were resistant to fluconazole. The highest fluconazole resistance rate (25.4%) was observed in *C. parapsilosis* isolated from all departments. Voriconazole resistance ratio was 4.9%. The susceptibility rate of caspofungin and micafungin were 94.7% and 96%, respectively. The resistance rates of flucytosine and amphotericin B were 1.4% and 4.5%, respectively.

Conclusion: In present study, the most common NAC species was determined as *C. parapsilosis*. The high prevalence and high fluconazole resistance of C. parapsilosis in our hospital may demonstrate that empirical fluconazole treatment is debatable.

Keywords: *Candida species, antifungal susceptibility, epidemiology, retrospective.*

Öz

Amaç: Bu çalışmada Kocaeli Üniversite Hastanesinde *Candida* türlerinin dağılımının ve antifungal duyarlılık profillerinin değerlendirilmesi amaçlanmıştır.

Yöntem: Kocaeli Üniversitesi Hastanesinde Ocak 2017-Aralık 2021 arası izole edilen *Candida* türlerinin dağılımı ve antifungal duyarlılık profili hakkında retrospektif bir çalışma yürütülmüştür. Toplanan klinik örnekler Sabouraud dekstroz agarda ekilmiş ve uygun sürede inkübe edilmiştir. *Candida spp*. MALDI-TOF MS yöntemi ile tanımlanmıştır. Antifungal duyarlılık profilleri ise VITEK 2 Compact sistemi (bioMérieux, Fransa) ile belirlenmiştir.

Bulgular: Bu çalışmaya 1046 hastadan izole edilen toplam 1667 klinik örnek dahil edilmiştir. Klinik örneklerin %83,4'ü yetişkinlerden (≥18 yaş) ve %16,6'sı pediatrik gruptan (<18 yaş) alınmıştır. Tüm izolatların 1072'si (%64,3) *C. albicans* ve 596'sı (%35,7) non albicans-*Candida* (NAC) olarak tanımlanmıştır. Erişkinlerde en çok *C. albicans* izole edilirken, pediatrik gruptan en çok *C. parapsilosis* izole edilmiştir. Tanımlanan *Candida spp.*'lerin %88,7'si flukonazole duyarlı ve %9,3'ü dirençli idi. En yüksek flukonazol direnç oranı (%25,4) tüm bölümlerden izole edilen *C. parapsilosis*'te gözlendi. Vorikonazol direnç oranı %4,9 idi. Kaspofungin ve mikafungin duyarlılık oranları sırasıyla %94,7 ve %96 idi. Flusitozin ve amfoterisin B'nin direnç oranları sırasıyla %1,4 ve %4,5 idi.

Sonuç: Bu çalışmada en sık görülen NAC türü *C. parapsilosis* olarak belirlenmiştir. Hastanemizde *C. parapsilosis*'in yüksek prevalansı ve yüksek flukonazol direnci, ampirik flukanozol tedavisinin tartışmalı olduğunu gösterebilir.

Anahtar Kelimeler: *Candida türleri, antifungal duyarlılık, epidemiyoloji, retrospektif.*

Introduction

Candida species are the most common cause of fungal infections, leading to a range of invasive candidiasis such as blood stream candidiasis to non-life-threatening mucocutaneous candidiasis such as oro-pharyngeal candidiasis, genito-urinary candidiasis and vulvovaginal candidiasis.[1] They are also important causes of superficial mycosis such as onychomycosis. Among fungal infections, invasive candidiasis is commonly associated with high morbidity and mortality rate. *Candida* species are 4th pathogens causing bloodstream infections in Turkey[2], resulting in increased mortality rate, patient hospitalization, and healthcare costs especially in intensive care units.[3] Mucocutaneous candidiasis is one of the indirect signs for cell-mediated immunodeficiency and estimated to have more than 90% positive predictive value for invasive candidiasis.[4] Until recently, *C. albicans* was recognized as the commonest species causing most of the cases of candidiasis. However, in the last few decades, several studies reported that non-albicans *Candida* species (NAC) such as *C. parapsilosis, C. tropicalis, C. glabrata* and *C. krusei* had been increasing.[5,6] NAC species have been reported to be a major cause of fungal opportunistic infection.[7,8] An increase in opportunistic fungal infections is the result of an increase in the number of immune-compromised patients. Excessive use of broad-spectrum antibiotics, metabolic disorders, immunodeficiency syndromes like HIV and even recently SARS-CoV-2 infection are among the various contributing factors for an increase in opportunistic fungal infections. [9–11]

Recently, the widespread use of empirical antifungal treatment resulted a significant change in sensitivity patterns against commonly used antifungal agents. Development of resistance to azoles or echinocandins, the treatment of choice for fungal infections, mainly by NAC species, differences in drug susceptibilities among *Candida* spp., and frequent isolation of NAC species in clinical samples initiated the use of accurate species identification and in vitro susceptibility testing methods.[12]

Consequently, the distribution of *Candida* species and their antifungal resistance ratio is a matter of curiosity for our University hospital as well as our country. Therefore, in this study, it was aimed to evaluate the distribution of *Candida* spp. isolated form different clinical specimens and their antifungal susceptibilities retrospectively. It was assumed that the results of this study would be an important epidemiologic data in order to enlighten the antifungal treatment choice of clinicians.

Methods

Clinical Samples

In this study totally 1667 clinical samples of 1046 patient were evaluated in Mycology Laboratory of Kocaeli University Hospital between January 2017 and December 2021. Patients were grouped as pediatric group for 0-18 years of age and the adult group for older than 18 years of age. The clinical samples sent from different clinics were categorized as samples from internal medicine department, surgical department and intensive care unit.

Identification and Antifungal Susceptibility of Isolates

All clinical samples were inoculated on Sabouraud dextrose agar (Oxoid, Basingstoke, UK) to which 50 µg/ml gentamicin is incorporated. Inoculated plates were incubated at a temperature of 37 ℃ for at least 72 hours aerobically and colonies were identified using MALDI-TOF MS (bioMérieux, France). The VITEK 2 system (bioMérieux, France) and AST-YS08 cards were used to determine antifungal susceptibilities of *Candida* species, against amphotericin B, flucytosine, fluconazole, voriconazole, caspofungin and micafungin. The results were evaluated as as susceptible (S), intermediate (I) or resistant (R) according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) guideline13. *C. albicans* ATCC 90028 and *C. parapsilosis* ATCC 22019 strains were used as quality control strains.

Results

In this study, *Candida* species isolated from 1667 different clinical samples of 1046 patients were evaluated retrospectively. Median age of patients was 55.9 with a range of 0-99. Among these patients, 528 (50.5%) were male and 518 (49.5%) female. Of 928 (88.7%) were adults and 118 (11.3%) were pediatric patients. Clinical samples sent from surgical department, intensive care unit and internal medicine were 633 (60.5%), 309 (29.5%) and 104 (9.9%), respectively (Table 1).

Table 1. Distribution of clinical samples according to patient's demographic features

Gender	**N**	**%**
Male	528	50.5
Female	518	49.5
Age groups		
Pediatrics	118	11.3
Age (Mean±STD)	6.30 ± 5.365	
Adults	928	88.7
Age (Mean±STD)	64.97 ± 17.571	
Departments		
Surgical	633	60.5
Intensive care unit	309	29.5
Internal Medicine	104	9.9

The distribution of *Candida* species with respect to clinical sample was variable where *C. albicans*, *C. parapsilosis* and *C. tropicalis* recovered in all clinical specimens. Among these *Candida* species, 1072 (64.3%) were *C. albicans*, 595 (35.7%) were non-albicans Candida (NAC) species. Among NAC species the rates of isolation were as follows: *C. parapsilosis* 18.4%, *C. tropicalis* 13.1%, *C. krusei* 2.9%, *C. glabrata* 0.5%, C. *lusitaniae* 0.5%, *C. kefyr* 0.2%, *C. famata* 0.1%. Of isolates, 822 (49.3%), 326 (19.6%) and 130 (7.8%) were isolated from urine, blood and wound, respectively. The ratio of other clinical samples was 389 (23.3%) (Table 2). *C. albicans* were most isolated from urine 52.4% and secondly from blood 9.7%. *C. parapsilosis* isolation rates from blood and urine were 55.4% and 55.1%, respectively. Whereas *C. tropicalis* were mostly isolated from blood (64.7%) and secondly from urine (15.6%). Of *Candida* spp. isolated from blood samples, 52.1% were *C. parapsilosis* and 31.9% were *C. albicans.* The numbers of *Candida spp.* isolated from sterile body fluids were as follows: one *C. parapsilosis* from pericardial fluid; one *C.albicans* from pleural fluid; 3 *C.albicans* from joint fluid; 11 (10 *C.albicans* and one *C.tropicalis*) from peritoneal fluid (Table 2).Between

Candida spp. isolated, 1390 were from adult patients and *C. albicans* 972 (69.3%), *C. tropicalis* 181 (13.1%), *C. parapsilosis* 177 (12.3%) were mostly isolated species. *C. parapsilosis* 130 (46.9%) were the most common isolated *Candida* spp. in pediatric group followed by *C.albicans* 100 (36.1%). *Candida* spp. according to age groups are given in Table 3.The antifungal susceptibility profile of *Candida* spp. against six antifungal drugs; fluconazole, caspofungin, micafungin, voriconazole, flucytosine, amphotericin-B were evaluated. Antifungal drug profile according to *Candida* spp. are given Table 4. Among all isolates, 88.7% were susceptible while 9.3% were resistant to fluconazole, 94.7% were susceptible while 3.3% were resistant to caspofungin, 96% were susceptible while 3.4% were resistant to micafungin. *C. albicans* (n=1072), *C. parapsilosis* (n=307), *C. tropicalis* (n=218) and *C. krusei* (n=48) exhibited 2.5%, 25.4%, 1.4% and 100% resistance to fluconazole and, 5.1%, 8.1%, 0% and 4.2% resistance to voriconazole, respectively. Overall resistance to voriconazole was 4.9% and to flucytosine was 1.4 %

Whereas amphotericin B resistance was detected in 54 (5%) *C. albicans*, 8 (2.6%) in *C. parapsilosis*, 5 (2.3%) in *C. tropicalis* and 7 (14.6%) in *C. krusei* isolates. The rate of amphotericin B susceptibility was 95.5%. *C. albicans* and *C. parapsilosis* exhibited 3.4% and 5.2% resistance to caspofungin, and 3% and 6.8% resistance to micafungin, respectively (Table 4), except *C. krusei* of which all 48 isolates were susceptible to both echinocandins. The highest susceptibility ratio (96%) was observed in micafungin against all Candida isolates. All *C. glabrata*, *C. lusitaniae*, *C. kefyr*, *C. famata* isolates were susceptible against six antifungal drugs tested.

The resistance of *C. parapsilosis* and *C. albicans* relevant to hospital departments was shown in Table 5. In comparison to *C. albicans*, *C. parapsilosis* demonstrated higher resistance rate to fluconazole; 23.1% in surgery, 24.8% intensive care unit, 23.4% internal medicine departments.

The changing antifungal resistance profile of *C. albicans*, *C. parapsilosis* and *C. tropicalis* between 2017 and 2021 was evaluated (Figure 1). *C. parapsilosis* that was the most resistant isolate that showed resistance to caspofungin as 2% in 2019 and 19% in 2021; whereas increasing rate of fluconazole resistance was found as 5% in 2018, 18% in 2019, 36.5% in 2020, 46.7% in 2021. However, voriconazole resistance of *C. parapsilosis* decreased by the year; 50% in 2018, 18% in 2020, 12.2% in 2021. Caspofungin and micafungin showed very similar resistance pattern that was the highest around 19% in 2021. Moreover, *C. tropicalis* showed the highest flucytosine resistance ratio (19,1%) in 2021.

Table 2. Distribution of *Candida spp.* isolates per clinical samples

Candida spp/ Clinical samples	***C. albicans***		***C. parapsilosis***		***C. tropicalis***		***C. krusei***		***C. glabrata***		***C. lusitaniae***		***C. kefyr***		***C. famata***		**Total**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Urine	562	**52.4**	77	**25.1**	141	**64.7**	35	**72.9**	3	**33.3**	1	**12.5**	2	**66.7**	1	**50**	822	**49.3**
Blood	104	**9.7**	170	**55.4**	34	**15.6**	4	**8.3**	6	**66.7**	7	**87.5**	-	-	1	**50**	326	**19.6**
Wound	103	**9.6**	18	**5.9**	8	**3.7**	1	**2.1**	-	-	-	-	-	-	-	-	130	**7.8**
Sputum	84	**7.8**	6	**2.0**	6	**2.8**	2	**4.2**	-	-	-	-	-	-	-	-	98	**5.9**
Abscess	56	**5.2**	9	**2.9**	11	**5.1**	1	**2.1**	-	-	-	-	-	-	-	-	77	**4.6**
Catheter	31	**2.9**		**2.6**	11	**5.1**	-	-	-	-	-	-	-	-	-	-	50	**3.0**
Vaginal Swab	43	**4.0**	-	-	-	-	3	**6.3**	-	-	-	-	-	-	-	-	46	**2.8**
CSF*	25	**2.3**	7	**2.3**	-	-	1	**2.1**	-	-	-	-	-	-	-	-	33	**2.0**
BAL*	24	**2.2**	-	-	5	**2.3**	-	-	-	-	-	-	-	-	-	-	29	**1.7**
Peritoneal Fluid	10	**0.9**	4	**1.3**	1	**0.5**	-	-	-	-	-	-	-	-	-	-	15	**0.9**
Pus	7	**0.7**	1	**0.3**	-	-	-	-	-	-	-	-	-	-	-	-	8	**0.5**
Drain Fluid	5	**0.5**	1	**0.3**	-	-	1	**0.1**	-	-	-	-	-	-	-	-	7	**0.4**
Throat Swab	5	**0.5**	-	-	-	-	-	-	-	-	-	-	1	**33.3**	-	-	6	**0.4**
Tissue Biopsy	2	**0.2**	2	**0.7**	-	-	-	-	-	-	-	-	-	-	-	-	4	**0.2**
Oral Mucosa	2	**0.2**	-	-	1	**0.5**	-	-	-	-	-	-	-	-	-	-	3	**0.2**
Vitreous Fluid	3	**0.3**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	**0.2**
Joint Fluid	3	**0.3**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	**0.2**
Bone marrow	1	**0.1**	1	**0.3**	-	-	-	-	-	-	-	-	-	-	-	-	2	**0.1**
Ear Swab	-	-	2	0.7	-	-	-	-	-	-	-	-	-	-	-	-	2	0.1
Pleural Fluid	1	**0.1**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	**0.1**
Nasopharyngeal Swab	1	**0.1**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	**0.1**
Pericardial Fluid	-	-	1	0.3	-	-	-	-	-	-	-	-	-	-	-	-	1	0.1
Total	**1072**	**100**	**307**	**100**	**218**	**100**	**48**	**100**	**9**	**100**	**8**	**100**	**3**	**100**	**2**	**100**	**1667**	**100**

*CSF=Cerebrospinal Fluid, BAL=Bronchial Alveolar Lavage

Table 3. Distribution of *Candida spp.* according to age groups

***Candida* species**	**Adults**		**Pediatrics**		**Total**	
	N	**%**	**n**	**%**	**n**	**%**
C. albicans	972	**69.9**	100	36.1	1072	64.3
C. parapsilosis	177	12.7	130	**46.9**	307	18.4
C. tropicalis	181	13.0	37	13.4	218	13.1
C. krusei	47	3.4	1	0.4	48	2.9
C. glabrata	8	0.6	1	0.4	9	0.5
C. lusitaniae	1	0.1	7	2.5	8	0.5
C. kefyr	3	0.2	-	-	3	0.2
C. famata	1	0.1	1	0.4	2	0.1
Total	**1390**	**100.0**	**277**	**100.0**	**1667**	**100.0**

Table 4. Antifungal drug susceptibility profile of *Candida* species

***Candida* species**	**Fluconazole**			**Caspofungin**			**Micafungin**			**Voriconazole**			**Flucytosine**			**Amphotericin-B**	
	S	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**	**S**	**R**
	N /%	**N /%**	**N /%**	**N /%**	**N /%**	**N /%**	**N /%**	**N /%**	**N /%**	**N /%**	**N /%**	**N /%**	**N /%**	**N /%**	**N /%**	**N /%**	**N /%**
C. albicans	1028 95.9 %	17 1.6 %	27 **2.5 %**	1027 95.8 %	9 0.8%	36 **3.4 %**	1037 96.7 %	3 0.3 %	32 **3%**	1013 94.5 %	4 0.4%	55 **5.1 %**	1061 98.9 %	6 0.6%	5 **0.5 %**	1018 95%	54 **5%**
C. parapsilosis	216 70.4 %	13 4.3 %	78 **25.4 %**	286 93.2 %	5 1.6%	16 **5.2 %**	278 90.6 %	8 2.6 %	21 **6.8 %**	234 76.2 %	48 15.7 %	25 **8.1 %**	305 99.3 %	1 0.3%	1 **0.3 %**	299 97.4 %	8 **2.6 %**
C. tropicalis	210 96.3 %	5 2.3 %	3 **1.4 %**	210 96.8 %	5 2.3%	2 **0.9 %**	214 98.2 %	*	4 **1.8 %**	216 99.1 %	2 0.9%	*	202 92.7 %	1 0.5%	15 **6.9 %**	213 97.7 %	5 **2.3 %**
C. krusei	*	*	48 100 %	33 68.8 %	15 31.3 %	*	48 100 %	*	*	46 95.8 %	4 0.4%	2 **4.2 %**	8 16.7 %	37 77.1 %	3 **6.3 %**	41 85.4 %	7 **14.6 %**

*Not detected; S: susceptible; I: intermediate susceptibility; R: resistant

Table 5. Antifungal resistance profile of *C. albicans* and *C. parapsilosis* relavant to hospital departments

Department	Antifungal Drug	*C. parapsilosis* (%)	*C. albicans* (%)
Surgery	Fluconazole	**23.1**	-
	Voriconazole	6.3	3.3
	Caspofungin	6.3	0.8
	Amphotericin-B	6.3	0.8
	Micafungin	6.3	0.8
	Flucytosine	-	-
Intensive Care Unit	Fluconazole	**24.8**	1.4
	Voriconazole	6.8	4.2
	Caspofungin	1.4	0.6
	Amphotericin-B	2.1	3.1
	Micafungin	0.7	0.6
	Flucytosine	-	0.2
Internal Medicine	Fluconazole	**23.4**	3.7
	Voriconazole	9.7	4.1
	Caspofungin	9	5.5
	Amphotericin-B	2.8	7.1
	Micafungin	12.4	4.9
	Flucytosine	0.7	0.4

Discussion

The increase in fungal infections has prompted an increase in the use of antifungal agents and in practice resulted in measurable rates of acquired or innate fungal resistance in *Candida* species that necessitates each institution to assess this for the welfare of patients[1] This retrospective study revealed *Candida* species distribution and antifungal resistance profiles in last 5 years period. Some variations in species distribution and the susceptibility to antifungals have been shown to occur among institutions or countries. Local *Candida* species distribution and their susceptibility patterns are crucial for clinician and treatment decision.

In our study, *C. albicans* (64.3%) was the most frequently isolated species followed by *C. parapsilosis* (18.4%) followed by *C. tropicalis* (13.1%). In Kantarcıoğlu's study, 16 years analysis of invazive candidiasis patients in Istanbul, Turkey, isolation rates were as follows: *C. albicans* (48%), *C. parapsilosis* (20%) and *C. glabrata* and *C. tropicalis* (12%)[14]. Öztürk *et al.* also reported the prevalence as *C. albicans* (53%), *C. parapsilosis* (30%) and *C. glabrata* (5.5%).[15] In fact, our previous study in 2015 showed that *C. glabrata* was the second mostly isolated species and *C. albicans* was the topped ranked.[16] The shift in NAC species towards *C. parapsilosis* could be due to an improved detection rates of NAC species or a true prevelance change. *C. parapsilosis* was the second most frequently isolated Candida spp. in several studies from other countries as well. [17,18] In our study, *Candida* spp. were mostly isolated from surgical department (60.5%). Isolations were mostly from urine (49.3%) and secondly from blood (19.6%). This might be related to intensive use of antibiotics and duration of hospitalization after surgical operations. This results were similar to previous studies in hospitalized patients and in intensive care unit.[19,20] According to results of our study, the mean age of adult patients was >64 years, thus old patients especially hospitalized in surgical departments should be considered carefully in aspect of Candida infections or candidemia possibly due to changes in fungal microbiota related to comorbidities or immune-compromised status.[21]

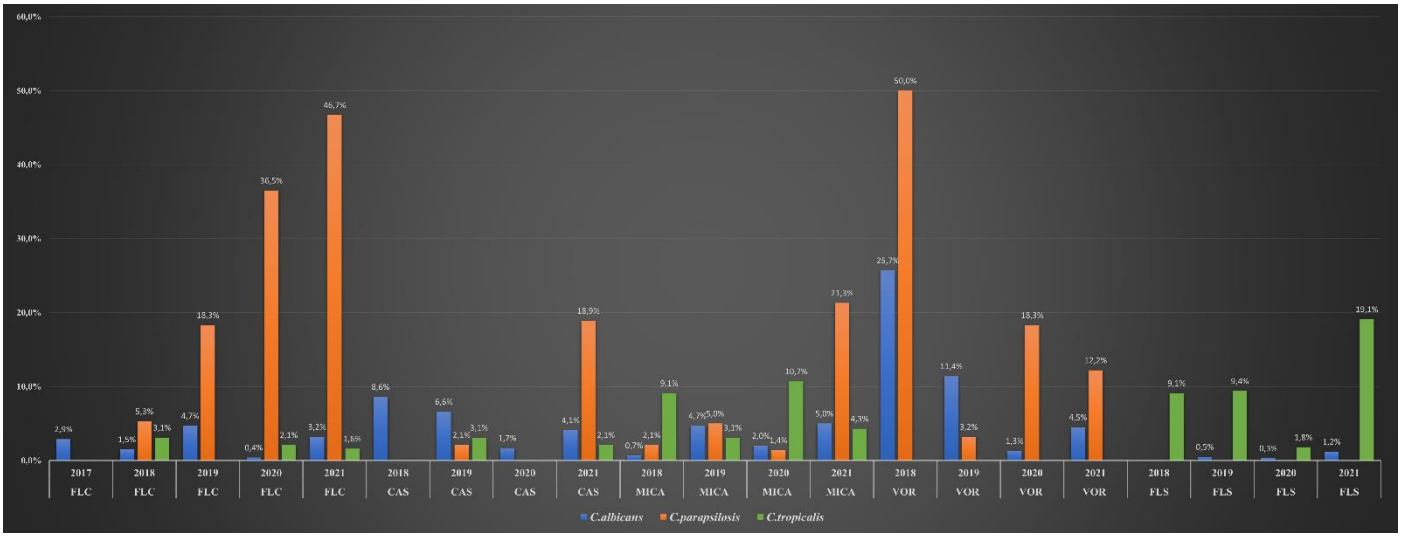

Figure 1. Antifungal drug resistance profile of *C. albicans*, *C. parapsilosis* and *C. tropicalis* by year

In our study, the most frequent *Candida spp*. isolated from blood samples and from pediatric patients was *C. parapsilosis*. *C. parapsilosis* is a significant neonatal pathogen, comprises a third of all Candida infections and is associated with 10% mortality. The reasons for predilection of *C. parapsilosis* infection in neonates are not clear but adherence to skin and biomaterials leading to biofilm formation may be important determinants.[22] In a neonatal intensive care unit in Finland, long-term fluconazole prophylaxis has resulted in persistence of a fluconazole-resistant strain of *C. parapsilosis* causing repeated infections.[23] The echinocandins, caspofungin or micafungin though not the first choice in the treatment of neonatal invasive candidiasis or candidemia may be useful in resistant cases.

Antifungal susceptibilities of 1667 *Candida* isolates were tested by VITEK-2 system. The results showed that overall fluconazole resistance was 9.3% that is similar to rates obtained in other studies in our country.[24,25] However, less than 5% fluconazole resistance rates were reported in China and Canada [18,26]. In present study, it was observed that fluconazole resistance increased by years and reached to 46.7% in 2021. The high resistance rate of *C. parapsilosis* (25.4%) to fluconazole is quite remarkable and it may demonstrate that the fluconazole treatment of Candida infections empirically is questionable. Of all Candida

isolates, 309 (29.5%) were from Intensive Care Unit. *C. parapsilosis* isolated from intensive care unit was more resistant (24.8%) than isolates from surgical or internal medicine departments. Empirical treatment with fluconazole was suggested to enhance the selection of resistant NAC species by shifting and/or colonization to more intrinsically resistant isolates chiefly as *C. krusei* or *C. glabrata*.[27] We assume that high prevalence of *C. parapsilosis* in pediatric group (46.9%) and high resistance rates to fluconazole could be due to empirical widespread use of fluconazole in pediatric clinics and pediatric or neonatal intensive care unit of our hospital. Another azole group antifungal agent, voriconazole, might be a good alternative in fluconazole resistant isolates since low resistance rates to voriconazole obtained in this study. In addition, a remarkable increase (50%) in voriconazole resistance was observed in 2018 and declined to 12.2% in 2021.

Amphotericin B resistance rates reported from Turkey and abroad are between 2%-20%.[25,28,29] In this study, amphotericin resistance was 4.5%. However, it is not surprising that 7(14.6%) *C. krusei* isolates were also resistant to amphotericin B since *C. krusei* was identified as one of the multidrug resistant *Candid*a species.[30] Fortunately, all *C. krusei* isolates was 100% susceptible to echinocandins. The high susceptibility rates of Candida isolates to caspofungin and micafungin were very close to each other. The resistant isolates to echinocandins were determined as *C. albicans, C. parapsilosis* and *C. tropicalis*.

Conclusion

C. albicans was the most commonly isolated species followed by *C. parapsilosis.* Primarily in pediatric patients, the increased rate of *C. parapsilosis* was remarkable. It seems that fluconazole resistance of *C. parapsilosis* in all departments should be considered carefully by clinicians. Empirical or prophylactic antifungal treatment strategies including voriconazole, echinocandins, flucytosine and amphotericin B or combination of these antifungals instead of fluconazole should be preferred. The surveillance of local hospital epidemiology and appropriate antifungal treatment strategies are necessary to preserve the utility of available antifungal agents.

Conflict of Interest

No conflicts of interests to disclose.

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Author Contributions

GA, SAK: The hypothesis of the study; GA, SAK: Study design; SAK: Data collection; SAK, BMS: Literature search; GA, SAK: Data analysis and interpreatiton; GA, SAK, BMS: Manuscript drafting/writing/editing; GA, SAK, BMS: Experimental review; SAK: Resources

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