

Emergence of non-albicans *Candida* species; evaluation of *Candida* species and antifungal susceptibilities according to years.

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Abstract

Background: Fungal infections have become frequently identified causative agents of nosocomial infections in the recent years, leading to more common use of empirical antifungal therapies. It results in increased development of drug-resistant fungal strains and resistance. In this study, we aimed to identify the *Candida* species isolated from various clinical samples and examine annual distribution of susceptibility to antifungals to keep a track of local resistance rates and guide treatment planning.

Methods: A total number of 169 *Candida* isolates, which were isolated in the samples obtained from the patients during a period of five years. Fungal identification and antifungal susceptibility tests were performed using VITEK® 2 automated system and using the mass spectrometry (Maldi-TOF).

Results: Of the strains isolated, 91 (53.5%) were identified as *C. albicans*, 33 (19.5%) as *C. parapsilosis*, 15 (8.8%) as *C. glabrata*, 14 (8.2%) as *C. tropicalis*, 5 (2.9%) as *C. kefyr*, 5 (2.9%) as *C. famata*, 2 (1.1%) as *C. lipolytica*, 1 (0.5%) as *C. guilliermondii*, and 1 (0.5%) as *C. dubliniensis*. Antifungal susceptibility analyses showed that there were seven strains (4.1%) resistant to each of amphotericin B, fluconazole and flucytosine, two strains resistant to voriconazole (1.1%) and one strain resistant to caspofungin (0.5%). The annual distribution of the isolation rates showed that both *C. albicans* and non-albicans species became more frequently isolated over years. All drug-resistant strains were found to emerge within the past one-year period.

Conclusion: Both *C. albicans* and non-albicans species have become more frequently isolated within the recent years, while all of the resistant strains developed within the past one-year period. In addition to previous studies, our study results are of utmost importance, as they likely to contribute to the local monitoring of the resistance rates as well as planning or tailoring empirical therapies.

Keywords: *Candida* species, *Candida albicans*, non-albicans *Candida*, Fungal infections, Antifungal susceptibility.

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Introduction

Fungal infections, which have become rather frequent causative agents of nosocomial infections within the recent years, have gained importance, as they are difficult-to-treat, associated with a high risk of mortality, and require long-term hospital stay. Immunosuppressive therapies, cytotoxic therapies with prolonged neutropenia, more common use of invasive catheters and wide-spectrum antibiotics, and increased numbers of patients requiring emergency care have been previously listed as the factors causing the current increase in *Candida* species [1,2]. While *Candida albicans* is still the most common causative agent of nosocomial fungal infections, some studies have reported increasing rates of species other than *C. albicans*. In particular, cases of Candidemia caused by the infrequent *C. krusei*, *C. guilliermondii*, and *C. ciferrii* species

have been reported at an increasing rate over the recent years [3,4].

Gradually increasing frequency of invasive fungal infections and the widespread use of empirical antifungal therapy have resulted in the development of drug-resistant fungal strains with increased resistance rates [5]. Amphotericin B and fluconazole resistance, particularly noted in the non-albicans *Candida* species, obligates a review of the empirical therapies. Therefore, in vitro antifungal susceptibility tests need to be performed to select the appropriate and effective antifungal therapy [5]. Automated identification and antibiotic susceptibility systems are currently used by the majority of microbiology laboratories, providing more than 90% consistent results with liquid microdilution (LMD) which is considered to be the reference method to identify antifungal susceptibility [6]. Moreover, the introduction of recent methods such as molecular systems and matrix-assisted laser desorption/

ionization time-of-flight mass spectrometry (Maldi-TOF) have increased the rate of accuracy in microbiological identifications to almost 100% and shortened the time to obtain results [7-9]. The strain-level identification of the *Candida* species isolated as infectious agents in the hospitals and determination of their antifungal susceptibility contribute to the tracking of species and regional resistance rates, as well as to the planning of antifungal therapies. In this study, we aimed to identify the *Candida* species isolated from various clinical samples and examine annual distribution of susceptibility to antifungals to keep a track of local resistance rates and guide treatment planning.

Materials and Methods

A total number of 169 *Candida* isolates, which were isolated in the samples obtained from the patients hospitalized in different services between January 2011 and December 2015, were analysed in the Clinical Microbiology Laboratories of Ministry of Health, Sakarya University Training and Research Hospital. The same isolates with were reproduced from the same sample of individual patients were excluded from the analyses.

Suspected fungal colonies isolated from tracheal aspirates, wound, CSF, urine or blood samples were planted on Sabouraud Dextrose Agar (SDA) growth medium and incubated for 18-24 hours at 37°C. At the end of the incubation period, identification of the proliferated fungi species and antifungal susceptibility tests for amphotericin B, flucytosine, fluconazole, voriconazole and caspofungin were performed by VITEK® 2 system (Biomerieux, France), using AST-YS01 cards between 2011 and 2013, and AST-YS07 cards between 2014 and 2015. The infrequent *C. famata*, *C. lipolytica*, *C. guilliermondii*, *C. dubliniensis*, and *C. ciferrii* species were confirmed by the mass spectrometry method (Maldi-TOF, VITEK® MS, Biomerieux, France). The results for all of these strains were found to be consistent with the results obtained by VITEK® 2 system.

The susceptibility for amphotericin B and flucytosine was assessed based on the reference ranges specified in the Clinical Laboratory Standards Institute (CLSI) M27-A3, while susceptibility for fluconazole, voriconazole and caspofungin was determined according to the reference ranges provided for antifungal agents in the CLSI M27-S4 [10,11].

Table 2. Resistance rates of *Candida* isolates against antifungal drugs.

Isolate	n (%)	Antifungal drugs									
		Amfotericin B		Fluconazole		Flucitocin		Voriconazole		Caspofungin	
		n	%	n	%	n	%	n	%	n	%
<i>C. albicans</i>	91 (54)	2	2.1	1	1.1	2	2.1	1	1	0	0
<i>C. parapsilosis</i>	33 (19.5)	2	6.1	2	6.1	2	6.1	0	0	1	3.03
<i>C. tropicalis</i>	14 (8.2)	2	14.2	2	14.2	1	7.1	0	0	0	0
<i>C. kefyr</i>	5 (2.9)	0	0	0	0	1	20	0	0	0	0

Results

The distribution of the clinical samples included in the study was as follows: blood (n=79), wound (n=16), urine (n=51), tracheal aspirates (n=14), catheter (n=8), cerebrospinal fluid (n=1). Table 1 shows the distribution of these samples based on the services. While 91 (53.5%) of the strains isolated in this study were *C. albicans*, 78 (46.5%) strains were non-*albicans*. Among the non-*albicans* group, the most frequently isolated was *C. parapsilosis* (n=33, 42.3%) species. Table 1 shows the distribution of identified clinical samples according to the clinics and the number of *C. albicans*/non-*albicans* isolates. The number of candida isolates at species level and their susceptibility to the antifungals are presented in Table 2. During the study period, a marked increase was overall noted in the number of both *albicans* and non-*albicans* *Candida* isolates over the years (Figure 1).

The infrequent *C. famata*, *C. lipolytica*, *C. guilliermondii*, *C. dubliniensis*, and *C. ciferrii* species were confirmed by the mass spectrometry method. The results for all of these strains were found to be consistent with the results obtained by VITEK® 2 system. According to the results of antifungal susceptibility tests performed for all isolates, 7 (4.1%) strains were found to be resistant to each of amphotericin B, fluconazole and flucytosine, while 2 (1.1%) strains were resistant to voriconazole and one (0.5%) strain was resistant to caspofungin (Table 2). The annual distribution analysis of antifungal susceptibility test results showed that all resistant strains had developed within the past one-year period. Since no threshold value was recommended for *C. famata* species in the CLSI M27-S4 guidelines, no comments can be made on the antifungal susceptibility of these species.

Table 1. Distribution of the *Candida* spp. according to the clinics.

Clinics	<i>Candida albicans</i>	non- <i>albicans candida</i>
Intensive Care Unit	56	60
Internal Medicine	26	10
Oncology	3	5
Paediatric Surgery	3	3
Urology	3	-

<i>C. lipolytica</i>	2 (1.1)	1	50	0	0	0	0	0	0	0	0
<i>C. glabrata</i>	15 (8.8)	0	0	2	13.3	1	6.6	1	6.6	0	0
<i>C. guilliermondii</i>	1 (0.5)	0	0	0	0	0	0	0	0	0	0
<i>C. famata</i>	5 (2.9)	-	-	-	-	-	-	-	-	-	-
<i>C. dubliniensis</i>	1 (0.5)	0	0	0	0	0	0	0	0	0	0
<i>C. ciferrii</i>	2 (1.1)	0	0	0	0	0	0	0	0	-	-
	169	7	4.1	7	4.1	7	4.1	2	1.1	1	0.5

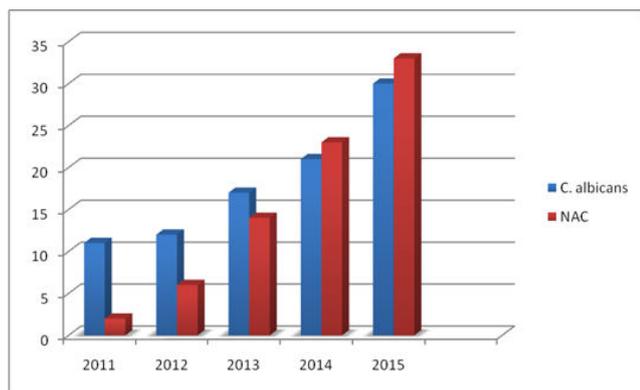


Figure 1. Distribution of *C. albicans* and non-albicans *Candida* species per year (NAC: non-albicans *Candida*).

Discussion

Nosocomial fungal infections have increasingly become an important cause of the increased morbidity and mortality and the leading one of these infections involve fungemia due to *Candida* species [12,13]. Along with the increased rates of infections caused by *Candida* species, the diversity of the species causing such infections has also changed. While *C. albicans* is the leading cause of nosocomial *Candida* infections, the infections caused by non-albicans species such as *C. tropicalis*, *C. lusitanae*, *C. krusei*, *C. parapsilosis*, and *C. glabrata* have also increasingly become more common [14].

In the Artemis Global antifungal susceptibility follow-up study, a total number of 205,329 yeast samples were collected at 134 centers between the years 1997 and 2005. Among the isolated yeast fungi, almost 95.7% were found to be *Candida* species and *C. albicans* was identified at a rate of 65.6%. When the 1997 and 2000 and 2001 and 2005 periods were compared, *C. albicans* frequency was found to decrease from 70.9% to 63.5%, while significant increases were recorded for *C. glabrata* (from 10.2% to 11.4%), *C. tropicalis* (from 5.4% to 7.5%), and *C. parapsilosis* (from 4.8% to 6.6%) species. These findings support the increased number of the non-albicans species [15]. In the present study, the evaluation of the annual distribution of *Candida* species showed a significant increase in the frequencies of both albicans and non-albicans *Candida* infections over years (Figure 1).

In the studies investigating the distribution of *Candida* species in Turkey, the most frequently isolated *Candida* strain in the

clinical samples was *C. albicans*. Among the non-albicans species, the most commonly isolated strains are *C. parapsilosis*, *C. tropicalis*, and *C. glabrata* [16-19]. The results obtained from the present study as well as the other studies performed in the recent years highlight the year by year increasing importance of non-albicans *Candida* species [18-20].

Delayed diagnosis may also result in increased mortality rates of invasive fungal infections. Therefore, methods which provide strain-level identification of the *Candida* species in a rapid and reliable manner are required to initiate the antifungal therapy. Since identification of the *Candida* species by conventional methods takes a long time and requires experience as well as manpower, the laboratories currently prefer utilizing methods such as VITEK[®] 2 automated system, and API 20C AUX (Biomérieux, France) which offer rapid identification. Several previous studies reported that the results of VITEK[®] 2 automated system, which we have also used in the present study, are 92-95% consistent with the results obtained by conventional methods [7,21-23].

Rapidly and accurately provided antifungal susceptibility test results are expected to contribute to the treatment planning, while reducing mortality. Since 1997, the liquid microdilution (LMD) method has been used as the commonly accepted reference method to test susceptibility of *Candida* isolates to amphotericin B, flucytosine, fluconazole and itraconazole, and voriconazole was also added to this list in 2002. However, the results of this method are obtained only in a long time and it imposes a high workload. Tests which spectrophotometrically identify *Candida* proliferation have been developed in the recent years and the availability of systems such as VITEK[®] 2 offers an opportunity to perform fully-automated antifungal susceptibility studies [6]. The results of VITEK[®] 2 automated system, which we have also used in the present study, are known to be more than 90% consistent with the result obtained by the reference LMD method [6].

Amphotericin B resistance is a rare entity with varying rates between 0-7 and 7% in the previous studies on amphotericin B resistance in *Candida* isolates [12,19,24-26]. In the present study, 4.1% of the *Candida* strains were found to be resistant to amphotericin B. Two (2.1%) of the *C. albicans* isolates, and two for each of the non-albicans *C. parapsilosis*, and *C. tropicalis* isolates (6.1-14.2%) were found to be resistant to amphotericin B.

In the previous studies, the rate of fluconazole resistance in *Candida* isolates varied between 0 and 7% [14,16,27,28]. Consistent with these findings, the rate of fluconazole resistance in the present study was 4.1%. When the distribution of fluconazole resistance between different species was evaluated, one (1.1%) of the *C. albicans* isolates was resistant and among the non-*albicans* species, two isolates were resistant in each of the *C. parapsilosis* (6.1%), *C. tropicalis* (14.2%), and *C. glabrata* (13.3%) species. Studies performed in Turkey and worldwide have established that fluconazole resistance shows regional variability, varying between 0 and 25% [15,16,29-32]. On the other hand, the rate of fluconazole resistance was as high as 13.3% in *C. glabrata* isolates in the present study. This can be attributed to the regional differences and widespread use of fluconazole as an empirical antifungal therapy.

Among the recent studies performed by voriconazole, a wide-spectrum antifungal drug, some were unable to identify any case of voriconazole resistance, while some reported a resistance rate of 4% in *C. albicans*, 1% in *C. parapsilosis*, and 1.8% in *C. glabrata* species [19,33]. Wang et al. previously reported voriconazole resistance in *C. albicans* (0.7%), *C. glabrata* (17.8%), *C. krusei* (11.1%), *C. lipolytica* (90%), and *C. tropicalis* (5.7%) strains [34]. In another study, Odds et al. reported voriconazole resistance at a rate of 4.5% in *C. glabrata* species [35]. In the present study, voriconazole resistance was found in 1.1% of all strains (one in each of *C. albicans* and *C. glabrata*). Based on these resistance rates, voriconazole currently appears to be the safest and the most useful agent among azole derivatives.

Caspofungin and the other echinocandins are the agents which are usually preferred, when the patients fail to response to other antifungals [36-38]. In the present study, caspofungin resistance was detected only in one *C. parapsilosis* isolate. Among the other studies performed in Turkey, Yenisehirli et al. did not identify caspofungin resistance in any of the *Candida* strains and reported moderate susceptibility in 15% [39]. Caspofungin susceptibility rates previously reported by the similar studies varied between 98 and 100% [32,33,38].

For the *Candida* species, several studies reported rates of flucytosine resistance at a range of 0% to 9.05% [33,40]. Flucytosine resistance was identified in *C. albicans* (2.4%), *C. glabrata* (0%), *C. parapsilosis* (0.5%), and *C. tropicalis* (10.3%) isolates [40]. In the present study, flucytosine resistance was detected at a rate of 4.1% (2 *C. albicans*, 2 *C. parapsilosis*, 1 *C. tropicalis*, 1 *C. glabrata*, 1 *C. kefyr*).

In the present study, due to limited resources, not all isolates were able to be identified using the mass spectrometry method and analysed by broth dilution in terms of antifungal susceptibility.

In conclusion, species-level identification and antifungal susceptibility assessment of *Candida* strains should be obviously performed to ensure treatment success, shorten the duration of hospital stay, and reduce the mortality rates in cases with *Candida* infections. Our study results suggest that the

number of all *Candida* strains and, in particular, the number of non-*albicans* isolates, have increased over years. All drug-resistant strains were found to emerge within the past one-year period. In addition to previous studies, our study results are of utmost importance, as they likely to contribute to the local monitoring of the resistance rates as well as planning or tailoring empirical therapies.

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