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Determination of Antifungal Susceptibilities of Candida Species Isolated from Various Clinical Samples: An 8-Year Retrospective Study

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Abstract

Background: The rate of fungal infection has increased due to advances in medical and surgical treatment. Recently, Candidiasis has become one of the major fungal infections among hospitalized patients. While various Candida species may cause the same clinical manifestations, they may also have different antifungal susceptibility patterns. The aim of this study was to determine the distribution and antifungal susceptibilities of Candida species isolated from various clinical specimens.

Methods: Various Candida species were isolated from different clinical samples sent to Acıbadem Labmed Medical Laboratory between 2015 and 2023. Antibiotic susceptibility studies of isolated Candida species were performed with Yeast one kit (Thermo Scientific™, USA) and the results were evaluated according to CLSI data.

Results: From 922 samples, most common species isolated was *C. albicans* (30.9%), followed by *C. parapsilosis*, *C. glabrata*, *C. tropicalis* and *C. krusei*. Candida species were sensitive to Fluconazole 76.2%, Itraconazole 64.1%, Voriconazole 93.1%, Anidulafungin 99.1%, Micafungin 99.1%, Caspofungin 98.9% and Flucytosine 92.6%. The antibiotic resistance rates of Candida species were Fluconazole 15.5%, Itraconazole 8.1%, Voriconazole 4.5%, Anidulafungin 0.7%, Micafungin 0.2%, Caspofungin 0.8% and Flucytosine 1.9%.

Conclusion: Speciation of Candida and antifungal susceptibility testing should be done routinely to prevent therapeutic failures.

Keywords: Candida, Drug Resistance, Fungal, Antifungal Agents / pharmacology

INTRODUCTION

Fungal infections (Candidiasis) are common infections caused by *Candida* species. The skin, mucosal membranes and internal organs are particularly affected (1). These infections occur in all age groups and are associated with risk factors. Candida is the third leading cause of sepsis in European countries and has a mortality rate of 37% within 30 days (2). Although *Candida albicans* is the most common species (3) causing infection in humans, a shift from *C. albicans* to non-albicans Candida (NAC) species has been reported by many countries. *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei* and *C. glabrata* are responsible for more than 90% of *Candida* infections. Species such as *C. guilliermondii*, *C. lusitaniae* and *C. kefyr* have recently been known to cause candidemia, which poses a risk to the health of hospitalized patients (1,4).

Currently, invasive candidiasis is quite common and is directly associated with high morbidity and mortality. Therefore, it is imperative to develop effective methods to ensure accurate diagnosis and appropriate antifungal treatment (5,6). Many studies have examined the therapeutic outcomes of clinically important *Candida* species and have indicated that they should be separated, identified and their resistance to antifungal drugs should be understood (1,7). Immunocompromised individuals

are also at increased risk of candidemia. The reasons for this depend on many variables such as broad-spectrum antibiotics, chemotherapy, neutropenia and invasive procedures. Blood cultures are the most reliable method for the detection of *Candida* infections. However, due to false-negative results, the time required for diagnosis and the detrimental effects of delayed or ineffective antifungal therapy, doctors should determine diagnosis and treatment based on the clinical picture and risk factors (8).

Numerous methods have been developed to identify Candida species; phenotypic, genotypic and proteomic techniques (9). Although phenotypic techniques have disadvantages in terms of sensitivity and speed, molecular techniques such as polymerase chain reaction, DNA sequencing and MALDI-TOF MS are very important in the identification of *Candida* species (9,10). The use of molecular techniques allows us to understand the distribution and frequency of different *Candida* species in clinical settings (11).

Candidiasis management is increasingly affected by the development of antifungal resistance in the world. *Candida* species show different levels of resistance to commonly used antifungal drugs such as azoles (e.g. fluconazole), echinocandins (e.g. caspofungin) and polyenes (e.g. amphotericin B) (10,12,13,14). Understanding the resistance patterns shown by *Candida* species and selecting the appropriate antifungal treatment is crucial for the success of treatment (1,15,16).

Increased resistance to antifungal drugs has been influenced by factors such as efflux pumps, genetic mutations, and changes in drug targets (13,17,18). *Candida* species also play an important role in human diseases due to their capacity to form biofilms resistant to antifungal drugs (19,20).

Treatment options are limited due to *Candida* isolates that are resistant to many drugs. Therefore, the development of new antifungals is very important. There is also an increase in the global prevalence of intrinsic resistance in *Candida* species other than *C. albicans* (21,22). As a result, resistance to antifungals is increasing in the treatment of candidiasis in the World and this is a therapeutic obstacle (23,24).

The distribution of causative species and antifungal susceptibilities for candidemia, which is associated with high mortality and morbidity, may vary between countries and even between hospitals. In this study, we aimed to determine the distribution and antifungal susceptibilities of *Candida* species isolated from various clinical specimens sent to Acıbadem Labmed Medical Laboratory between 2015 and 2023. Antifungal susceptibility studies of isolated *Candida* species were performed with Sensititre Yeast One kit and the results were evaluated according to CLSI data

MATERIAL AND METHODS

Samples and Identification

Data from clinical samples (Sputum, Throat, Bronchoalveolar lavage, Tissue, Blood Cathater, Pus, Tracheal aspirate, Body fluid, Wound, Vaginal swab) of patients hospitalized in various clinics (ICU, Surgery Unit, Hematology and Oncology) sent to Acıbadem Labmed Microbiology laboratory between 2015-2023 were used. The distribution and antifungal susceptibilities of Candida species isolated from clinical specimens were evaluated retrospectively.

Sensititre Yeast One is a microdilution method used to determine the antifungal susceptibility of Candida species and contains 9 lyophilized antifungal drugs. Dilutions of antifungal agents and colorimetric indicator had been added to each well of the plate in the test kit by manufacturer company. Solutions of the yeast to be tested in the study are prepared and added to each test well. Test results were determined by determining the lowest antifungal concentration that inhibited growth. Identification of Candida species was performed by MALDI-TOF MS Microflex, LT (Bruker, Germany).

Antifungal Susceptibility Test

The study was performed according to the Sensititre Yeast One protocol (25).

The Assessment of the Test Results

Sensititre Yeast, One plates were examined after 24 hours of incubation. Here yeast growth was assessed by color change from blue (negative, no growth) to red (positive, growth). As in the test protocol, the MIC value was determined as the first well without color change (first blue). As recommended in Sensititre Yeast One method, interpretation of MIC results was performed according to CLSI criteria (**Table 1**) (25).

Table 1. MIC interpretative criteria for Candida species as per CLSI M27.

Antifungal Agent	Susceptible	Dose-dependent susceptible	Intermediate	Not Susceptible	Resistant
Fluconazole	≤8	16-32	-	-	≥64
Itraconazole	≤0.12	0.25-0.5	-	-	≥1
Voriconazole	≤1	2	-	-	≥4
Anidulafungin	≤2	-	-	4-8	>8
Micafungin	≤2	-	-	4-8	>8
Caspofungin	≤2	-	-	4-8	>8
Flucytosine	≤4	-	8-16	≥32	≥32

RESULTS

Candida species grown in the cultures of 922 samples sent to Acıbadem Labmed Microbiology Central Laboratory between 2015 and 2023 were analyzed. The distribution of *Candida* species according to type of clinical samples is shown in **Table2.**

Antifungal susceptibility testing was performed on all 922 isolates for fluconazole, itraconazole, voriconazole, anidulafungin, micafungin, caspofungin and flucytosine (**Table 3**).

A total of 42 (4.6%) isolates resistant to voriconazole, including 11 *C. tropicalis* (26.1%), 10 *C. parapsilosis* complex (23.8 %), nine *C. albicans* (21.4%), nine *C. glabrata* (21.4 %), and three *C. auris* (7.14%).

A total of 143 (15.5%) isolates resistant to fluconazole, including 11 *C. albicans* (7.7%), 22 *C. glabrata* (15.3%), 17 *C. parapsilosis* complex (11.8%), 11 *C. tropicalis* (7.7%), 71 *C. krusei* (49.6%), eight *C. auris* (5.6%), one C. lusitaniae (0.7%) and two other yeasts (1.4%).

A total of 74 (8.1%) isolates resistant to itraconazole, 12 *C. albicans* (16.2%), 35 *C. glabrata* (47.3%), seven *C. parapsilosis* complex (9.4%), 14 *C. tropicalis* (19%), one *C. dubliniensis* (1.3%), two *C. auris* (2.7%) and three other yeasts.

A total of 17 (1.9%) isolates resistant to flucytosine, including two *C. albicans* (11.7%), two *C. parapsilosis* complex (11.7%), four *C. tropicalis* (23.5%), two *C. krusei* (11.7%), five *C. lusitaniae* (29,4%), one *C. dubliniensis* (5.8%) and one *C. auris* (5.8%).

A total of seven (0.8%) isolates resistant to caspofungin, including one *C. albicans* (14.2%), one *C. glabrata* (14.2%), one *C. parapsilosis* complex (14.2%), one *C. tropicalis* (14.2%) and three *C. auris* (42.8%). A total of six *C. parapsilosis* complex (0.7%) resistant to anidulofungin and a total of two isolates (0.2%) were resistant to micafungin.

DISCUSSION

In recent years, alongside the increase in infections caused by Candida species, changes have also been observed in the diversity of species responsible for these infections. While *C. albicans* remains the most common cause of nosocomial Candida infections, there has been a rapid increase in the incidence of non-albicans Candida species, such as C. *tropicalis, C. lusitaniae, C. krusei, C. parapsilosis*, and *C. glabrata* (3).

The frequency of Candida species varies depending on the patient group and geography, but in most studies, *C. albicans* is identified as the most common species, while among non-albicans species, *C. parapsilosis, C. glabrata*, and *C. tropicalis* are the most frequently observed (26-29). In this study, the majority of the isolated Candida species were identified as *C. albicans* at a rate of 31%, followed by *C. parapsilosis* complex (19.2%), *C. glabrata* (17%) and *C. tropicalis* (13.6%).

Candidiasis is the most common opportunistic fungal infection, caused by Candida yeasts, though only 10% of its over 200 species are pathogenic to humans and animals (30,31). The clinical findings of infections caused by non-albicans Candida strains are generally indistinguishable, and these strains are either naturally resistant or have acquired resistance to commonly used antifungal drugs. As a result, identifying Candida isolates at the species level in clinical samples and accurately determining their in vitro susceptibility profiles in a timely manner is crucial for antifungal treatment protocols (32).

The CLSI and EUCAST broth microdilution method is the gold standard for assessing antifungal susceptibility of Candida strains, but it is expensive and difficult to implement. Challenges include a lack of expert personnel and the standardization of commercial systems. The recommended commercial systems are E-test, Sensititre

Table 2. Distribution of *Candida* species according to clinical sample types and ages

Candida species/ Clinical Samples	Sputum n= 96	Throat n= 23	Bronchoalveolar lavage n= 43	Tissue n=25	Urine n= 155	Blood n= 248	Cathater n= 24	Pus n= 38	Tracheal aspirate n= 130	Body fluid n= 36	Wound n= 25	Vaginal swab n= 79
C. albicans	33	10	8	11	31	53	4	12	45	8	7	63
C. auris	0	0	0	0	0	4	3	1	0	2	0	1
C. dubliniensis	1	3	0	1	0	5	0	1	2	0	0	1
C. famata	0	1	0	0	0	1	0	1	1	0	0	0
C. glabrata	20	1	10	2	45	28	3	6	17	12	7	6
C. guilliermondii	1	0	1	0	0	0	0	0	2	0	0	0
C. haemulonii	0	0	0	0	0	1	0	0	0	0	0	0
C. inconspicua	0	0	1	2	1	2	0	0	2	0	0	0
C. keyfr	3	0	0	1	6	12	1	2	9	1	3	1
C. krusei	18	4	2	1	8	22	0	2	6	3	1	4
C. lusitaniae	2	0	2	0	6	5	2	2	3	0	1	0
C. metapsilosis	0	0	1	0	0	2	0	0	1	0	1	0
C. norvegensis	0	0	0	0	0	1	0	0	0	0	1	0
C. orthopsilosis	0	0	0	0	0	9	0	0	1	0	0	0
C. parapsilosis	3	2	10	4	23	76	7	5	23	6	2	1
C. tropicalis	15	2	8	3	35	27	4	6	18	4	2	2
Total	96	23	43	25	155	248	24	38	130	36	25	79

Table 3. Antifungal susceptibility results of Candida strains

Candida species		FCA			ITR			VOR		
		S		R	S	DDS	R	S	DDS	R
C. albicans	285	261 (91.5%)	13	11 (0.38%)	242 (85%)	31 (11%)	12 (0.42%)	269 (94%)	7 (0.24%)	9 (0.31%)
C.parapsilosis complex*	177	140 (79,1%)	20	17 (9.6%)	148 (83.6%)	22 (12.4%)	7 (3.9%)	165 (93.2%)	2 (1.12%)	10 (5.6%)
C. glabrata	157	108 (68.7%)	27	22 (14%)	36 (23%)	86 (54.7%)	35 (22%)	136 (86.6%)	12 (7.6%)	9 (5.7%)
C. tropicalis	126	110 (87.3%)	5	11 (8.7%)	60 (47.6%)	52 (41.2%)	14 (11%)	114 (90.4%)	1 (0.79%)	11 (8.7%)
C. krusei	71	0 (0%)	0	71 (100%)	22 (30.9%)	49 (69%)	0 (0%)	71 (100%)	0 (0%)	0 (0%)
C. keyfr	39	39 (100%)	0	0 (0%)	35 (89.7%)	4 (10.2%)	0 (0%)	39 (100%)	0 (0%)	0 (0%)
C. lusitaniae	23	22 (95.6%)	0	1 (4.3%)	17 (73.9%)	6 (26%)	0 (0%)	23 (100%)	0 (0%)	0 (0%)
C. dubliniensis	14	13 (93%)	1	0 (0%)	13 (93%)	0 (0%)	1 (0.71%)	14 (100%)	0 (0%)	0 (0%)
C. auris	11	1 (9%)	2	8 (72%)	7 (63%)	2 (18%)	2 (18%)	8 (72%)	0 (0%)	3 (27%)
Other yeasts**	19	9 (47.3%)	8	2 (10.5%)	11 (57.8%)	5 (26.3%)	3 (15.7%)	19 (100%)	0 (0%)	0 (0%)
Total	922	703 (76.2%)	76	143 (15.5%)	591 (64.1%)	257 (27.8%)	74 (8.1%)	858 (93.1%)	22 (2.4%)	42 (4.5%)

*: C.parapsilosis, C.ortopsilosis, C.metaparapsilosis, ** other yeast: C. inconspicua (n=8), C. famata (n=4), C.guilliermondii (n=4), C. haemulonii (n=1), C. norvegensis(n=2), FCA: Fluconazole, ITR: Itraconazole, VOR: Voriconazole, AND: Anidulofungin, MF: Micafungin, CAS: Caspofungin, FCY: Flucytosine, S: Susceptible, DDS: Dose Dependent Susceptible, I: Intermediate, NS: Not Susceptible, R: Resistant

Candida species		**AND**			**MF**				**CAS**			**FCY**	
		S	**NS**	**R**	**S**	**NS**	**R**	**S**	**NS**	**R**	**S**	**I**	**R**
C. albicans	285	284	1 (%0.4)	0 (0%)	284 (99.6%)	0 (0%)	1 (0.35%)	282 (99.3%)	2	1 (0.35%)	283	0 (0%)	2 (0.07%)
C.parapsilosis complex*	177	171	0 (0%)	6 (3.4%)	172 (97.2%)	4 (2.3%)	1 (0.6%)	176 (99.4%)	0 (0%)	1 (0.6%)	174	1 (0.6%)	2 (1.12%)
C. glabrata	157	156	1 (0.6%)	0 (0%)	155 (98.7%)	2 (0.12%)	0 (0%)	156 (99.3%)	0 (0%)	1 (0.6%)	157	0 (0%)	0 (0%)
C. tropicalis	126	126 (100%)	0 (0%)	0 (0%)	126 (100%)	0 (0%)	0 (0%)	124 (98.4%)	1	1 (0.79%)	122	0 (0%)	4 (3.1%)
C. krusei	71	71 (100%)	0 (0%)	0 (0%)	71 (100%)	0 (0%)	0 (0%)	71 (100%)	0 (0%)	0 (0%)	24	45 (63.3%)	2 (2.8%)
C. keyfr	39	39 (100%)	0 (0%)	0 (0%)	39 (100%)	0 (0%)	0 (0%)	39 (100%)	0 (0%)	0 (0%)	36	3 (7.6%)	0 (0%)
C. lusitaniae	23	23 (100%)	0 (0%)	0 (0%)	23 (100%)	0 (0%)	0 (0%)	23 (100%)	0 (0%)	0 (0%)	17	1 (4.3%)	5 (21.7%)
C. dubliniensis	14	14 (100%)	0 (0%)	0 (0%)	14 (100%)	0 (0%)	0 (0%)	14 (100%)	0 (0%)	0 (0%)	13	0 (0%)	1 (0.71%)
C. auris	11	11 (100%)	0 (0%)	0 (0%)	11 (100%)	0 (0%)	0 (0%)	8 (72%)	0 (0%)	3 (27%)	10	0 (0%)	1 (9%)
Other yeasts*	19	19 (100%)	0 (0%)	0 (0%)	19 (100%)	0 (0%)	0 (0%)	19 (100%)	0 (0%)	0 (0%)		1 (5.2%)	0 (0%)
Total	922	914	2 (0.2%)	6 (0.7%)	914 (99.1)	6 (0.7%)	2 (0.2%)	912 (98.9%)	3 (0.3%)	7 (0.8%)		51 (5.5%)	17 (1.9%)

*: *C.parapsilosis, C.ortopsilosis, C.metaparapsilosis,* ** other yeast: *C. inconspicua (n=8), C. famata (n=4), C.guilliermondii (n=4), C. haemulonii (n=1), C. norvegensis(n=2): FCA: Fluconazole, ITR: Itraconazole, VOR: Voriconazole, AND: Anidulofungin, MF: Micafungin, CAS: Caspofungin, FCY: Flucytosine, S: Susceptible, DDS: Dose Dependent Susceptible, I: Intermediate, NS: Not Susceptible, R: Resistant*

Yeast One, and VITEK 2 (33).

The Sensititre Yeast One method shows high concordance with the CLSI reference method and is a simple method for antifungal susceptibility testing. It provides excellent results in terms of accuracy and reproducibility compared to the CLSI method, making it widely used in clinical and research laboratories (34).

We selected the Sensititre Yeast One method for our study due to its commercial availability, ability to test various antifungals at once, and user-friendliness. In the study conducted by Kararslan et al. using Sensititre Yeast One, *C. albicans, C. parapsilosis, C. glabrata and C. tropicalis* were susceptible to caspofungin and amphotericin B. One *C. albicans* strain showed resistance to voriconazole. Fluconazole resistance was detected in one *C. glabrata* and one *C. albicans* strain. Itraconazole resistance was detected in one *C. albicans* and one *C. glabrata* strain, while one *C. tropicalis* strain showed dose-dependent susceptibility to itraconazole. The multiazol resistance with high MICs was determined for one *C. albicans* strain. The all isolates that they studied did not show any resistance to echinocandins (35).

Siqueira et al. compared the VITEK 2 and Sensititre Yeast One systems with the gold standard broth dilution method for antifungal susceptibility of 80 Candida

isolates. They concluded that both methods performed well and were reliable for antifungal testing. However, they recommended caution in interpreting results for *C. krusei* and *C. glabrata* against caspofungin due to low observation numbers with the Sensititre Yeast One method (34).

The study Avolio et al. concluded that the Sensititre Yeast One system provides accurate antifungal MIC determination and saves about 24 hours compared to standard procedures (36). Resistance to fluconazole, which is widely used in the treatment of candida infections due to its broad spectrum of action and low toxicity, has been reported to increase in recent years (37).

In this study, fluconazole resistance was detected in 11 C. albicans isolates (0.38%), 22 *C. glabrata* isolates (14%), 17 *C. parapsilosis* isolates (10.4%), and 11 *C. tropicalis* isolates (8.7%). In the study conducted by Temiz et al. fluconazole resistance was found in two *C. albicans* isolates (4%), one *C. glabrata* isolate (5%) and one *C. tropicalis* isolate (5%). In addition, one *C. albicans* isolate (2%) and one *C. dubliniensis* isolate (5%) showed moderate susceptibility to fluconazole. No fluconazole resistance was detected in *C. parapsilosis* strains. Fluconazole resistance was found in 5.7% of all candida strains, 4% in *C. albicans* strains and 10% in non-*C. albicans* strains (3). In our country, fluconazole resistance varies according to regions and has been increasing over the years, with resistance rates between 0-38% reported (38-42).

Flucytosine is an antifungal with limited use due to its high toxicity. In our study, flucytosine resistance was found to be <5 % for candida species. In their studies, Bayram Y. et al. (39) found flucytosine resistance rate as 4% and Erdem F. et al. (29) found it as 1.7%. Özbek et al. did not find any flucytosine resistance in their study (40).

Voriconazole is the first available second-generation triazole with potent activity against a broad spectrum of clinically significant fungal pathogens, including Aspergillus, Candida, *Cryptococcus neoformans*, and some less common molds (43). In our study, voriconazole resistance rates were determined as 21.4%; 23.8%; 21.4% and 26.2% for *C. albicans, C. parapsilosis complex, C. glabrata*, and *C. tropicalis*, respectively, and were found to be compatible with the previous studies conducted by Temiz et al. (3).

According to the fungal priority pathogens list published by the World Health Organization in 2022, *Candida auris* was ultimately ranked as a critical priority pathogen (44). *C. auris* has been reported to show resistance to many antifungals. In our study, antifungal susceptibility of 11 *C. auris* strains were tested and fluconazole resistance rate was found to be high in accordance with previous studies (45-47).

Limitations

Our study has some limitations. We used Sensititre Yeast One, instead of the gold standard Broth microdilution, as a comparator. However, these panels have shown promising results for antifungal susceptibility testing worldwide.

CONCLUSION

The Sensititre antifungal sensitivity test is a valuable tool due to its accessibility, ability to test nine antifungal agents simultaneously, and compatibility with CLSI reference values. Based on the low MIC values, we found that drugs like anidulafungin, micafungin, caspofungin, flucytosine, and others are effective against Candida strains, including fluconazole-resistant ones. While secondary antifungal resistance among common Candida species isn't an increasing threat in our hospitals, continuous monitoring of Candida and non-Candida species with reduced susceptibility is crucial. This highlights the need for local epidemiological and antifungal susceptibility studies to support clinicians in managing invasive fungal infections.

DECLERATIONS

Ethics Committee Approval: ATADEK-2024/1.
Informed Consent: Informed consent is not necessary.
Referee Evaluation Process: Externally peer-reviewed.
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