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In Vitro Susceptibilities of Non-*albicans Candida* Species to Echinocandins, Azoles, and Amphotericin B in Tokat, Turkey

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Abstract

Background: Prophylactic and therapeutic uses of antifungal agents have given rise to a significant shift to more resistant non-*albicans Candida* species associated with fungal infections.
Objectives: This study aimed at identifying the distribution and antifungal susceptibility patterns of non-*albicans Candida* spp. isolated from clinical specimens in Tokat, Turkey.
Methods: The authors determined the susceptibility of 103 non-*albicans Candida* isolates to the following antifungal agents: amphotericin B, anidulafungin, caspofungin, fluconazole, ketoconazole, itraconazole, voriconazole, and posaconazole, using the Etest method. Interpretation of susceptibility was carried out using species specific breakpoints suggested by the Clinical and Laboratory Standards Institute (CLSI) M27-S4 document.
Results: The most frequently isolated non-*albicans Candida* species were *Candida kefyr* (44 isolates, 42.8%) followed by *C. tropicalis* (36 isolates, 35%), *C. parapsilosis* (17 isolates, 16.5%), *C. glabrata* (four isolates, 3.8%) and *C. famata* (two isolates, 1.9%). None of the strains had MIC values of > 2 μg/mL for amphotericin B except three of the 44 *C. kefyr* isolates. Resistance to caspofungin and anidulafungin were not detected in *C. tropicalis*, *C. parapsilosis*, and *C. glabrata* isolates. Only two of the 36 *C. tropicalis* isolates were categorized as intermediate resistant to anidulafungin, according to the new CLSI criteria. None of the *C. parapsilosis* isolates were found to be resistant to azole drugs.
Conclusions: Most of the non-*albicans Candida* species were found to be susceptible to tested antifungal drugs. Therefore, use of routine antifungal agents like amphotericin B and fluconazole, which are available in this region, are suggested.

Keywords: Antifungal Agent, Susceptibility, Non *albicans* - *Candida* Species

1. Background

The incidence of fungal infections caused by *Candida* spp. is increasing worldwide, especially among immunocompromised patients (1). Prophylactic and therapeutic uses of antifungal agents have given rise to a significant shift to more resistant non-*albicans Candida* species associated with fungal infections (1-4). Hence, these more resistant fungal infections may become an important cause of both clinical treatment failure and higher mortality rate (5, 6). Previous studies have shown that significant geographical variations exist in species distribution and antifungal drug susceptibility profiles (4, 7). Therefore, species identification and antifungal minimum inhibitory concentration (MIC) determination have become important for the determining the treatment strategies of *Candida* infections. In addition, performing of antifungal susceptibility testing is also necessary to study the development of antifungal resistance.

Although most *Candida* species remain susceptible to amphotericin B, there have been new reports about increasing MICs to amphotericin B among *C. krusei* and *C. glabrata* isolates (1). The triazoles are commonly used effective drugs for the treatment of fungal infections. The widespread use of these drugs has resulted in a reduced azole susceptibility among *Candida* species (1). According to results of the ARTEMIS DISK Antifungal Surveillance Program, the incidence of fluconazole resistance among the isolates was as follows: *C. tropicalis* (4.1%), *C. parapsilosis* (3.6%), *C. kefyr* (2.7%) and *C. glabrata* (15.7%) (8).

Echinocandins inhibit fungal cell wall synthesis by blockage of 1.3-β-D glucan synthase. These drugs have a spectrum of action against most *Candida* species as well as azole resistant strains (1). The clinical laboratory stan-

dard institute (CLSI) revised species-specific breakpoints for *Candida* isolates (9). These species-specific breakpoints are more sensitive for detecting antifungal resistance in *Candida* spp. (10). Moreover, the use of these new breakpoints has resulted in detection of higher resistance rates than those obtained from previous studies.

2. Objectives

There is no previous data available about species distribution and antifungal susceptibility patterns of *Candida* species other than *C. albicans* in the region of the current study. Therefore, in the current study, the researchers aimed at identifying the distribution and antifungal susceptibility patterns of non-*albicans Candida* spp. isolated from clinical specimens in Tokat, Turkey.

3. Methods

3.1. Ethics Statement

The non *albicans Candida* isolates used in this study were obtained from the culture collection of the mycology laboratory of Gaziosmanpasa University Hospital. Yeast isolates are exempted from ethical approval in Turkey.

3.2. Candida Isolates

One hundred and three non-*albicans Candida* isolates were obtained from the culture collection at the mycology laboratory of Gaziosmanpasa University hospital. Distribution of non-*albicans Candida* species by specimens is shown in Table 1. These isolates were collected during a five-year period between January 2009 and December 2014. Isolates were identified by the germ tube test, formation of chlamydospore on Cornmeal-Tween 80 agar (11), and with the use of the RapID Yeast Plus System (Remel, USA). Isolates were stored in skimmed milk (Oxoid Limited, UK) at -80°C until use. Each isolate was sub-cultured on Sabouraud Dextrose Agar (Oxoid Limited, UK) before applying susceptibility testing.

3.3. Antifungal Assay

The researchers determined the susceptibility of 103 non-*albicans Candida* isolates with the E test method. For this purpose, amphotericin B (0.002 - 32 μg/mL) (LiofilChem Diagnostic Ltd, Italy), anidulafungin (0.002 to 32 μg/mL) (LiofilChem Diagnostic Ltd, Italy), caspofungin (0.002 to 32 μg/mL) (LiofilChem Diagnostic Ltd, Italy), fluconazole (0.016 to 256 μg/mL) (LiofilChem Diagnostic Ltd, Italy), ketoconazole (0.002 to 32 μg/mL) (LiofilChem Diagnostic Ltd, Italy), itraconazole (0.002 to 32 μg/mL) (LiofilChem Diagnostic Ltd, Italy), voriconazole (0.002 to 32 μg/mL) (LiofilChem Diagnostic Ltd, Italy), and posaconazole (0.002 to 32 μg/mL) (LiofilChem Diagnostic Ltd, Italy) E test strips were used.

The E test method was performed according to the supplier's recommendation. The RPMI-1640 medium (Sigma, USA) supplemented with 1.5% agar and 2% glucose and buffered to a pH of 7.0 with 0.165 molL^{-1} MOPS (3-[N-morpholino] propanesulfonic acid) (Sigma, USA) in 130-mm diameter plates were used for application of E test strips. The final yeast inoculum was adjusted to 0.5 McFarland in a sterile saline solution by CrystalSpec (Becton Dickinson, USA). The final inoculum was then spread on the agar plates by a sterile cotton swab. E test strips were placed on the agar surface after the plates were dried in the safety cabinet for 15 minutes. The MIC was read after incubation in ambient air at 35°C for 48 hours. The MIC was determined as 80% inhibition for azoles and echinocandins and 100% inhibition for amphotericin B. *Candida albicans* ATCC 90028 and *C. krusei* ATCC 6258 were used as quality strains.

Interpretation of susceptibility was carried out using species-specific breakpoints suggested by the CLSI M27-S4 document (9). Because species-specific breakpoints for *C. kefyr* have not been proposed in the CLSI document, the researchers did not calculate sensitivity rates for *C. kefyr* isolates. The CLSI has not determined breakpoints for amphotericin B, therefore for amphotericin B, MIC breakpoints suggested by Park et al. were used (12) (Table 2). The One-way Analysis of Variance (ANOVA) test was used to compare resistance rates for each species and $P < 0.005$ was considered as statistically significant.

4. Results

The most frequently isolated non-*albicans Candida* species were *C. kefyr* (44 isolates, 42.8%) followed by *C. tropicalis* (36 isolates, 35%), *C. parapsilosis* (17 isolates, 16.5%), *C. glabrata* (four isolates, 3.8%), and *C. famata* (two isolates, 1.9%). The *in vitro* activities of amphotericin B, anidulafungin, caspofungin, fluconazole, ketoconazole, itraconazole, voriconazole, and posaconazole against *C. kefyr*, *C. tropicalis* and *C. parapsilosis* are represented in Table 3. For *C. kefyr* isolates, the Geometric Mean (GM) MIC values of caspofungin and anidulafungin were significantly lower than those of amphotericin B, fluconazole, itraconazole, and posaconazole ($P < 0.001$). Resistance to caspofungin and anidulafungin were not detected in *C. tropicalis*, *C. parapsilosis*, and *C. glabrata* isolates. Only two of the 36 *C. tropicalis* isolates were categorized as intermediate resistant to anidulafungin, according to the new CLSI criteria.

Although no significant differences were observed between the GM MIC values of caspofungin and voriconazole

Table 1. Distribution of Non-*albicans Candida* Species by Specimens

Specimen	*C. kefyr*	*C. tropicalis*	*C. parapsilosis*	*C. glabrata*	*C. famata*	Total
Urine	22	20	6	2	2	52
Sputum + endotracheal aspirate	8	7	4	-	-	19
Vaginal swab	12	3	-	2	-	17
Blood	1	4	6	-	-	11
Wound	1	2	1	-	-	4
Total	44	36	17	4	2	103

Table 2. Clinical Breakpoints for *Candida* Species (μg/mL)

Organism/Antifungal	Susceptible	Susceptible Dose Dependent	Intermediate	Resistant
C. tropicalis				
Amphotericin B[a]	≤ 1	-	-	≥ 1
Anidulafungin[b]	≤ 0.25	-	0.5	≥ 1
Caspofungin[b]	≤ 0.25	-	0.5	≥ 1
Fluconazole[b]	≤ 2	4	-	≥ 8
Itraconazole[b]	≤ 0.12	0.25 - 0.5	-	≥ 1
Voriconazole[b]	≤ 0.12		0.25 - 0.5	≥ 1
C. parapsilosis				
Amphotericin B[a]	≤ 1	-	-	≥ 1
Anidulafungin[b]	≤ 2	-	4	≥ 8
Caspofungin[b]	≤ 2	-	4	≥ 8
Fluconazole[b]	≤ 2	4	-	≥ 8
Itraconazole[b]	≤ 0.12	0.25 - 0.5	-	≥ 1
Voriconazole[b]	≤ 0.12	-	0.25 - 0.5	≥ 1
C. glabrata				
Amphotericin B[a]	≤ 1	-	-	≥ 1
Anidulafungin[b]	≤ 0.12	-	0.25	≥ 0.5
Caspofungin[b]	≤ 0.12	-	0.25	≥ 0.5
Fluconazole[b]	-	≤ 32	-	≥ 64
Itraconazole[b]	≤ 0.12	0.25 - 0.5	-	≥ 1
Voriconazole[b]	-	-	-	-

[a] Park et al. (12).
[b] CLSI M27-S4 document (9).

($P > 0.05$), the GM MIC values of anidulafungin was significantly lower than that of voriconazole for *C. tropicalis* isolates ($P < 0.01$). Anidulafungin was found to be more effective than amphotericin B ($P < 0.001$), fluconazole ($P < 0.001$), itraconazole ($P < 0.001$), voriconazole ($P < 0.01$) and posaconazole ($P < 0.001$) for *C. tropicalis* isolates. Caspofungin was more active than amphotericin B ($P < 0.01$), fluconazole ($P < 0.001$), and itraconazole ($P < 0.001$) for *C. tropicalis* isolates. Anidulafungin was also found to be more active than amphotericin B ($P < 0.001$), fluconazole ($P < 0.001$), itraconazole ($P < 0.01$), and posaconazole ($P < 0.01$) against *C. parapsilosis* isolates. On the other hand, caspofungin was as active as itraconazole, ketoconazole, and voriconazole, and was more active than amphotericin B ($P < 0.01$) and fluconazole ($P < 0.001$) against *C. parapsilosis* isolates.

None of the *C. parapsilosis* isolates were found to be resistant to fluconazole, itraconazole, and voriconazole according to revised CLSI breakpoints. Only one of four *C. glabrata* isolates was detected as resistant to fluconazole,

Table 3. *In Vitro* Antifungal Activities of Amphotericin B, Anidulafungin, Caspofungin, Fluconazole, Itraconazole, Ketoconazole, Voriconazole and Posaconazole Against *C. kefyr*, *C. tropicalis* and *C. parapsilosis* Isolates

Non *albicans Candida* Species/Antifungal Drugs	MIC Range, μg/mL	MIC50, μg/mL	MIC90, μg/mL	GM, μg/mL	Mean ± SEM MIC, μg/mL	Resistant, %
***C. kefyr* (n = 44)**						
Amphotericin B	0.038-32	1	2	1.15	2,49 ± 0.98	-
Anidulafungin	< 0.002 - 0.38	0.003	0.047	0.008	0.02 ± 0.009	-
Caspofungin	< 0.002 - 0.38	0.032	0.19	0.01	0.06 ± 0.01	-
Fluconazole	0.032 - > 256	0.125	0.38	0.19	11.79 ± 8.12	-
Itraconazole	0.004 - > 32	0.016	0.064	0.02	0.75 ± 0.72	-
Ketoconazole	0.003 - 2	0.006	0.012	0.007	0.08 ± 0.05	-
Voriconazole	0.002 - > 32	0.008	0.016	0.008	0.73 ± 0.72	-
Posaconazole	0.003 - > 32	0.032	0.064	0.04	0.8 ± 0.7	-
***C. tropicalis* (n = 36)**						
Amphotericin B	0.25 - 1.5	0.5	0.75	0.55	0.6 ± 0.04	0
Anidulafungin	< 0.002 - 0.75	< 0.002	< 0.002	0.002	0.03 ± 0.02	0
Caspofungin	< 0.002 - 0.125	< 0.002	0.047	0.003	0.01 ± 0.004	0
Fluconazole	0.094 - > 256	0.25	1	0.39	7.5 ± 7.0	2.7
Itraconazole	0.016 - > 32	0.064	0.094	0.05	0.94 ± 0.88	2.7
Ketoconazole	< 0.002 - 1	0.012	0.032	0.01	0.04 ± 0.02	-
Voriconazole	0.004 - 0.125	0.023	0.047	0.02	0.02 ± 0.004	0
Posaconazole	0.012 - > 32	0.032	0.064	0.03	0.92 ± 0.88	-
***C. parapsilosis* (n = 17)**						
Amphotericin B	< 0.002 - 0.75	0.38	0.75	0.1	0.47 ± 0.11	0
Anidulafungin	< 0.002 - 0.002	< 0.002	< 0.002	0.002	0.002 ± 0.0	0
Caspofungin	< 0.002 - 0.75	< 0.002	0.38	0.009	0.1 ± 0.05	0
Fluconazole	0.19 - 3	0.25	2	0.52	0.94 ± 0.24	0
Itraconazole	0.012 - 0.094	0.016	0.064	0.02	0.03 ± 0.006	0
Ketoconazole	0.006 - 0.064	0.008	0.047	0.01	0.02 ± 0.005	-
Voriconazole	0.002 - 0.032	0.016	0.032	0.01	0.01 ± 0.002	0
Posaconazole	0.006 - 0.094	0.023	0.047	0.02	0.03 ± 0.006	-

Abbreviations: GM, geometric mean; MIC_{50}, MIC for 50% of the isolates; MIC_{90}, MIC for 90% of the isolates, SEM, standard error of mean.

while the other three isolates were dose-dependent susceptible. One of the 36 *C. tropicalis* isolates was determined to be resistant to all tested azoles, except voriconazole.

5. Discussion

In this study, *C. kefyr* was the most prevalent non-*albicans Candida* species (44 isolates, 42.8%) followed by *C. tropicalis* (36 isolates, 35%). In a previous study from Turkey, Eksi et al. reported that *C. parapsilosis* was the most common non-*albicans Candida* species isolated from blood cultures (13). In a recent study from Turkey, Dagi et al. documented that the majority of non-*albicans Candida* isolates were *C. glabrata* (14). These differences in species distribution might be attributed to geographical and local variations.

The current research found that most of the isolates were susceptible to amphotericin B. The MIC values of > 2 μg/mL was observed in only three of the *C. kefyr* isolates. Similar to the current results, Dagi et al. reported that *C. kefyr* isolates had MIC values of 2 μg/mL for amphotericin B (14). In another study from Turkey, Eksi et al. reported that the MIC values for amphotericin B were in the range of 0.003 to 1 μg/mL in *Candida* species (13). Even though several studies from different countries have indicated that

amphotericin B has good activity against all *Candida* spp. (15-19), Bustamante et al. reported the amphotericin B resistance rate as 7% among *C. parapsilosis* isolates (20). Krogh-Madsen et al. also documented the emergence of amphotericin B-resistant *C. glabrata* isolates during therapy (21). In a *Candida* surveillance study from the USA, Lyon et al. reported amphotericin B MICs in the range of 0.5 to $\geq$ 8 mg/L for *C. glabrata* isolates (22). The rates of amphotericin B resistance were reported as 10% in *C. krusei*, 15% in *C. glabrata*, 22.3% in *C. parapsilosis*, and 33.3% in *C. tropicalis* strains isolated from immunocompromised patients in a study from Iran (23).

In this study, resistance to anidulafungin and caspofungin was not observed at any of the non-*albicans Candida* isolates. Similar results were reported by other researchers (14, 20, 24-26). Lyon et al. reported that echinocandins had significant activity against all *Candida* spp., except *C. parapsilosis* (22). Pfaller et al. summarized the results of the Sentry antimicrobial surveillance program between 2010 and 2011 (26). They had not detected any caspofungin or anidulafungin resistant *C. tropicalis* isolate in North America, Europe, Latin America, and Asia-Pacific Regions (26). They also reported that all strains of *C. parapsilosis* were susceptible to caspofungin, while 1% and 1.2% of *C. parapsilosis* isolates from Latin America and North America, respectively, were resistant to anidulafungin (26).

One of the *C. tropicalis* isolates was found to be resistant to fluconazole and itraconazole. The statistical analysis of MIC results showed that fluconazole was less active than ketoconazole, itraconazole, voriconazole, and posaconazole against *C. tropicalis* isolates ($P < 0.001$). Previous studies have documented that voriconazole and posaconazole had greater activity than fluconazole against most *Candida* species (1). In contrast to the current results, Orasch et al. have reported a higher resistance rate for voriconazole than for fluconazole in *C. tropicalis* isolates (24). In the current study, fluconazole was found to be a less effective azole drug against *C. parapsilosis* isolates ($P < 0.05$). No resistance to azole drugs was detected among the *C. parapsilosis* isolates. The current findings were in concordance with previous studies (13, 14, 19, 20). On the other hand, the current results were different from Tortorano et al. who documented a higher fluconazole resistance rate in *C. tropicalis* and *C. parapsilosis* isolates (25). In spite of the extensive use of fluconazole in Turkey, fluconazole remains effective against *C parapsilosis* and *C. tropicalis* isolates.

One of the *C. glabrata* isolates was detected to be resistant to fluconazole, while others were susceptible, in a dose dependent manner. The decreased susceptibility to fluconazole in *C. glabrata* isolates was noted in previous studies (8, 27). Pfaller et al. reported that voriconazole resistance was seen in 59.2% of fluconazole resistant *C. glabrata* isolates (8). Tortorano et al. detected that posaconazole and voriconazole resistance rates were higher than that of fluconazole in *C. glabrata* isolates (25).

6. Conclusions

Candida kefyr was the most common non-*albicans Candida* species followed by *C. tropicalis* and *C. parapsilosis*. Most of the non-*albicans Candida* species were found to be susceptible to tested antifungal drugs. Therefore, use of routine antifungal agents like amphotericin B and fluconazole, which are available in this region, are suggested.

Footnotes

Author's Contribution: Study concept and design and drafting of the manuscript: Gulgun Yenisehirli. Acquisition of data: Gulsen Ozveren. Analysis and interpretation of data: Aydan Yenisehirli and Yunus Bulut. Critical revision of the manuscript for important intellectual content: Aydan Yenisehirli.

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