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The antifungal susceptibilities of oral *Candida* spp isolates from HIV-infected patients

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Oropharyngeal candidiasis (OPC) is the most common HIV related oral lesion. Most patients are infected with a strain originally present as a commensal of the oral cavity. The resistance of *Candida* isolates to antifungal drugs is important due to morbidity and mortality. The aim of our study was to investigate the antifungal susceptibility profiles of oral *Candida* spp which were isolated from HIV-infected patients. *In vitro* susceptibility tests were performed using the broth microdilution method recommended by the Clinical and Laboratory Standard Institute (CLSI). A total of 67 oral *Candida* isolates from colonized HIV-infected patients, which were previously isolated and identified were included in this study. MIC ranges were 0.12 - 4.0, 0.12 - 16, 0.03 - 1.0, 0.03 - 1.0, and 0.03 - 0.25 µg/ml for amphotericin B, fluconazole, itraconazole, ketoconazole and voriconazole, respectively. All isolates were fully susceptible to voriconazole. Sixty five (97%) of all isolates were determined fully susceptible to amphotericin B, 66 (98.5%) to fluconazole, 64 (95.5%) to ketoconazole and 50 (88%) to itraconazole. No resistance was detected to fluconazole and voriconazole in oral *Candida* strains isolated from colonized Turkish HIV positive patients. Antifungal resistance was detected in 8.96% (6 strains) of all isolates tested.

Key words: HIV, *Candida*, oropharyngeal carriage, antifungal agents, antifungal susceptibility.

INTRODUCTION

Although the introduction of highly active antiretroviral therapy (HAART) has reduced the prevalence of most opportunistic infections (Ceballos-Salobreña et al., 2000; Diz et al., 2001). Oropharyngeal candidiasis (OPC) is the most common HIV related oral lesion. About 90% of patients were found to suffer from oropharyngeal or esophageal candidiasis in various stages of AIDS (Kamiru and Naidoo, 2002). The presence of *Candida* in the oral cavities of HIV/AIDS patients predicts the subsequent development of oral candidiasis (Gugnani et al., 2003; Sánchez-Vargas et al., 2005).

The high incidence of mucosal and deep seated forms of candidiasis has resulted in the use of systemic antifungal agents, especially fluconazole and itraconazole (Ellepola and Samaranayake, 2000; Nenoff et al., 1999). The widespread use of these antifungals causes resistance both in *C. albicans* and non-albicans strains. OPC due to drug resistant fungi is a major problem for HIV infected patients (Vanden et al., 1998). The resistance of *Candida* isolates to antifungal drugs is important due to morbidity and mortality. Consequently, *in vitro* susceptibility tests should be performed to detect resistant strains (Colombo et al., 2002; Sojakova et al., 2004).

The aim of our study was to investigate the antifungal susceptibility profiles of oral *Candida* spp which were isolated from HIV-infected patients. This is the first study which investigated the antifungal susceptibility of various *Candida* spp isolated from the oral cavity of Turkish HIV positive patients. Until now, only one study from Turkey (Tekeli et al., 2005) which reported only the susceptibility of oral *C. dubliniensis* strains isolated from HIV patients was published.

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Table 1. Distribution of oral *Candida* spp isolated from HIV-positive patients and presence of previous treatment.

Species	Number of isolates (%)	Without treatment (%)	With previous treatment (%)
C. albicans	49 (73.1)	32 (65.3)	17 (34.7)
C. glabrata	9 (13.4)	5 (55.5)	4 (44.5)
C. dubliniensis	4 (6)	4 (100)	-
C. krusei	2 (3)	-	2 (100)
C. kefyr	1 (1.5)	1 (100)	-
C. lusitaniae	1 (1.5)	-	1 (100)
C. tropicalis	1 (1.5)	-	1 (100)
Total of all isolates	67	42 (62.7)	25 (37.3)

MATERIALS AND METHODS

Isolates

A total of 67 oral *Candida* isolates from colonized HIV-infected patients, which were previously isolated and identified (Erkose and Erturan, 2007) in the Department of Microbiology and Clinical Microbiology, Istanbul Faculty of Medicine, Istanbul University, were included in this study. Informed consent was obtained from participants and procedures were performed according to institutional board of ethical committee.

Antifungal agents

The following agents were supplied as standard powders: Amphotericin B (Sigma-Aldrich, MO, USA), fluconazole (Sigma-Aldrich, MO, USA), itraconazole (Sigma-Aldrich, MO, USA), voriconazole (Pfizer, NY, USA), ketoconazole (Sigma-Aldrich, MO, USA). Fluconazole was dissolved in sterile distilled water. Amphotericin B, itraconazole, voriconazole and ketoconazole were dissolved in dimethyl sulfoxide (DMSO) (Sigma chemical Co, St. Louis, MO, USA) to make stock solutions.

Antifungal susceptibility testing

In vitro susceptibility tests were performed using the broth microdilution method recommended by the Clinical and Laboratory Standard Institute (CLSI) (CLSI M27- A3, 2008; CLSI M27-S3, 2008; NCCLS M27-A2, 2002). The range of concentrations tested was 0.125 - 64 µg/ml for fluconazole and 0.0313 - 16 µg/ml for amphotericin B, ketoconazole, itraconazole and voriconazole. The broth microdilution test was performed by using sterile, disposable multiwell microdilution plates (96 U-shaped wells) (LP Italiano SPA, Milano, Italy). Aliquots of 100 µl of each antifungal agent at a concentration two times the targeted final concentration were dispensed in the wells of the plates. The suspension of yeasts after 48 h of incubation onto Sabouraud dextrose agar (BBL, Sparks, MD, USA) was prepared in sterile saline (0.85%), adjusted spectrophotometrically at 530 nm to match the turbidity of a 0.5 Mc Farland standard and was diluted in RPMI 1640 in order to obtain a final concentration of 0.5×10^3 to 2.5×10^3 CFU/ml (CLSI M27-A3, 2008; CLSI M27-S3, 2008; NCCLS M27-A2, 2002) . A constant volume (100 µl) of the inoculum was added to each microdilution well containing 100 µl of the serial dilution of antifungal agents to reach final concentrations. The microplates were incubated at 35°C for 48 h. For amphotericin B and the four azoles, minimal inhibitory concentrations (MICs) were defined as the lowest concentration of the drug which resulted in a complete inhibition of visible growth and the lowest concentration of drug that produced a 50% reduction in fungal growth compared to that one of drug-free growth control, respectively (NCCLS M27-A2, 2002). In the case of the spectrophotometer readings, the azole cut-off value was 50% of the reading of growth control wells while for polyene antifungals, a cut-off value of 100% was used. *C. parapsilosis* ATCC 22019 was used for quality control.

The MIC values for fluconazole, itraconazole, voriconazole, ketoconazole and amphotericin B were compared to the CLSI interpretative guideline on antifungal susceptibility testing or based on previous investigations (Cheng et al ., 2006; CLSI M27-A3, 2008; CLSI M27- S3, 2008; NCCLS M27- A2, 2002) . For fluconazole: 64 µg/ml was used for resistant, 16 - 32 µg/ml was used for suscep-tible dose dependent and 8 µg/ml were used for susceptible. For itraconazole: 1 µg/ml was used for resistant, 0.25 - 0.5 µg/ml was used for susceptible dose dependent and 0.125 µg/ml were used for susceptible. For voriconazole: 4 µg/ml was used for resistant, 2 µg/ml were used for susceptible dose dependent and 1 µg/ml was used for susceptible. For ketoconazole: >0.125 µg/ml was used for resistant. For amphotericin B: 2 µg/ml was used for resistant.

RESULTS

A total of 67 oral *Candida* isolates from colonized HIV-infected patients, which were previously isolated and identified (Erkose and Erturan, 2007) were included in this study. The species distribution as presented in Table 1, *C. albicans* was the most frequently isolated species (49, 73.1%) followed by *C. glabrata* (9, 13.1%) and *C. dubliniensis* (4, 6%). Of the *Candida* isolates, 42 (62.7%) were from HIV-positive patients without any previous antimycotic treatment, while 25 (37.3%) were from HIV-positive patients with previous antimycotic treatment. *In vitro* susceptibility results of the *Candida* isolates are summarized in Table 2. The MICs for the quality control strains were within the accepted limits.

The determined MIC ranges were 0.12 - 4.0, 0.12 - 16, 0.03 - 1.0, 0.03 - 1.0 and 0.03 - 0.25 µg/ml for amphotericin B, fluconazole, itraconazole, ketoconazole and voriconazole respectively. The isolates demonstrated very low voriconazole MICs, in which 92.5% (62/67) presented values of 0.03 µg/ml, followed by ketoconazole, in which 89.6% (60/67) presented values of 0.03 µg/ml. All isolates were susceptible to voriconazole.

Table 2. *In vitro* antifungal susceptibilities of oral *Candida* isolates.

Species (number/%)	Antifungal agent	MIC (µg/ml)			SDD (%)	R (%)
		Range	MIC 50	MIC 90		
C. albicans (49/73.1)	Amphotericin B	0.25 - 1.0	1.0	1.0		-
	Fluconazole	0.12 - 4.0	0.12	0.25	-	-
	Itraconazole	0.03 - 0.25	0.06	0.12	3 (6.1)	-
	Ketoconazole	0.03 - 1.0	0.03	0.03		1(2)
	Voriconazole	0.03 - 0.25	0.03	0.03	-	-
C. glabrata (9/13.4)	Amphotericin B	0.25 - 4.0	1.0			1 (11.1)
	Fluconazole	0.12 - 4.0	0.5		-	-
	Itraconazole	0.03 - 1.0	0.12		1 (11.1)	2 (22.2)
	Ketoconazole	0.03 - 0.06	0.03			-
	Voriconazole	0.03	0.03		-	-
C. dubliniensis (4/6)	Amphotericin B	0.5 - 1.0	1.0			-
	Fluconazole	0.12	0.12		-	-
	Itraconazole	0.03 - 0.12	0.06		-	-
	Ketoconazole	0.03	0.03			-
	Voriconazole	0.03	0.03		-	-
C. krusei (2/3)	Amphotericin B	1.0 - 2.0	1.0			1 (50)
	Fluconazole	8.0 - 16	8.0		1 (50)	-
	Itraconazole	0.5	0.5		2 (100)	-
	Ketoconazole	0.25	0.25			2(100)
	Voriconazole	0.06	0.06		-	-
C. kefyr (1/1.5)	Amphotericin B	1				-
	Fluconazole	0.25			-	-
	Itraconazole	0.12			-	-
	Ketoconazole	0.03				-
	Voriconazole	0.03			-	-
C. lusitaniae (1/1.5)	Amphotericin B	0.12				-
	Fluconazole	0.12			-	-
	Itraconazole	0.03			-	-
	Ketoconazole	0.03				-
	Voriconazole	0.03			-	-
C. tropicalis (1/1.5)	Amphotericin B	1.0				-
	Fluconazole	0.12			-	-
	Itraconazole	0.03			-	-
	Ketoconazole	0.06				-
	Voriconazole	0.06			-	-
All *candida* (67/100)	Amphotericin B	0.12 - 4.0	1.0	1.0		2 (2.9)
	Fluconazole	0.12 - 16	0.12	2.0	1 (1.5)	-
	Itraconazole	0.03 - 1.0	0.06	0.25	6 (8.9)	2 (2.9)
	Ketoconazole	0.03 - 1.0	0.03	0.03		3(4.5)
	Voriconazole	0.03 - 0.25		0.03	-	-

Table 2. Continued.

	Amphotericin B	1.0 (0.5 - 4.0)
	Fluconazole	1.0 (1.0 - 4.0)
**C. parapsilosis* (ATCC22019)	Itraconazole	0.12 (0.12 - 0.5)
	Ketoconazole	0.06 (0.06 - 0.5)
	Voriconazole	0.03 (0.03 - 0.25)

**C. parapsilosis* (ATCC 22019) was used as reference strain; MIC ranges for 48 h were shown in parenthesis (22, 23, 24); S: Susceptible; SDD: Susceptible dose dependent (for fluconazole, itraconazole and voriconazole); R: Resistant.

65 (97%) of all isolates were determined susceptible to amphotericin B, 66 (98.5%) to fluconazole, 64 (95.5%) to ketoconazole and 50 (88%) to itraconazole.

Two (2.9%) of all isolates were found resistant to amphotericin B, 2 (2.9%) to itraconazole and 3 (4.5%) to ketoconazole. One of the two amphotericin B resistant strains was *C. glabrata* and the other was *C. krusei*. Both of the itraconazole resistant strains were *C. glabrata*, while one of three ketoconazole resistant strains was *C. albicans* and the remaining were *C. krusei*. Six (8.9%) of all isolates were found susceptible dose dependent (SDD) to itraconazole and 1 (15%) isolate to fluconazole. The strains SDD to itraconazole and fluconazole were *C. albicans* (3, 6.1%), *C. krusei* (2, 100%), *C. glabrata* (1, 11.1%) and C*. krusei* (1, 50%), respectively.

DISCUSSION

A variety of antifungal agents are now available for the treatment of OPC infections. Amphotericin B is both used topically in the treatment of superficial and systemic infections of hospitalized individuals (Ellepola and Samaranayake, 2000). Our findings showed that oral *Candida* spp isolated from HIV infected patients were highly sensitive to amphotericin B and only two (2.9%) isolates (one *C. glabrata* and one *C. krusei*) were resistant. The MIC distribution was concentrated in a very narrow range. HIV infected patients may have higher frequencies of amphotericin B resistant non-albicans *Candida* isolates (Blignaut et al., 2002; Kuriyama et al., 2005) . Some studies have also shown low (Magaldi et al., 2000; Pfaller et al., 2001) resistance or no resistance (Costa et al., 2006; Gugnani et al., 2003; Hamza et al., 2009; Sánchez-Vargas et al., 2005) for amphotericin B, which is in accordance with our findings. Authors noted out that all *Candida* isolates that presented *in vitro* resistance to amphotericin B were recovered from patients who had previously received this antifungal therapy, this was also the case in our study (Kuriyama et al., 2005; Luque et al., 2009; Magaldi et al., 2000).

Fluconazole is a triazole agent with a broad therapeutic range and little toxicity that is established as a first-line antifungal for the treatment of oral candidiasis (Sheehan et al., 1999). Several recent studies have reported fluconazole resistance in *Candida* strains isolated from HIV-infected patients with OPC (Barchiese et al., 1994; Luque et al., 2009; Vanden Bossche et al., 1994). In the present study, almost all *Candida* isolates were found to be susceptible to this drug. Only one strain (*C. krusei*) (1.5%) was SDD to fluconazole. This result is similar to that reported by other previous studies (Barchiese et al., 2002; Blignaut et al., 2002; Kamiru and Naidoo, 2002; Kuriyama et al., 2005; Sánchez-Vargas et al., 2005).

Itraconazole is used as an alternative to fluconazole for treating oral candidiasis. In our study two (2.9%) (*C. glabrata*) isolates were determined as resistant to itraconazole, while six (8.9%) strains were SDD (three *C. albicans*, one *C. glabrata*, and two *C. krusei*), which is a result similar to some other investigator's findings (Costa et al., 2006; Hamza et al., 2009; Kuriyama et al., 2005; Luque et al., 2009; Magaldi et al., 2000; Sánchez-Vargas et al., 2005).

Ketoconazole is usually preferred as a topical anti-fungal agent because of high hepatotoxicity in systemic use. In the present study sixty four (95.5%) of all isolates were determined susceptible to ketoconazole, a finding which supported some other studies results (Blignaut et al., 2002; Kuriyama et al., 2005; Magaldi et al., 2000).

Voriconazole belongs to a new generation of triazoles and possess potent broad-spectrum activity and a favorable pharmacokinetic profile (Odds, 2006; Sabatelli et al., 2006). In this study all isolates were found to be susceptible to voriconazole. Previous studies have shown low MICs of voriconazole against tested strains (Costa et al., 2006; Gugnani et al., 2003; Kuriyama et al., 2005) which are in accordance with our findings.

Our results show that 2 *Candida* isolates (8%) from patients with previous treatment were resistant to amphotericin B, 2 (8%) to itraconazole, and three (4.5%) to ketoconazole with a further 1 (4%) isolate SDD to fluconazole and 6 (24%) to itraconazole.

In our study, the *in vitro* susceptibility of *C* . *glabrata* and *C*. *krusei* to antifungal agents was tested for a low number isolates, but these showed a resistance to imidazolic compounds as previously described by other authors (Luque et al., 2009).

In conclusion, all *Candida* strains isolated from the oral cavity of Turkish HIV-infected patients were susceptible to fluconazole and voriconazole. In our study, only one *C.*

albicans, three *C*. *glabrata* and two *C*. *krusei* strains were found to be resistant to antifungals and all of antifungal resistant strains have been associated with prior use of antimycotics. Primary colonizing in the oral cavity strain may cause an infection once the immune function of the HIV positive patient has been destroyed (Li et al., 2006). Oral colonization by isolates resistant to the most commonly used antifungal agents could represent a serious therapeutic problem among immunocompromised individuals.

AUTHORS' CONTRIBUTIONS

All the authors participated in the design, implementation, analysis and interpretation of study and commented on the draft of the report.

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