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RESEARCH ARTICLE

Ketoconazole: A Re-emerging choice for Oral candidiasis in patients with human immunodeficiency virus infection/acquired Immunodeficiency Syndrome

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ABSTRACT:

Background: The long term use of antifungals for oral candidiasis (OC) in patients with Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) causes some strains to be resistant to certain antifungals. HIV/AIDS are currently most common in men. **Aim:** To evaluate ketoconazole sensitivity on *Candida* species in male HIV/AIDS patients with OC. **Method:** This is an observational descriptive study at the Outpatient Unit and Inpatient Installation of the Infectious Disease Intermediate Care Unit (UPIPI) Dr. Soetomo, Surabaya. Samples were taken from HIV/AIDS male patients with OC using sterile swabs. The smear was cultured in CHROMagar *Candida* incubated at 37°C for 48-72 hours, and Sabouraud Dextrose Agar media for 48 hours at 28°C. Species identification were done using carbohydrate and Cornmeal test. Resistance test was done by disk diffusion method. **Results:** There were 23 research subjects with 40 isolates of *Candida* species growing in culture. The most common species was *C. albicans* in 23(57.5%) isolates, while *Candida* non-*albicans* were found in 17(42.5%) isolates. The sensitivity test results showed that 34 (85%) isolates were sensitive, while 2(5%) isolates were resistant to ketoconazole. All *C. albicans* (23 [100%]) and most *Candida* non-*albicans* species (11 [64%]) were sensitive to ketoconazole. **Conclusion:** Ketoconazole can be recommended as a treatment option for OC patients with HIV/AIDS due to the high sensitivity of both *C. albicans and non-albicans* to this drug.

KEYWORDS: Ketoconazole, Antifungal agents, Candidiasis, oral, Drug resistance, Fungal, HIV.

INTRODUCTION:

Human's oral cavity contains various types of microorganisms which composition, metabolic activity and pathogenicity are influenced by external and internal factors. Among all fungi, the yeast from genus *Candida* is considered as the most widely found species in the oral cavity.[1-2] *Candida* species are the main cause of mucocutaneous infections namely oral, esophageal and vulvovaginal candidiasis.

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Oral candidiasis (OC) is most frequently found in patients with Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) worldwide.[1,3-4] Almost 90% of HIV/AIDS patients have experienced OC in the course of their illness. A high viral load and a low number of CD4 T lymphocytes are found in OC patients.[5-6] Although OC is caused by various types of *Candida*, *C. albicans* is the most common cause according to Reza's research in Malang in 2017, but some studies revealed an increase in OC caused by *Candida* non-*albicans* as showed in a study in Surabaya in 2008.[7-8]

Ketoconazole is a cheap, effective and available antifungal in Indonesia. Besides ketoconazole, topical nystatin or oral fluconazole and itraconazole are also

used as a therapeutic option in OC.[7] Nystatin, ketoconazole and fluconazole are currently listed as management for OC in the Clinical Practice Guide book of the Department of Dermatology and Venereology in our institution.[10] However, recent research has shown that the sensitivity of *Candida* species to azole antifungals, especially fluconazole, is decreased due to its widespread use.[1,9] Two factors influence this decrease in fluconazole sensitivity, namely: changes in causative species of OC from *Candida albicans* to non-*albicans* such as *C. glabrata* and *C. krusei* which have intrinsic resistance; and the emergence of resistance to the azole group.[11-14] Therefore, ketoconazole is another drug of choice for OC.[10] The objective of this study is to evaluate ketoconazole sensitivity on *Candida* species in male HIV/AIDS patients with OC.

MATERIAL AND METHODS:

Subjects:

This study was conducted with observational descriptive method with the approval of the Health Research Ethics Committee of Dr. Soetomo General Hospital Surabaya. Subjects were recruited by total sampling from HIV/AIDS patients with OC who visited the Outpatient Unit and Inpatient Installation of the Infectious Disease Intermediate Care Unit (UPIPI) Dr. Soetomo, Surabaya from May to July 2019. The inclusion criteria were male, aged 18 years or above, willing to participate in the study and sign informed consent. The exclusion criteria was negative culture result. The demographic data, such as gender, age, occupation, clinical features of candidiasis, including main complaint, location, frequency, history of previous treatment, diagnosis and treatment plan, and HIV status including HIV transmission, time of having HIV, clinical stadium of HIV, amount of absolute CD4, and ARV treatment of the research subjects were documented in the patient's medical record. Sampling was done using sterile swabs. Afterwards, the patients were examined for OC and verified by finding white plaque in the intraoral mucous layer and confirmed by the presence of yeast and hyphae through 10% KOH examination and fungal culture of the oral cavity. Those who were verified as OC were selected for this study.

Clinical isolate:

The smear was cultured in CHROMagar *Candida* incubated at 37°C for 48-72 hours. *Candida* was cultured on Sabouraud Dextrose Agar (SDA) media for 48 hours at 28°C for further examination. Grown *Candida* cultures were subjected to identification tests using the carbohydrate and Cornmeal test methods. Ater the species was identified, the resistance test was carried out using the diffusion disk method. The sensitivity test results are obtained in the form of the diameter of the inhibition zone. The susceptibility and resistance criteria of antifungal agents were determined according to the interpretation by Rosco Diagnostica Company. With ketoconazole 10μg/disk, diameter of the inhibition zone of ≥28 mm is interpreted as sensitive, 21-27mm as intermediate and ≤20 as resistant.[1]

RESULTS:

This study found 23 HIV/AIDS male patients with OC who fulfilled the inclusion criteria. Demographic profiles of the subjects showed that most of the subjects were young adults aged 18 to 35 years (30%), unemployed (48%), and with education level equivalent to high school (44%). The main complaint from clinical manifestation of OC in this study was found to be in the form of white spots in the oral cavity, found in all subjects of 23 people (100%). Most locations were found on the tongue, also found in all of 23 people (100%). The research subjects who experienced OC for the first time were 11 people (48%). Previous history of systemic and topical antifungal treatment was found in 15 people, 4 of whom had received systemic antifungals and 11 had received topical antifungals. One subject may have the main complaint, multiple location of the disease and a history of more than one antifungal treatment. The most common diagnosis of OC is pseudomembranous candidiasis, found in 19(82%) people, although in one subject can also have several types of OC. Most of the research subjects still received topical nystatin therapy, as much as 18 people (78%) (Table 1).

Table 1. Demographic and clinical features of the research subjects

No.	Features		N	%
1	Age	Late teenager 18 – 25 years old	3	13
		Early adult 26 – 35 years old	4	17
		Late adult 36 – 45 years old	7	31
		Early elderly 46 – 55 years old	5	22
		Late elderly 56 – 65 years old	4	17
		Geriatrics > 66 years old	0	0
2	Level of education	None	3	13
		Elementary School/Junior High School	7	31
		Senior High School	10	43
		Diploma/Bachelor	3	13
3	Occupation	None	11	48
		Civil Servant	2	9
		Private Employees	9	39
		Students	1	4
4	Main complaint	White spots in oral cavity	23	100
		Red spots in oral cavity	1	4
		Spots and wound in lips' corner	1	4
		Spots or wound with swallowing pain, or burning sensation in throat	4	17
5	Location	Mucous	1	4
		Tongue	23	100
		Lips' corner	1	4
6	Frequency	Recurrent	12	52
		First time	11	48

7	History of previous treatment	Systemic antifungal Yes No	 4 19	 17 83
		Topical antifungal Yes No	 11 12	 48 52
8	Diagnosis	Pseudomembranous candidiasis	16	70
		Hyperplastic plaque candidiasis	5	22
		Atrophic candidiasis	1	4
		Cheilitis candidiasis	1	4
9	Treatment plan	Systemic:		
		Fluconazole	5	22
		Ketoconazole	0	0
		Topical:		
		Nystatin	18	78

One subject can have more than one features.

The HIV/AIDS profiles of the subjects was quite diverse. The most common HIV transmission was through heterosexual intercourse (65%). Most of the subjects were in HIV stages III and IV, as much as 12 people (52%) and 9 people (39%). Patients who received ARV were found in 19 (83%) of the study subjects (Table 2).

From 23 research subjects, 40 isolates of *Candida* were found, because in 10 research subjects there were more than one type of *Candida* cause. The *C. albicans* species is still the main cause of OC in HIV/AIDS patients in Dr. Soetomo Hospital, which was found in 23 isolates (57.5%), while the non-*albicans* group was found in 17 isolates (42.5%) (Table 3).

Table 2. HIV status of research subjects

No.	HIV Status		N	%
	Category	**Group**		
1	HIV transmission‡	Homosexual	6	26
		Heterosexual/*Free sex*	13	57
		Bisexual	1	4
		Needle/Tattoo/Transfusion	3	13
2	Time of having HIV	< 1 year	11	48
		1- 3 years	9	39
		> 3 years	3	13
3	Clinical stadium of HIV	Stadium I	0	0
		Stadium II	2	9
		Stadium III	12	52
		Stadium IV	9	39
4	Amount of absolute CD4	> 500 cells/ μL	0	0
		200-500 cells/μL	8	35
		< 200 cells/μL	15	65
5	ARV treatment	Yes No	19 4	83 17

One subject can have more than one answers.

Table 3. Identification results of *Candida* species

No	Color of colony in CHROM agar	Urea Hydro -lysis	Fermentation						Temp 42-45 C	Microscopic appearance	Identification results	Total	%
			Glu	Lac	Suc	Mal	Gal	Tre					
1	Green	(-)	(+)	(-)	(-)	(+)	(-)	(-)	Grew	Chlamydospora terminalis, circular blastoconidia forming a unity on the pseudohyphae	*Candida albicans*	23	57.5
2	Tosca	(-)	(+)	(-)	(-)	(+)	(-)	(-)	Did Not Grow	Chlamydospora abounds in appearance, in pairs, or in groups. Pseudohyphae and hyphae in the blastoconidia cluster	*Candida dubliniensis*	0	0.0
3	White	(-)	(+)	(-)	(-)	(-)	(+)	(-)	-	Single blastoconidia form, small unity along the relatively short and curved pseudohyphae. There is a "Giant Cell"	*Candida parapsilosis*	1	2.5
4	Prussian Blue	(-)	(+)	(-)	(+)	(+)	(+)	(+)	-	Small and single blastoconidia with pseudohyphae and true hyphae	*Candida tropicalis*	6	15.0
5	Baby Purple	(-)	(+)	(-)	(-)	(-)	(-)	(+)	-	Yeast cells, without pseudohyphae	*Candida glabrata*	5	12.5
6	Pink	Variable	(+)	(-)	(-)	(-)	(-)	(-)	-	Pseudohyphae with oval to elongated blastoconidia which forms cross-match-sticks or resembles trees	*Candida krusei*	5	12.5
7	White-Pink	(-)	(+)	(-)	(+)	(-)	(+)	(+)		Blastoconidia are in small groups with short pseudohyphae and relatively few yeast cells	*Candida guilermondii*	0	0.0
										Total Species		40	100.0

Glu = glucose, Lac = lactose, Suc = sucrose, Mal = Maltose, Gal = Galactose, Tre = Trehalose, Temp = temperature.
One subject can have more than one *Candida* isolate that grew.

Table 4 Resistance of each isolate of *Candida* species to ketoconazole antifungals

S. No.	Species	Total	%	Ketoconazole					
				S	%	I	%	R	%
1	*Candida albicans*	23	57.5%	23	100	0	0	0	0
2	Non-*albicans Candida:*	17	42.5%	11	65	4	23	2	12
	-Candida dubliniensis	0	0.0%	0	0	0	0	0	0
	-Candida glabrata	5	12.5%	4	80	1	20	0	0
	-Candida guilermondii	0	0.0%	0	0	0	0	0	0
	-Candida krusei	5	12.5%	2	40	3	60	0	0
	-Candida parapsilosis	1	2.5%	1	100	0	0	0	0
	-Candida tropicalis	6	15.0%	4	66	0	0	2	34
	TOTAL	40	100.0%	34	85	4	10	2	5

The sensitivity test results of isolates on ketoconazole drugs showed that the number of *Candida* species sensitive to ketoconazole was 34(85%), while the number of *Candida* species resistant to ketoconazole was 2(5%). All 23 *C. albicans* (100%) and 11(64%) of the *Candida* non-*albicans* species were sensitive to ketoconazole. Of all *Candida non-albicans* species, 4(23%) were intermediate and only 2(13%) were resistant to ketoconazole (Table 4).

DISCUSSION:

Demographic profiles of the study participants showed that most of them are in the adult group. Data from Indonesian Ministry of Health in 2016 found that more than 50% of HIV/AIDS patients were young adult and within productive age groups ranging from 25-49 years old.[15] Adults in productive age are mostly sexually active and more likely to do unsafe sex which predispose themselves for HIV transmission.[16] Education level showed that 3 people (13%) never went to school and 7 patients (31%) graduated from elementary/junior high school. Occupational backgrounds of participants in this study showed that 11 patients (48%) are unemployed. HIV/AIDS patients from low educational and socioeconomic backgrounds may have a very limited access to oral health services. This reduce their ability to maintain the health of the oral cavity so they easily experience diseases in the oral cavity. Patients with HIV/AIDS during the course of their illness will also experience various kinds of opportunistic infections that affect the quality of life, including losing their job.[8,17]

The most prevalent HIV transmission in this study was from heterosexual intercourse, as found in 57% patients. This is similar to the general picture of HIV/AIDS in East Java where the main transmission of HIV/AIDS, especially through heterosexuals, was 69.6% while transmission through needle from drug users were 21.9%.[18] OC patients with HIV/AIDS in this study had more than one type of complaint. The most common major complaint is white patches in the oral cavity (100%) with a diagnosis of pseudomembranous OC. The results of the same study were carried out in India in 2013 where pseudomembranous OC was found in 76.2% research subjects.[19] The subjects in this study showed that 19 of them (83%) had received ARV therapy, while 4 of them (17%) had not received ARV. Although the incidence of opportunistic infections including OC have decreased with ARV therapy, OC remains a common problem in HIV/AIDS patients on active ARV therapy. This is because of the presence of other factors such as such as high virulence of *Candida* species and combinations of *Candida albicans* and non-*albicans* species infection, which further make OC to be recurrent and difficult to treat.[20] Research by Moges in Ethiopia in 2013 showed that OC was found in 58.7% patients who were not on ARV therapy, but only 41.3% patients who received ARV therapy were found to have OC.[1]

Identification of *Candida* species in this study used a combination of *Candida* CHROMagar, Cornmeal and carbohydrate tests. Identification of species by this method also has advantages especially for areas with limited facilities, and this method also has good accuracy compared to the latest methods such as Vitek-II which are more expensive.[21] Different *Candida* species grown in CHROMagar will produce colonies with distinct colors.[22] In this study, 23 research subjects and 40 *Candida* isolates were obtained. In 10 research subjects, growth of more than one species of *Candida* was found. The most common causes of OC in patients with HIV/AIDS infection in this study were *C. albicans* which was 57.5%, whereas infection from *Candida* non-*albicans* in this study was 42.5%, sequentially consisting of *C. tropicalis*, *C. glabrata*, *C. krusei* and *C. parapsilosis* species. A study by Reza in 2017 also showed that *C. albicans* is still the main cause of OC.[8] Similar finding was also found in various international studies that *C. albicans* was the main cause in OC patients with HIV/AIDS.[1]

In this study, a spectrum of changes in the causes of OC was found. Even though *C. albicans* was still more common but *Candida* non-*albicans* began to increase. Factors such as recurrent OC were considered to cause differences in *Candida* species and predispose to shift into *Candida* non-*albicans* species.[1] This was thought to be due to exposure to antifungals in patients with

recurrent OC. Most of the patients in this study have history of both systemic and topical antifungal therapy. Previous antibiotics and antifungal therapy have been related to the increase in the number of *Candida* non-*albicans* colonies in the oral cavity of individuals infected with HIV/AIDS.[1,21,23] Prior antifungal therapies may cause selective pressure and results in replacement of *C. albicans* by *C. glabrata*.[1] The broad-spectrum antibiotics has shown to be able to change normal flora bacteria by killing bacteria and increasing the proliferation of *Candida* species.[24,25] A study conducted by Mushi in 2016 in Tanzania stated that the use of previous antibiotics is a statistically significant factor in increasing colonization of *Candida* non-*albicans* species.[24] In addition, in the course of advanced HIV/AIDS, extensive fungal colonization was also found.[17] Presence of *Candida* non-albicans species can be a concern to public health because this species is often associated with resistance to azole antifungals and will be difficult to treat.[24]

All *Candida* samples were tested for sensitivity to ketoconazole by the disk diffusion method. In this study, the number of *Candida* species sensitive to ketoconazole is 34 samples (85%) while the number of resistant *Candida* species is in 2% samples. All 23 *C. albicans* (100%) were sensitive to ketoconazole and 11(64%) of the *Candida* non-*albicans* species sensitive to ketoconazole, while 4(23%) were intermediate and only 2(13%) were resistant to ketoconazole. Both of ketoconazole-resistant *Candida* species were *C. tropicalis.* The results above are in accordance with research conducted by Anna in 2012 in Cameroon which is also a pandemic area for HIV/AIDS. Fluconazole is a first-line therapy in OC patients with HIV/AIDS and also given free of charge in the country. The widespread use increased the incidence of fluconazole resistance. In that study most of the *C. albicans* species (80%) were sensitive to ketoconazole. The study recommended ketoconazole as the drug of choice in OC cases caused by fluconazole-resistant *C. albicans* species.[26]

Identification and sensitivity testing of causative *Candida* species in OC patients with HIV/AIDS should be investigated periodically to look at the changes in the spectrum of the species and to reevaluate and update the guidelines for OC therapy. This study showed a spectrum of change in the causes of OC in which *Candida* non-*albicans* began to increase although *C. albicans* was still more common. Sensitivity testing showed that all *C. albicans* and 64% of the *Candida* non-*albicans* species were sensitive to ketoconazole. All of the ketoconazole-resistant *Candida* species were *C. tropicalis*. Thus, ketoconazole can be recommended as a treatment option for OC patients with HIV/AIDS due to the high sensitivity of both *C. albicans* and *non-albicans* to this drug.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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