

Candiduria in the Patients Visiting At Kathmandu Model Hospital, Nepal

Niroj Man Amatya, MBCHB*

Department of Medical Microbiology,
Nobel College: Kathmandu, Nepal

Abstract

The effective management of Candiduria depends upon proper identification of Candida species and their antifungal susceptibility test. Therefore, this cross-sectional study is conducted to assess the occurrence of different Candida species in urine and determine their antifungal susceptibility pattern from productive age group 15-65. The isolation and identification of Candida species from clean catch midstream urine were done by culturing on Sabouraud Dextrose Agar with chloramphenicol followed by germ tube test, sugar fermentation test, chlamyospore production test, and further differentiated by using CHROM agar. The antifungal susceptibility test was done on Muller Hinton Agar with 2% glucose and 0.5 µg/mL methylene blue, and result interpretation was done as recommended to CLSI guidelines (M 44-A2). *Candida parapsilosis* (14, 31.1%) and *C. albicans* (12, 26.67%) were the two most common isolates. From 586 urine samples, 45 Candida species were isolated in which the predominant one is *C. parapsilosis* (14, 31.1%) followed by *C. albicans* (12, 26.6%). The antifungal susceptibility test showed that fluconazole resistant (29.41%) was comparatively more than voriconazole (21.87%). Since non albicans Candida are emerging pathogen and its antifungal resistant pattern is hiking, it is crucial to incorporate fungus identification in routine testing and identify their antifungal susceptibility pattern to ensure effective treatment and monitor for any antifungal resistance.

Keywords: Candiduria; *Candida parapsilosis*; Fluconazole; Voriconazole

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Introduction

Candiduria refers to the presence of Candida species in urine causing urinary tract infections [UTIs] which should not be neglected or treated hastily in both asymptomatic and symptomatic cases of UTI [1]. In UTI, the most dominating fungus is *Candida albicans* but some report shows a significant increase of "Non albicans Candida (NAC) [2]. Further, recent study has shown that candiduria is becoming more common than bacteriuria in immunocompromised patients [3].

The lack of standardized laboratory diagnosis and treatment options is a contentious issue surrounding candiduria. Many cases of candiduria are asymptomatic, making it difficult to determine whether the presence of Candida in urine indicate a true infection or simply colonization of urinary tract, as it is a normal flora of the urinary tract [1]. Hence, infections due to Candida species are largely a condition associated with medical progress and are widely recognized as a major cause of mortality and morbidity in the healthcare environment. The emergence of fungal infections is highly problematic and may be attributed due to the extensive use of broad-spectrum antibiotics and immune-suppressive

agents, as well as an increase in immunocompromised individuals with autoimmune diseases, cancers, and transplants [4]. Thus, proper diagnosis and susceptibility testing of Candida species in clinical specimens has become increasingly important for the management of fungal infections.

In Nepal, the field of mycology faces limitation due to the scarcity of sophisticated healthcare facilities and lack of awareness in the community. Consequently, managing candiduria in asymptomatic and symptomatic individuals has become a challenging task. So, this descriptive cross-sectional study was conducted to assess candiduria with antifungal susceptibility patterns for better management and treatment strategies.

Material and Methods

A total of 586 clean catch midstream urine samples (CCMSU) were collected from 1st April 2021 to 30th June 2021. The homogenized urine sample (4 µL) was streaked on SDA agar with 0.5 mg per 1000 mL chloramphenicol and incubated at 37°C. The culture plates were examined for growth at 24 hrs, 48 hrs and 72 hrs. Since there is no established guideline for candiduria similar to bacteriuria, a lower cut-off value of 103 CFU/mL was adopted as

described elsewhere [5]. The colony characteristics of the yeast colonies were examined for preliminary identification. Additional tests such as Gram staining, colony morphology on Cornmeal agar, germ tube test, sugar fermentation test and CHROM agar test were done to aid in the identification of yeast.

The Antifungal Susceptibility Test (AFST) was done on Mueller-Hinton agar supplemented with 2 % glucose and 0.5 µg/mL methylene blue dyes. Antifungal disks (fluconazole and voriconazole) were placed on the surface of each agar plate and incubated aerobically at 37°C for 24-48 hrs. The zone size was interpreted based on CLSI guidelines [6].

All the data were input in SPSS version 23 for descriptive statistical analysis.

Results

This trimester study includes 586 urine samples from which 45 *Candida* species were isolated. Overall, there were a higher number of female participants compared to male participants and concomitantly the number of isolates from the female was also three times more than males. The age group 30-40 covers most of the samples and two out of 10 patients with antifungal treatment have fungal growth (Table 1).

Among the *Candida* species, *C. parapsilosis* (31.1%, 14) and *C. albicans* (26.6 %, 12) were the two most frequent isolates. The overall distribution of isolates is present in Figures 1 and 2.

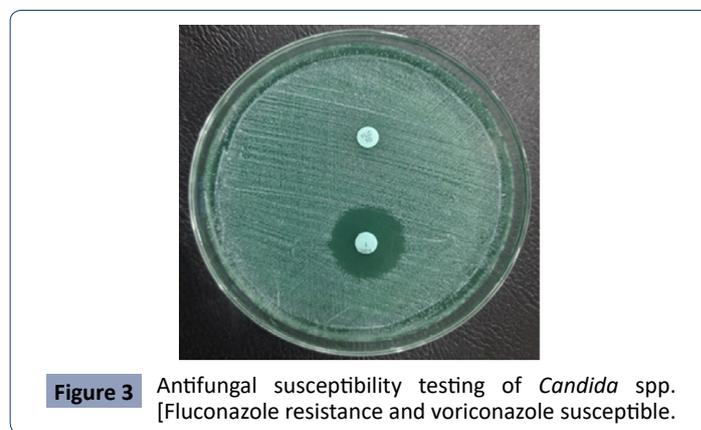
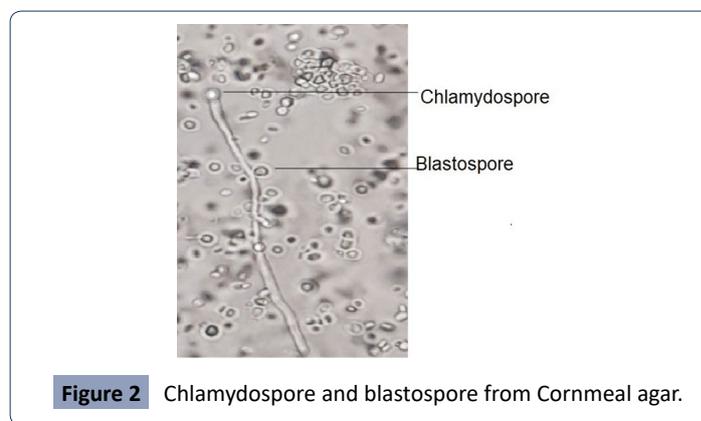
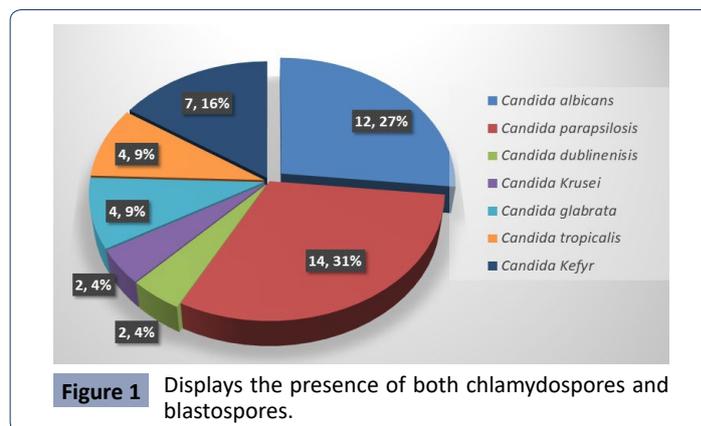
In this study, two antifungal agents; Fluconazole and Voriconazole, were tested to determine antifungal susceptibility pattern of isolates in which Voriconazole was found as more susceptible than Fluconazole. The overall susceptibility pattern of *Candida* species to different antifungal agents is shown in Table 2 and AFST of *Candida* species were shown in Figure 3.

Discussion

Candida albicans is considered as a normal flora on the mucous membrane of the oral cavity, alimentary canal, urogenital tract and integumentary system of healthy individuals. They can also act as an opportunistic pathogen and responsible for causing both superficial and systemic infections [7]. But from few years, there has been a notable increase in infections caused by non-*albicans*

Table 1. Socio-Demographic and Clinical Characteristics of Participants.

Variables		Growth of <i>Candida</i>			Total
		Yes	No	Insignificant	
Sex	Male	11	153	12	176
	Female	34	355	21	410
	Total	45	508	33	586
Age group	< 20	2	16	2	20
	20-30	8	136	9	153
	30-40	16	133	5	154
	40-50	9	116	7	132
	>50	10	107	10	127
	Total	45	508	33	586
Antifungal Treatment	Yes	2	5	3	10
	No	43	503	30	576
	Total	45	508	33	586



Candida (NAC). There are altogether 200 species of *Candida* of which *C. dubliniensis*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, *C. lusitanae*, *C. kefyr* and *C. auris* are NACs that have gained clinical significance [8]. Most of these NACs with clinical importance are known to show resistance to certain commonly used antifungal agents. So, for optimizing the treatment of the infections caused by *Candida* species, it is necessary to identify the *Candida* species up to the species level and perform antifungal susceptibility testing [9].

This study identified the specific species of *Candida* along with their antifungal susceptibility pattern. *C. albicans* and NAC are closely related but they differ from each other in term of their epidemiology, virulence characteristics and antifungal susceptibility. In our study, the culture positivity rate is 7.68 % and most of the cases were reported from the age group 30-40.

Table 2. Antifungal Susceptibility Pattern of Candida species.

Antifungal agents		Candida					Total
		albicans	tropicalis	glabrata	parapsilosis	krusei	
Fluconazole (10µg)	S	8	3	0	8	-	19
		-66.60%	-75.00%		-57.10%		-55.80%
	SDD	2	1	2	2	-	7
		-16.60%	-25%	-50%	-14.20%		-20.50%
	R	2	0	2	4	-	10
		-16.60%		-50%	-28.50%		-29.40%
Total		12	4	4	14		34
		-33.30%	-11.10%	-11.10%	-38.80%		
Voriconazole (1µg)	S	10	3	-	9	2	24
		-83.30%	-75.00%		-64.20%	-100.00%	-75.00%
	SDD	0	1	-	0	0	1
			-25.00%				-3.10%
	R	2	0	-	5	0	7
		-16.60%			-35.70%		-21.80%
Total		12	4		14	2	32
		-37.50%	-12.50%		-43.70%	-6.20%	

A similar but contradictory result was shown by Saud in which most of the cases were found in the age group 46-55 years [10]. This might be due to differences in sample size, study duration, study area, study type and so on. Colonization of Candida species in females was found to be three times higher than the males (i.e. 34, 75.55% in females and 11, 24.44% in males). The probable cause for higher candiduria in females than males may be due to the urethral anatomy and hormonal factors that contribute the colonization of Candida species in the urethral area in females [11,12].

The rate of isolation of NAC causing UTI was found to be 73.3% in our study, which is higher than other studies conducted in Nepal and India [9,13]. Among the 45 Candida isolates, the most predominant was *C. parapsilosis* (14, 31.1%) which aligns with the findings of study done by Sajjan in Nepal [14]. Following *C. parapsilosis*, *C. albicans* was the second most prevalent species (26.6%, 12), while *C. kefyr*, *C. glabrata*, *C. tropicalis*, *C. dubliniensis*, and *C. krusei* accounted for varying proportions of isolates. Our findings present a different scenario regarding the frequency of Candida species compared to previous two independent studies from Nepal showing *C. albicans* as the most prevalent one [10,13]. A relatively higher proportion of *C. parapsilosis* isolates in our study may be related to a higher sample size and other factors including the improved laboratory diagnosis, type of patient population studied, previous exposure to polyene and azole agents, changing demographics pattern of patients (older age, increased environmental exposure), use of indwelling medical devices, study duration, study area, methods of identification, study type, study time and so on. Overall, the present study along with the findings of other researchers suggests the emergence of NAC for Candiduria. Therefore, increasing awareness about fungal infections and their impact on health within community is crucial to reduce the burden of disease. The identification of Candida has a paramount effect on successful treatment, as it helps to optimize the selection of the

therapeutic agent and the use of CHROM agar is a simple, rapid, and inexpensive method for the identification of Candida species, especially in the laboratory with limited resources settings. The risk factors associated with Candiduria must be kept in mind for both the clinician and laboratory personnel.

Furthermore, a study with a larger samples sizes and follow-up for outcome would contribute to better understanding of prognosis and response. In conclusion, the correct identification of Candida species is of utmost importance due to its prognostic and therapeutic significance, facilitating early and appropriate antifungal therapy.

In our study, the rate of fluconazole resistant isolates was found to be 29.4%. A similar study conducted in Nepal showed slightly lower (20%) fluconazole resistance isolates [15]. The two different studies conducted in India by Pramodhini and Yashavanth showed the fluconazole resistant profile as 22.72% and 24% respectively [16,17] but a study in Cameroon showed fluconazole resistant rate of 42% [18]. Among the different Candida species, the highest rate of fluconazole resistance was observed in *C. glabrata* (2/4, 50.0%) followed by *C. parapsilosis* (4/14, 28.5%) while its rate is only 16.6% for *C. albicans*. Similarly, the rate of voriconazole resistant isolates were 21.8% in our study which is more or less similar to the study conducted in India by Yashavanth in 2012 (18.1%) [17] But it is lower than study conducted by Pramodhini (12.9%) in 2021 [16]. The antifungal susceptibility test shows that voriconazole (75.0%) was more effective than fluconazole (52.7%). In fact, fluconazole and voriconazole-resistant Candida species are rising in the community. The exact reasons for this high resistance is unclear, but it could be due to the easy availability, irrational use, and consumption without proper consultation with clinicians and limited access to diagnostic centers for fungus culture and identification. Thus, this study emphasizes the need for speciation of Candida isolates and recommends performing antifungal susceptibility for all the clinical isolates.

Conclusion

The shift from *Candida albicans* to NAC as a predominant species causing candiduria, along with increased resistance to fluconazole, raises concerns about a potential paradigm shift in candiduria. This limit the effectiveness of treatment options and lead to persistent or recurrent infections, increased healthcare

cost, and higher morbidity and mortality rates. Hence, it is important to implement appropriate antifungal stewardship program to optimize antifungal use, implement infection control practices and promote research efforts to combat this emerging problem otherwise we have to again asked the question do we verge facing the antifungal resistance same as antibacterial resistance?

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