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Original Research Article

Candiduria: its characterization, antifungal susceptibility pattern and biofilm formation

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ABSTRACT

Background: Candida are the fourth most common species causing urinary tract infections. The last two decades has shown rapid increase in Candida associated UTI along with change in its distribution. The indiscriminate use of antifungal drugs, especially azole group have contributed in emergence of resistant strains of *Candida*. Biofilm producing property of *Candida* also contributes to antifungal resistance. Aims and objectives was to detect the occurrence of Candida as causative agent of UTI and a potent bio film producer. The susceptibility of Candida to antifungal drugs and their correlation with the production of bio film and presence of Foleys catheter was also determined.
Methods: A total of 4192 urine specimens were analysed. *Candida* species isolated from urine samples were characterized using CHROM agar, sugar assimilation tests and micro morphology on corn meal agar. The antifungal susceptibility testing was performed by modified disc diffusion method on MHA with two drugs; fluconazole 25µg, and voriconazole 1µg discs. The biofilm production capability was tested according to the protocol proposed by Branchini et al.
Results: Out of 113 Candida species isolated, 16.8% were Candida albicans as compared to 83.2% non albicans, with *Candida tropicalis* as the most common species. Antimicrobial sensitivity by modified Kirby Bauer disc diffusion method showed 74.3 % of *Candida* isolates to be fluconazole sensitive while sensitivity to voriconazole was 100%. 60.2% of *Candida* were biofilm producers out of which 48.5 % were from urine samples of catheterized patients. Similarly, 26.4 % of fluconazole resistant strains were also biofilm producers.
Conclusions: The increased incidence of Non albicans candiduria which are also biofilm producers and resistant to commonly used drug fluconazole is a matter of concern. Therefore, the species identification of *Candida* isolates along with their antifungal susceptibility pattern should be routinely performed to help the clinicians in better treating the patients with candiduria.

Keywords: Antifungal susceptibility pattern, *Candida*, *Non albicans Candida*

INTRODUCTION

Candida species accounts for 10-15% cases of urinary tract infection and have become the fourth most common pathogen of UTI specially in catheterized patients. Urinary catheters have been held responsible for 80% of hospital acquired UTI.[1,2] 90% of invasive infections are caused by *Candida albicans* but Non albicans *Candida* like *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Candida krusei* are increasingly becoming important as causative agents of UTI.[3] Non *albicans Candida* species appear better adopted to the urinary tract

environment and are more resistant to antifungal drugs as compared to *C. albicans*.

Candiduria is very common in patients exposed to risk factors, mainly in hospitalized patients, diabetic, and in patients admitted in ICU. Catheterization process increases chances of UTI by allowing migration of the organisms into the bladder from external periurethral surface. Candida species can also form drug resistant bio films on Foleys catheter which may be a constant source of nidus of infection.[4]

With the increased incidence of *Candida* infections, there has also been development of resistance to antifungal agents specially the azole group. The indiscriminate, inadequate use of antifungal drugs, especially azole group have contributed for increase in emergence of resistance strains of *Candida*.[4] Thus, the role of *in-vitro* laboratory tests in selection of antifungal therapy has become crucial. The diagnosis and identification of *Candida* species along with its antimicrobial susceptibility pattern in patients with candidal UTI will help the clinician in selecting the appropriate antifungal agent and thus contribute to overall reduction in cost of treatment and duration of hospital stay.

Keeping the above mentioned facts in mind, the present study was carried out to detect the prevalence of Candiduria, its characterization to species level, along with the antifungal susceptibility pattern in immunocompromised, immunocompetent and catheterized patients of our institute.

METHODS

This study was carried out in the Department of Microbiology, Rohillkhand Medical College and Hospital, Bareilly, India between December 2016 to June 2017 after taking permission from the ethical committee of the hospital. 113 urine specimens showed single isolation of *Candida* species out of total 4192 urine specimens obtained from patients admitted as well as attending OPD of various clinical departments of this institute. All the urine samples were subjected to culture on 5% Blood agar, and MacConkey agar, following the calibrated loop technique. Gram staining of all the positive cultures was performed, and those showing yeast like budding cells were sub-cultured on SDA and HiChrome agar for species identification.

Germ tube test was performed to differentiate *Candida albicans* and NACA. Further identification was done by Chrom agar, sugar assimilation tests using commercially prepared sugar discs sucrose, maltose, dextrose, trehalose, lactose and dulcitol from HiMedia and studying micro morphology on corn meal agar.

The antifungal susceptibility testing was performed by modified disc diffusion method on MHA containing, 0.5µg/mL methylene blue and 2% dextrose with two drugs; fluconazole 25µg, and voriconazole 1µg discs. The zone of inhibition was measured to the nearest whole millimeter and interpreted according to CLSI guidelines, M44-A document (fluconazole:S>19mm, R<14mm, S-DD 15-18mm; voriconazole: S>17mm, R<13mm, S-DD 14-17mm).[5] All strains found to be resistant or S-DD by modified disc diffusion method on MHA were further confirmed by detecting MIC values by E-test using Ezy MIC test strips. *C. albicans* ATCC 90028 was used as a quality control strain in identification as well as antimicrobial susceptibility test.

The Biofilm production capability of all the Candida isolates was also tested in accordance with the protocol proposed by Branchini et al, where in 3ml of Sabourauds dextrose broth supplemented with 8% glucose was dispensed in plastic tubes and candida isolates adjusted to 0.5 Mc Farlands.[6,5]

After the incubation for 24hours , the broth was aspirated out with the help of the semiautomated pipette and stained with 1% aq. safranine stain, biofilm formation was considered positive when a visible film lined the walls and bottoms of the tubes. Biofilm formation was observed visually by two separate observers and correlated. Biofilm production by each isolate was scored as negative, weak (+), moderate (++/+++), or strong (++++).

RESULTS

In our study, mono microbial growth of Candida was isolated in 113(2.7%) out of total 4192 urine cultures performed in the laboratory. Out of these 113 Candida species isolated from urine, 16.8% of isolates were *Candida albicans* as compared to 83.2% non albicans Candida. Amongst the Non albicans *Candida*, *Candida tropicalis* was seen to be the most common species, with 35.8%, incidence, followed by *C. glabrata* 32.7% and *C. krusei* 8.0%, while *Candida parapsilosis* and *Candida guilliermondii* 1.8% each (Table 1).

Tables 1: Distribution of various *Candida* species, isolated in the urine samples, studied; n=113.

Species	Isolation No. (%)
Candida albicans	19 (16.8)
Candida tropicalis	45 (39.8)
Candida krusei	9(8.0)
Candida glabrata	37 (32.7)
Candida parapsilosis	2 (1.8)
Candida guilliermondii	1 (0.9)
Total	113(100)

Antimicrobial sensitivity by modified Kirby Bauer disc diffusion method showed, 74.3 % of *Candida* isolates to be fluconazole sensitive (Figure 1), 23.9 % resistant, and 1.8% to be susceptible-dose dependant (S-DD) (Table 2).

Table 2: Antifungal sensitivity pattern of *Candida* isolates by modified Kirby Bauer disc diffusion method: n=113.

Species	Fluconazole (25µg)			Voriconazole (1µg)	
	S (%) ≥ 19mm	S-DD (%) 15-18mm	R (%) ≤14mm	S (%) ≥17mm	R (%) ≤13mm
Candida albicans	15 (13.3)	0	4 (3.5)	19 (16.8)	0
Candida tropicalis	35 (31.0)	1 (0.9)	9 (8.0)	45 (39.8)	0
Candida krusei	0	0	9 (8.0)	9 (8.0)	0
Candida glabrata	31 (27.4)	1 (0.9)	5 (4.4)	37 (32.7)	0
Candida parapsilosis	2 (1.8)	0	0	2 (1.8)	0
Candida guilliermondii	1 (0.9)	0	0	1 (0.9)	0
Total	84 (74.3)	2 (1.8)	27 (23.9.)	113 (100)	0
Species		**No. of resistant strains by DDM No. (%)**		**Fluconazole MIC >64 BY E-test No. (%)**	
Candida albicans		4 (14.8)		4 (13.8)	
NACA		23 (85.2)		25 (86.2)	
Total resistance		27 (23.9)		29 (25.7)	

The sensitivity of *Candida albicans* to fluconazole was 78.9% while that of NACA species were 61.1%. Voriconazole was found to be 100 % sensitive for all the studied isolates (Table 2, Figure 2). No azole cross resistance was observed in our study. All the fluconazole resistant and S-DD isolates were further confirmed by E-test. The 2 S-DD isolates were detected to be resistant with MIC values >64 (Figure 3) thereby, increasing resistance of fluconazole from our institute to 25.7% (Table 3).

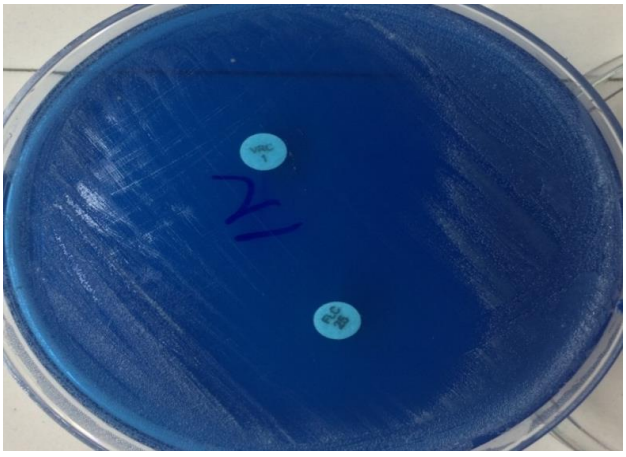

Figure 1: Anti fungal susceptibility testing by disk diffusion method showing showing fluconazole ≥19mm and voriconazole ≥17mm sensitive.

Out of all 113 *Candida* isolated, 68 (60.2%) were found to be biofilm producers with, 48.4% showing grade 3 intensity, 29.4% grade 2, and 22.2% grade 1, respectively. Upon correlating the Foley's catheterization, which is considered to be one of the chief predisposing risk factors vs, biofilm production, it was found that, out of all 68 (60.2%) biofilm producers, 48.5% were urine samples from catheterized patients as shown in Table 5.

Figure 2: AST by Kirby Bauer disk diffusion method showing fluconazole resistance (zone size ≤14mm) voriconazole sensitive (zone size ≥17mm).

Figure 3: E-TEST for fluconazole showing MIC ≥64.

Table 3: Percentage of fluconazole resistant candida isolates from our institute.

Species	No. Of resistant strains by DDM No. (%)	Fluconazole MIC > 64 by E-test No. (%)
Candida albicans	4 (14.8)	4 (13.8)
NACA	23 (85.2)	25 (86.2)
Total resistance	27 (23.9)	29 (25.7)

Table 4: Prevalence and scoring of bio- film producing *candida* species.

Species	Isolation	Biofilm produced				Biofilm non producers
	No. (%)	No. (%)	Scoring of biofilm by grading No. (%)			No. (%)
			(+)	(++)	(+++)	
Candida albicans	19 (16.8)	13 (68.4)	4 (30.8)	3(23.1)	6(46.1)	6 (31.6)
Candida tropicalis	45 (39.8)	28 (62.2)	3 (10.7)	9(32.1)	16(57.2)	17 (37.8)
Candida krusei	9 (8.0)	5 (55.6)	1 (20)	1 (20)	3 (60)	4 (44.4)
Candida glabrata	37 (32.7)	20 (54.1)	5 (25)	7 (35)	8 (40)	17 (45.9)
Candida parapsilosis	2 (1.8)	1 (50)	1 (100)	0	0	1(50)
Candida guilliermondii	1 (0.9)	1 (100)	1 (100)	0	0	0
Total	113(100)	68(60.2)	15(22.2)	20(29.4)	33(48.4)	45(39.8)

Table 5: Correlation of biofilm production with foley's catheterization.

Species	Biofilm produced No. (%)	Foley's Catheter	
		Present No. (%)	Absent No. (%)
Candida albicans	13 (19.1)	5 (38.5)	8 (61.5)
Candida tropicalis	28 (41.2)	15 (53.6)	13 (46.4)
Candida krusei	5 (7.3)	3 (60)	2 (40)
Candida glabrata	20 (29.4)	10 (50)	10 (50)
Candida parapsilosis	1 (1.5)	0	1 (100)
Candida guilliermondii	1 (1.5)	0	1 (100)
Total	68 (100)	33 (48.5)	35 (51.5)
Yates chi square = 0.352; df = 5; p = >0.05.			

Table 6: Correlation of biofilm producing *Candida* isolates with their antimicrobial resistance patter.

Species	Biofilm produced No. (%)	Fluconazole resistant No. (%)	Voriconazole resistant No. (%)
Candida albicans	13 (19.1)	2 (15.4)	0
Candida tropicalis	28 (41.2)	6 (21.4)	0
Candida krusei	5 (7.3)	5 (100)	0
Candida glabrata	20 (29.4)	4 (25)	0
Candida parapsilosis	1 (1.5)	1 (100)	0
Candida guilliermondii	1 (1.5)	0	0
Total	68 (100)	18 (26.4)	0

On correlating biofilm producing *Candida* isolates with their antimicrobial sensitivity pattern, 26.4% fluconazole resistance was observed amongst the biofilm producing isolates. The species wise distribution of biofilm producing isolates with fluconazole resistance is shown in Table 6.

DISCUSSION

A marked increase in the incidence of *Candida* associated UTI has also been reported from India, with *C. albicans* as the main species. Novel species of non-*albicans* *Candida* are also emerging as causes of UTI and various

reports have even indicated, the increasing incidence of non- *albicans candida* in fungal opportunistic infections.

Biofilm production has been widely acknowledged as an important component of virulence factors of *Candida* species, because it aids the producing organism, to withstand or evade host defence mechanisms, and it also enables the organism to survive and exist as reservoir of recurrent source of infection, as well as development of resistance to antimicrobial agents. The management of Candidal infections is difficult as it requires an accurate early diagnosis of the strains involved in these infections and selection of appropriate therapy, keeping in view, the rising trend of drug resistance amongst strains of *Candida* species.

The prevalence of *Candida* associated UTI in our study was found to be 2.7% which was close to the reports of Anita Singhal et al, M. Bhatt et al, but lower than Prakash V et al, which may be due to inclusion of only pure candidal growths from the urine samples in our study.[7-9] Characterization of *Candida* species, on the basis of methods used, showed non- *albicans candida* to be more prevalent 94 (83.2%) than *Candida albicans* which were identified in 19 (16.8%) of the total isolates. Among non *albicans Candida*, *C. tropicalis* was found to be the predominant isolate, followed by *C. glabrata* (32.7%), *C. krusei* (8%), *C. parapsilosis* (1.8%) and *C. guilliermondii* (0.9%), respectively.

This shift in epidemiology of *Candida* towards Non albicans group with *C. tropicalis* as the most predominant species has also been reported by other authors like Singh T et al, Pahwa N et al, Malhotra S and Gupta S et al.[10-13] This transition in epidemiology could be due to severe immunosuppression, more exposure to broad spectrum anibiotics, older patients as well as prematurity in infants and extensive use of antimycotic drugs.[14] Also biofilm formation as a virulence factor shows a higher significance for non- *albicans Candida* species than for *C. albicans*, and this ability to form biofilm is intricately linked with the ability of the organisms to adhere, colonize, and subsequently cause infection in susceptible individuals.[15]

The *in vitro*, susceptibility testing of 113 isolates was also performed in the present study by modified Kirby Bauer Disc diffusion method, using two drugs, Fluconazole 25 µg and Voriconazole 1µg, according to CLSI guidelines, M 44-A document to determine an institutional antibiogram of *Candida*. Resistance in 29/113 (25.7%) strains of *Candida* (Table 2) was seen, of which *Candida albicans*, constituted only 1/6th, i.e., 4 out of 29 (14.8%). The distribution of rest 25, resistant NACA species, were *C. tropicalis* (10), *C. glabrata* (6) and *C. krusei* (9). Overall the sensitivity of Candida species including both albicans and non albicans to fluconazole was found to be 74.3% while that of voriconazole as 100%. Shaik N et al, Gupta S and Malhotra S, have also reported sensitivity of Candida species to fluconazole ranging from 63.3% to 95%.[16,13,12] The sensitivity to Voriconazole as recorded by these authors was in the range of 76.6% to 100%. Similar results for fluconazole and voriconazole sensitivity have also been obtained by Padawer D et al from Israel, Alkilani AA et al from Egypt and Khadke S et al from Nepal.[17-19]

Two strains out of 113 (1.8%) isolated *Candida* were found as Susceptible dose dependant (S-DD). All the fluconazole resistant and S-DD isolates were further confirmed by E-test in our study, and it was found that both S-DD isolates proved to be resistant with MIC values >64. Thus, making the overall resistance of Candida species to fluconazole from our institute constituted to be 25.7 % (Table 3).

The resistance to fluconazole is of great concern, because it is the most common azole used for the treatment of candiduria, and also in disseminated candidiasis. It is available in both intravenous and oral formulation with high bio availability and is more cost effective than other antifungal agents. Although, Amphotericin-B is effective against most strains of *Candida* species, it is not the first drug of choice for the treatment of candidemia because of nephrotoxicity associated with it.

In our study no *Candida* isolates were found to be resistant to voriconazole (100% sensitive), and no azole cross resistance was observed. Voriconazole is an expanded spectrum traizole derivative of fluconazole. The drug structurally resembles fluconazole, except for the replacement of one of the triazole ring with a fluorinated pyrimidine, and an additional methyl group.[20] Many authors have evaluated voriconazole activity to be better than that of fluconazole and have considered voriconazole as a better alternative than fluconazole for the primary therapy of candiduria.[21,22]

In the present study one of the virulence traits of *Candida*, *i.e.*, biofilm production was also investigated. Other virulence traits, like gelatinase activity, phospholipase, hemolysis production, cell adherence could not be tested due to resource and time constraint and served as an important limitation of our study. Biofilm production was seen in 68 (60.2%), out of total 113 strains isolated, out of which 13 were *C. albicans* and 55 NACA (Table 4). These biofilms not only serve as a nidus for disease but are also associated with high level antimicrobial resistance. The mechanisms by which *Candida* biofilms resist the functions of antifungal agents are poorly understood, one of the factors being, restricted penetration of antimicrobials caused by exopolymeric material that may act as a barrier to fluconazole penetration in biofilms.[23]

We further assessed biofilm formation, an important trait of *Candida*, with the presence of indwelling Foley's catheter in the sample population. The Foley's catheter gets colonized by the microorganisms to form a bio film on their inner and outer surfaces, once they are inserted.

In our study it was found that out of 68 biofilm producing strains, Foley's catheter was present in 33 (48.5%) of patients. Although a strong correlation of biofilm producing strains with Foley's catheter was observed, on applying chi square test with Yates correction, this association was not found to be statistically significant (p 0.05). Species wise prevalence showed 60% strains of *C. krusei* to be associated with candidal UTI in catheterized patients followed by *C. tropicalis* 53.6%, *C. glabrata* 50% and *C. albicans* 38.5%, respectively.

We also correlated the bio film production to fluconazole resistance by comparative analysis of the sensitive and resistant strains. Of the total, 29 resistant strains of *Candida* 18 (62.1%) were found to be biofilm producers. Of these, 2 (11.1%) were *C. albicans*, 6 (33.3%) *C. tropicalis*, 5 (27.8%) *C. krusei*, 4 (22.2%) *C. glabrata* and 1 (5.6%), *C. parapsilosis*. Amongst the resistant strains which were also bio film producers 35 (51.5%) were (+, 2+) while, 33 (48.5%) (3+) scrorers by visual methods, (Table 5, Table 6). Our results suggest that Fluconazole resistant isolates appear to be more potent bio film producers. Other workers like Mukherjee et al, and Ann M, have also found *Candida* biofilms to be associated with high fluconazole resistance.[23,24]

Thus, biofilm formation serves as an important virulence trait, playing a significant role in the persistence of candidal infection and restricted penetration of antimicrobials, caused by exopolymeric materials. Other causes of resistance due to bio film, may be slow growth rate of microorganism inside biofilm, due to limited nutrition, which in turn affects the susceptibility of microorganism to antimicrobial agent as virtually all antimicrobial agents are more effective in killing rapidly growing cells. Contact induced gene expression leading to acquisition of new properties serves as an additional mechanism by which drug resistance is acquired which could be the underlying mechanism of biofilm production in catheterized patients.

To sum up, in the present study an attempt was made to isolate and characterize *Candida* causing UTI in our region by conventional methods, from all the cases of urinary tract infection attending the OPD's or admitted in our hospital. From the observation made in our study it is evident that, NACA has largely replaced *C. albicans*, as one of the chief causes of fungal UTI. The property of NACA being more resistant to azole along with, strong bio film production, have become a matter of concern and further studies on therapeutic use of new antifungal drugs or combinational antifungal therapy for better management of candidiasis are now required.

CONCLUSION

The increased incidence of non albicans candiduria which are also biofilm producers and resistant to commonly used drug fluconazole is a matter of concern. Biofilms may cause perpetuation of infection in catheterized patients because of their ability to adhere to various medical devices due to which candiduria in catheterized patients have to be interpreted carefully. With the increasing emergence of strains resistant to commonly used azoles, search for new antifungal products with lesser side effects are required.

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