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Original Article

Microbiology Section

Clinico-mycological and Antifungal Susceptibility Profiles of Candiduria in A Tertiary Care Hospital From South India

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ABSTRACT

Introduction: *Candida* is one of the common causative agent of Urinary Tract Infections (UTI) worldwide. The most common reported species causing UTI is *Candida albicans*. Incidence of UTI due to non-albicans *Candida* species. is on rise in recent years because of their better adaptability and increased resistance to antifungals. Susceptibility profile reports of various *Candida* species. to newer azoles like voriconazole and beta-glucan inhibitors (e.g., caspofungin) are deficient in India, since the reference broth microdilution method is not widely utilized. In this study, a rapid reliable and easier alternative, VITEK 2 compact system was utilized to determine the antifungal susceptibility profile.

Aim: To analyse the clinical and mycological profile with determination of drug susceptibility pattern of *Candida* isolates from urine samples.

Materials and Methods: This observational study was conducted in PSG Institute of Medical Sciences and Research, during April to September 2015. *Candida* isolated with a colony count of ≥103 CFU/ml of urine from clinically suspected cases of UTI were included in the study. Urine samples (n=3821) from clinically suspected UTI cases (n=3821) were subjected to microscopic examination and semi quantitative estimation of yeast culture obtained by inoculated of calibrated volume of urine onto blood, Mac-conkey and HiCrome UTI agar. Clinical parameters of the cases were obtained for analysis. Speciation of *Candida* was performed using germ tube test, observation of morphology in corn-meal agar and pigment production in HiChrome *Candida* differential agar. Confirmation of the species identification and anti-fungal susceptibility profile were obtained using VITEK-2 compact system.

Results: Total 101 patients were identified with significant candiduria. Community-Acquired Candiduria (CAC) was seen in 11 (10.8%) of the cases. 23 (22.7%) cases of candiduria were associated with pyuria. Concomitant candidemia was observed in 4 (3.9%) cases of candiduria The most common species identified was *Candida* albicans (n=53, 52.4%). The commonest non-albicans *Candida* species causing significant candiduria cases were *C. glabrata* and *C. tropicalis* (n=18, 17.8% each). The antifungal susceptibility testing revealed an overall 94% susceptibility to amphotericin B, 89% susceptibility to flucytosine, 84% & 88% susceptibility to azoles, fluconazole and voriconazole respectively with 90% susceptibility to caspofungin. Significant high linear correlation existed between fluconazole and voriconazole resistance for *C. glabrata*, *C. albicans* and *C.tropicalis*. [Pearson's correlation coefficient, *C. glabrata* [r =1.00 (p<0.001)], *C. albicans* [r=0.91 (p<0.001)] and *C.tropicalis* [r=0.79 (p<0.001)].

Conclusion: *C. albicans* was found to the commonest species in our Tertiary Care Center in contrast to the reporting of non-*albicans Candida* species as the commonest species in most other recent studies. Determination of the antifungal susceptibility profile showed increasing trend of resistance to most antifungal agents, particularly azoles.

Keywords: Antibacterial agents, Antibiotics, Immunosuppression

INTRODUCTION

Candida species. has been reported as one of the common etiological agent of UTI, especially in a hospital setting. Advances in critical care management, immunosuppression and widespread use of antibacterial agents have led to their increased prevalence. Common risk factors associated with candiduria are extremes of age, diabetes mellitus, females in reproductive age group, structural abnormalities of the urinary tract, broad-spectrum antibiotic use, immunosuppression, indwelling catheters, abdominal surgeries, admission in ICU etc., [1]. Identification and susceptibility testing of the yeast helps targeted therapy of the infection and yields epidemiological

data for assessment of the prevalence and resistance pattern. Fungal UTI are mostly asymptomatic, occasionally can present with upper or lower urinary tract symptoms. Despite the lack of symptoms, increased colonization burden may predispose to invasive candidiasis particularly in debilitated individuals. It necessitates differentiation of asymptomatic and symptomatic candiduria since unnecessary treatment, catheter changes, and hospital prolongation can be avoided, since hospital cost burden and patient morbidity increases substantially. The scenario of presence of yeast in microscopic examination or isolation in culture needs to be evaluated with the clinical picture to determine its relevance and the decision on the commencement of antifungal therapy. Semi-quantitative/ quantitative urine culture is performed in evaluation of significant candiduria and a colony count of ≥1000 CFU/ml of urine, obtained in culture media in most situations represents significant candiduria. Significant candiduria occurs as 2 clinical presentations, asymptomatic and symptomatic candiduria. Patients with symptomatic candiduria need to be started on antifungal therapy, whereas asymptomatic candiduria needs to be interpreted with care. The significance of asymptomatic candiduria arises when the patient is severely debilitated/immunosuppressed, or is planned for urological instrumentation/procedures. Asymptomatic candiduria can also represent a picture of sample contamination (inappropriate collection) or colonization (in catheterized patients). In these cases, evaluating a repeat urine sample rules out contamination and colonization when the repeat sample has been collected after removal of indwelling catheter [2]. The most common reported species causing UTI is *Candida albicans* [3]. Incidence of Non-*albicans Candida* species. (e.g.: *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis* etc.,) causing UTI have been increasingly reported due to enhanced adaptation potential and increased resistance to antifungal agents [4]. In the past few years, there has been emergence of drug-resistance in *Candida* species causing clinical infections, leading to high morbidity and mortality in hospitalized patients [5]. Testing for antifungal drug susceptibility in clinically significant *Candida* species isolates guides prompt treatment thereby improving the patient's outcome. Susceptibility profile reports of various *Candida* species. to newer azoles like voriconazole and beta-glucan inhibitors (eg: caspofungin) are deficient in India, since disc diffusion interpretation guidelines are not available for all antifungals and the reference broth microdilution method is not widely practiced. The VITEK 2 antifungal drug susceptibility determination system has emerged as an easier and an expeditious alternative to the reference broth microdilution method (CLSI and EUCAST) [6]. Studies report 95-100% essential agreement between the results of VITEK 2 and the reference methods [7,8]. This study was undertaken to analyse the clinical and mycological profile with determination of drug susceptibility pattern of *Candida* isolates from urine.

MATERIALS AND METHODS

This was an observational study conducted in PSG Institute of Medical Sciences and Research (PSGIMS&R) during the period April 2015 - September 2015 (6 months). The Institute's ethics committee approval was obtained before the conduct of the study. (IHEC approval number: 15/039).

Inclusion criteria: *Candida* being isolated with a colony count of ≥1000 CFU/ml of urine either in pure culture or as one among the 2 isolates obtained from urine samples collected from clinically suspected cases of urinary tract infection (UTI)/ screening prior to urological instrumentation/intervention of all ages and both sex.

Exclusion criteria: If growth of *Candida* with a colony count of <1000 CFU/ml of urine or when >3 types of growth was obtained.

Urine samples were received in sterile screw capped leak-proof container, immediately transported from the collection center to the microbiology laboratory and stored in refrigerator until further investigations were undertaken. Urine wet mount examination was performed to look for the presence of pus cells, epithelial cells, red blood cells, casts, crystals, budding yeast cells with/without pseudohyphae. The urine samples were inoculated onto blood, mac-conkey and chromogenic media (HiCrome UTI agar, HiMedia Laboratories) by a calibrated wire loop standardized to deliver 5µl for semi-quantitative estimation of yeast growth. The inoculated culture plates were incubated aerobically at 37°C for 24-48 hours. *Candida* isolates with colony count of ≥1000 CFU/ml of urine were considered significant and included in the study. Clinical parameters of the cases were obtained in the case study form which included age, sex, details of admission (outpatient/ ward/ICU), presence/absence of any risk factors like extremes of age (elderly and pre-mature neonates), diabetes mellitus, structural abnormalities of the urinary tract, broad-spectrum antibiotic use in preceeding 30 days, immunosuppression (neutropenia, HIV etc.,), indwelling catheters, abdominal surgeries and admission in ICU etc. Significant candiduria was classified as hospital-acquired and community-acquired. CAC was defined as candiduria observed in outpatients with no prior hospitalization or within 48 hours of hospitalization. When the onset of candiduria is >48 hours of hospitalization, it was classified as Hospital-Acquired Candiduria (HAC) [9]. Preliminary speciation of *Candida* was performed using Germ Tube Test (GTT), observation of morphology in corn-meal agar and pigment production in chromogenic medium (HiChrome *Candida* differential agar, HiMedia Laboratories) [10]. Confirmation of the species identification and anti-fungal susceptibility profile were obtained using VITEK-2 compact system (YST ID and AST card, bioMerieux, Marcy-l'Etoile, France) for the following antibiotics: amphotericin B, flucytosine, fluconazole, voriconazole and caspofungin. The VITEK 2 cards were stored at 2-8°C until testing was performed. An inoculum turbidity equivalent to 2.0 McFarland was prepared in sterile saline as per the manufacturer's instructions using the DensiChek instrument, for antifungal susceptibility testing [11]. *Candida albicans* ATCC 10231 was used as the control

strain for the antifungal susceptibility testing.

STATISTICAL ANALYSIS

The data obtained were analyzed using SPSS software version 19. Fischer' exact/Chi-square test were used for comparative analysis and a p value of ≤0.05 was considered significant. Association/correlation between variables were analysed using Pearson's correlation coefficient (r).

RESULTS

During the study period of April - September 2015 (6 months), 101 patients were identified with significant candiduria. The mean age of the study population was 55.9±16.9 years (Median age-60 years). The age distribution of the study population ranged between 12-89 years and the majority of the candiduria cases (76%) were observed in the 41-80 years age group with a peak observed in the 61-70 years age group [Table/Fig-1]. In the study population, males (n=56, 55.4%) were more commonly affected than females (n=45, 44.6%). Candiduria was observed more commonly in the in-patient wards (n=58, 57.4%), followed by intensive care units (n=32, 31.8%) and outpatient department (n=11, 10.8%).

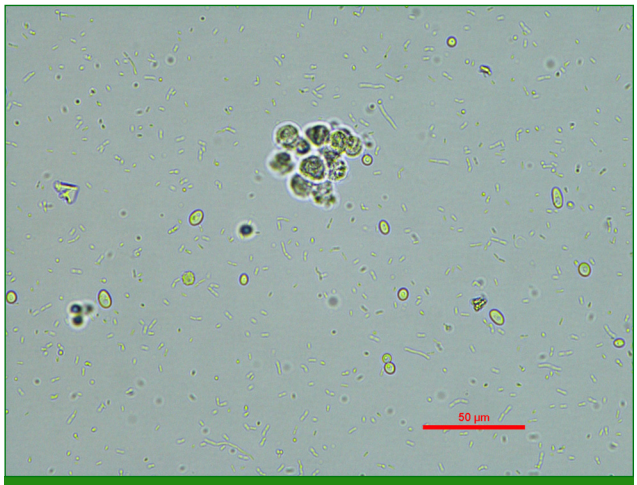
Age Group (in years)	Number (n)
0-10	0
11-20	4
21-30	9
31-40	9
41-50	10
51-60	22
61-70	30
71-80	15
81-90	2

[Table/Fig-1]: Age distribution of the patients with significant candiduria.

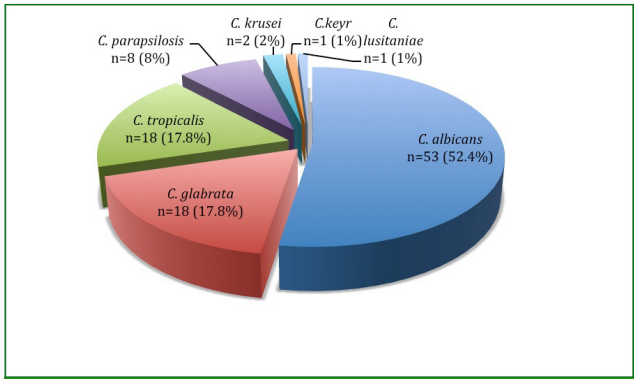
Among the risk factors, the commonest cause was broad-spectrum antibiotic usage (67.3%) followed by indwelling foley's catheterisation (56.4%), diabetes mellitus (16.8%), immunosuppression (13.8%), previous abdominal surgeries (1.9%) and urinary tract structural abnormality (0.9%) [Table/Fig-2]. Among the broad spectrum antibiotics, cephalosporin (68%) and fluroquinolone (32%) were the common antibiotics observed to be used in patients with significant candiduria, in the preceeding 30 days. Pyuria was observed in 23 (22.7%) cases of significant candiduria [Table/Fig-3], while concomitant candidemia was observed in 4 (3.9%) cases. The various species of *Candida* identified in the candiduria cases are depicted in [Table/Fig-4]. The most common species of *Candida* identified was *Candida albicans* (52.4 %). A case of significant candiduria had both *C. albicans* and *Trichosporon* species. The commonest non-*albicans Candida* species causing significant candiduria cases were *C. tropicalis* and *C. glabrata* (18% each).

Risk Factors	Number (n)	Percentage (%)
Diabetes Mellitus	17	16.8
Structural abnormalities of Urinary Tract	1	0.9
Broad Spectrum Antibiotic usage	68	67.3
Immunosuppressive Conditions	14	13.8
Indwelling Foley's Catheter	57	56.4
Underwent Abdominal Surgeries	2	1.9

[Table/Fig-2]: Distribution of risk factors in patients with significant candiduria.



[Table/Fig-3]: Wet mount examination of urine from showing pus cells and budding yeast cells (Magnification – 400X).



[Table/Fig-4]: Frequency of *Candida* species in the study population.

The antifungal susceptibility testing revealed an overall 94% susceptibility to amphotericin B, 89% susceptibility to flucytosine, 84% and 88% susceptibility to azoles, fluconazole and voriconazole respectively with 90% susceptibility to caspofungin. Susceptible-Dose Dependent (SDD) for fluconazole was observed in 5 isolates (9.4%) of *C. albicans*, 2 isolates of *C. glabrata* and *C. tropicalis* (11.1% each). The species-based susceptibility profiles to the antifungal agents tested are provided in [Table/Fig-5]. A significant high linear correlation existed between fluconazole and voriconazole

Candida species	Sensitive									
	Amphotericin B		Flucytosine		Fluconazole		Voriconazole		Caspofungin	
	n	%	n	%	N	%	N	%	N	%
C. albicans	50	94.3	47	88.6	46*	86.7	47	86.7	48	90.5
C. glabrata	17	94	16	88.8	15*	83.3	15	83.8	17	94
C. tropicalis	17	94	16	88.8	15*	83.3	16	88.8	14	77.7
C. parapsilosis	7	87.5	7	87.5	7	87.5	7	87.5	8	100
C. krusei	2	100	2	100	1	50	2	100	2	100
C. kefyr	1	100	1	100	1	100	1	100	1	100
C. lusitaniae	1	100	1	100	1	100	1	100	1	100
All species	95	94	90	89	85	84	89	88	91	90

[Table/Fig-5]: Antifungal susceptibility pattern of the isolated *Candida* species.
* includes susceptible-dose dependent (SDD) isolates

resistance for *C. glabrata* [Pearson correlation coefficient, r =1.00 (p<0.001)], *C. albicans* [r=0.91 (p<0.001)] and *C. tropicalis* [r=0.79 (p<0.001)].

DISCUSSION

Candiduria is a common nosocomial phenomenon and large scale observational surveys reveal *Candida* as the third most common organism isolated from urine in hospitalized patients [12]. During the study period, a total of 101 *Candida* species were isolated from cases of significant candiduria. Candiduria cases proportionally increased with age and were predominantly observed in the 41-80 years age group (76.2%). This observation could be due to the increased prevalence of co-morbid conditions like diabetes mellitus, benign prostatic hypertrophy, immunosuppression, frequent use of broad-spectrum antibiotics and foley's catheter etc. seen in the elderly age group. The median age and age distribution was similar to observational study reports by Nayman Alpat S et al., and Bobade O et al., [13,14].

Males and females were almost equally affected in our study population, whereas most reports from literature show the incidence of candiduria being more common in females [14,15]. Significant candiduria were observed commonly in hospitalized patients (inpatient and ICU settings) probably because of the presence of risk factors like broad spectrum antibiotic use, long term indwelling catheters and also to presence of other debilitating illness like uncontrolled diabetes commonly in the inpatient population than the outpatients. The broad-spectrum antibiotics implicated in cases of significant candiduria cases in our study population were cephalosporins (68%) and fluoroquinolones (32%) use in the preceding 30 days. There are documented reports of use of broad-spectrum antibiotics like cephalosporins attributing to causation of candiduria [16]. CAC was seen in 10.8% of the cases and the risk factors associated were diabetes mellitus, pregnant women and chronic indwelling catheters. Similar risk factors for CAC have been reported by Colodner R et al., [9].

Pyuria is defined as the presence of ≥3 leucocytes/hpf of unspun urine or ≥10 leucocytes per cubic mm of urine or positive dipstick test for leucocyte esterase [17]. In our study, 23 (22.7%) cases of candiduria were associated with pyuria. Pyuria is an important sign of candiduria yet lacks sensitivity and doesn't differentiate colonization from infection (lacks specificity) [18]. Concomitant candidemia was observed in 4 (3.9%) cases of candiduria. Studies report that approximately 1-8% of patients with candiduria particularly ICU admissions may have concomitant candidemia [3,12,19].

The commonest *Candida* species identified in our study was *Candida albicans* (52.4%), while non-*albicans Candida* species attributed to the remaining 47.6% of cases of significant candiduria. Among the non-*albicans Candida* species, *C. glabrata* and *C. tropicalis* were the common species isolated. Earlier multicentric reports on candiduria had similar findings of *Candida albicans* being the commonest species yet recent studies report the emergence of non-*albicans Candida* species as the commonest cause of significant candiduria due to the widespread use of antifungal agents for antifungal prophylaxis and treatment, particularly increasing incidence of *C. glabrata* and *C. krusei* infections which are intrinsically less susceptible to the commonly used azole drug, fluconazole [14,20,21]. Our report suggests relatively lower prevalence of non-*albicans Candida* species, in contrast to reports from other centers in India [22,23].

Analysis of the antifungal susceptibility pattern showed that most isolates were susceptible to amphotericin B. Resistance to the polyene drug, amphotericin B was observed in 6 isolates (6%) (3-*C. albicans*, 1-*C. tropicalis*, 1-*C. glabrata* and 1-*C. parapsilosis*). Increasing resistance was observed for azole group of drugs particularly fluconazole in non-*albicans Candida* species (16.7% for both *C. glabrata* and *C. tropicalis*, 50% for *C. krusei*) when compared to *C. albicans* (13.3%). These drugs (fluconazole and voriconazole) belong to triazole group of azoles and exert their action by inhibiting cytochrome P450-dependent enzyme lanosterol 14 alpha-demethylase. Voriconazole have better activity against *Candida* species (16-32 fold potent than fluconazole) due to effective binding to the cytochrome P450 enzyme. Yet, cross-resistance between fluconazole and voriconazole have been increasingly reported

in *Candida* species, particularly *C. glabrata* [24]. Pfaller et al, (2007) had reported the use of fluconazole as a surrogate marker to predict voriconazole susceptibility in resource-poor settings [25]. In our study, high cross-resistance correlation between azoles was observed in *C. albicans*, *C. glabrata* and *C. tropicalis*. One *C. glabrata* isolate was resistant to three classes of drugs (Polyene, azoles and β-glucan inhibitors). This is of high-concern because azoles and β-glucan inhibitors are increasingly recommended for prophylaxis, thereby leading to selection of drug-resistant non-*albicans Candida* strains [26,27]. The echinocandin, caspofungin had excellent activity against most *Candida* isolates, while 5 isolates of *C. albicans* (9.5%) and 4 isolates of *C. tropicalis* (22.3%) were found to be resistant. This observation predicts that echinocandins like caspofungin and micafungin may emerge in the recent future as the drug of choice for prophylaxis and treatment of cases with symptomatic candiduria.

LIMITATION

The limitation of our study was the lack of genomic characterization of the resistant isolates with MIC correlation and follow-up assessment of clinical/microbiological outcome.

CONCLUSION

This study describes the clinical profile and the distribution of various *Candida* species causing significant candiduria, where *C. albicans* was found to the commonest species in our Tertiary Care Center, in contrast to the reporting of non-*albicans Candida* species as the commonest species in most other recent studies. Although, *C. albicans* was the predominant cause of candiduria, increasing trend towards non-*albicans Candida* species causing significant candiduria was observed. Most health care centers in India do not routinely test for antifungal susceptibility for the clinical isolates due to the laborious phenotypic procedures, lack of expertise and lack of availability of updated interpretative guidelines, thereby leading to lack of drug-resistance data for fungal infections. Newer automated technologies like VITEK 2 compact system have emerged as an effective and promising alternative in determination of antifungal susceptibility thereby guiding prompt treatment and early detection of emerging drug resistance. In our study, antifungal susceptibility profile showed increased resistance to fluconazole and associated cross-resistance to voriconazole in commonly isolated *Candida* species., probably due to their increased usage for prophylaxis and treatment. Newer antifungal drugs like caspofungin and micafungin (echinocandins) are emerging as promising agents for prophylaxis and treatment of symptomatic candiduria. In addition, strengthening the hospital antimicrobial stewardship programs would taper this scenario of widespread drug resistance similar to Multi-Drug Resistant (MDR) bacterial isolates.

Declaration: A part of this study has been presented as a poster at the MICROCON 2015 conference organized by Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Puducherry. (Abstract available at http://microcon2015.co.in/abstracts/free_ePosters/Abstracts/abs-1153.html).

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