



CLINICOMYCOLOGICAL PROFILE OF CANDIDURIA IN SYMPTOMATIC PATIENTS IN A TERTIARY CARE HOSPITAL IN EASTERN INDIA

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ARTICLE INFO

Article History:

Received 10th August, 2021

Received in revised form 2nd

September, 2021

Accepted 26th October, 2021

Published online 28th November, 2021

Key words:

Candiduria, Urosepsis, MODS

ABSTRACT

Introduction: The detection of candiduria among hospitalised patients is not uncommon, but, candiduria in symptomatic patients are often significant. In ICU patients, candiduria is associated with increased mortality. Significant candiduria is presence of $\geq 10^5$ fungal CFU/ml of urine. Early detection and reporting of their susceptibility strongly determines the clinical outcome. **Aims:** To study the distribution of different *Candida* species in symptomatic candiduria patients, their risk factors, their susceptibility and patient's outcome. **Methods:** Midstream, clean catch and catheterized urines in 100 symptomatic patients developing candiduria were tested in R.G.Kar Medical College and hospital for identification of isolates and their susceptibility patterns using conventional techniques. Outcome were observed. **Results:** In 100 symptomatic candiduria patients, predominantly females (66%) and age group 41-60 years (39%) were affected. Broad-spectrum antimicrobials usage (64%) and >5 catheter days (22 out of 30 catheterized patients) were most important risk factors associated. Most of patients were from in-patient wards (57%). *Candida* species isolated were *Candida albicans* (most common-48%), *Candida tropicalis*-45%, *Candida glabrata*-4%, *Candida parapsilosis*-2% and *Candida guilliermondii*-1%. Sensitivities to Voriconazole-87%, Fluconazole-65%, Itraconazole-19% and Amphotericin B-37% of cases. 30% patients subsequently developed candidemia. 90% of patients recovered, 3% died of urosepsis with MODS and rest died due to other causes. **Conclusion:** *Candida albicans* was mostly isolated and Voriconazole was mostly sensitive. Candiduria in symptomatic patients can be an early indicator of an underlying sepsis and routine screening for candiduria should be done in all patients with high risk factors.

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INTRODUCTION

The detection of candiduria among hospitalized patients is not uncommon but candiduria in symptomatic patients are often significant. Asymptomatic candiduria is usually harmless and does not require antifungal therapy. The different risk factors for candiduria includes urinary indwelling catheters, use of broad spectrum antibiotics, diabetes mellitus including those with complications such as diabetic ketoacidosis and hyperosmolar Non-ketotic Coma (HONC), immune suppression, previous abdominal surgeries, urinary tract structural abnormality, history of COVID, prolonged ICU stay, pregnancy and burn wounds. It has been seen, in ICU patients, candiduria is associated with increased mortality. Use of antifungal drugs if required must not replace the correction of underlying risk factors. Unnecessary antimicrobial treatment, catheter changes and prolonged

hospitalization should be avoided, as it increases hospital cost burden and also increases morbidity of patients as eventually the patient is more prone to develop other various hospital acquired infections. Significant candiduria is defined as the presence of 10^5 CFU/ml of urine, though as little as 10^3 CFU/ml can result in disease in certain risk groups^[1]. The significant candiduria can be community acquired candiduria or hospital acquired candiduria^[2]. The most commonly reported *Candida* species causing UTI is *Candida albicans*. However, incidence of non-albicans *Candida* species causing UTI have been increasingly reported due to an increased potential to adapt, biofilm formation^[3] and emergence of resistance to antifungal agents. An early detection of candiduria including its speciation along with their susceptibility patterns in the clinical microbiology laboratory is strongly related to the clinical outcome of the patients. A routine screening for candiduria among high risk patients, even with mild symptoms should be done to establish an early diagnosis and hence prevent development of complications like sepsis. This study was undertaken to observe the distribution of different *Candida* species in symptomatic candiduria patients including

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identification of risk factors, antifungal susceptibility pattern of the isolates and outcome of patients.

MATERIALS AND METHODS

An observational study was conducted after institute level ethical committee approval for two years in randomly selected 100 patients with symptoms of urinary tract infection of all age groups with candiduria in R.G. Kar Medical College and Hospital, Kolkata; following the selection criteria:

Inclusion criteria: *Candida species* being isolated with a colony count of 10^3 CFU/ml of urine in pure culture collected from patients with symptoms of urinary tract infections.

Exclusion criteria: Growth of *Candida species* with a colony count $<10^3$ CFU/ml or where the urine culture shows growth of 2 types of colonies (one colony being *Candida species* , as only pure growth of candida was included).

Midstream, clean catch urine and catheterized urine samples were inoculated on Cysteine Lysine Electrolyte Deficient(CLED) media, growth of yeast was confirmed by gram staining from culture, was re-inoculated in Sabouraud’s Dextrose Agar slants. Wet mount preparation was looked for pus cells, R.B.Cs, yeast cells and pseudohyphae .Yeasts were identified by using Germ tube tests, Cornmeal agar (picture 2.), Chromogenic agar (Picture 1.), sugar assimilation test and sugar fermentation tests. Antifungal susceptibility testing was performed on Mueller Hinton Agar with 2% glucose and 0.5microgm/ml methylene blue using Voriconazole, Fluconazole, Itraconazole and AmphotericinB disks using Disk Diffusion Methods (Picture 3.) as per M60:Method for Antifungal Disk Diffusion Susceptibility Testing of Yeasts [4].Patients details including patients bed number and contact number were collected and they were observed for final clinical outcome.

RESULTS

During the study period of 2 years (2019-21)100 randomly selected patients fulfilling the selection criteria with symptoms of urinary tract infections with or without certain risk factors were detected with significant candiduria. The age distribution of the study population ranged between 0-80 years, and the majority of the candiduria cases were observed in the age group between 41-60 years (39%) [Table 1]. In the study population males were n=34, 34% and females were n=66,66%.Candiduria was observed more commonly in the inpatient wards n=57,57% ,followed by ICU n=7, 7% and outpatient department n=36, 36%.[Figure 2.]

Table 1 Shows number and percentages of candiduria seen in patients of different ages

Age groups (in years)	Male (number, %)	Female (number,%)	Total (number, %)
0-20	n= 7, 7%	n= 11, 11%	n= 18, 18%
21-40	n= 5 , 5%	n= 19, 19%	n= 24, 24%
41-60	n= 11, 11%	n= 25, 25%	n= 36, 36%
61-80	n= 12 , 12%	n= 10, 10%	n= 22, 22%

Several risk factors for developing candiduria were present, observed in our study [Figure1.]. It was observed that use of severalbroad spectrum antibiotics were associated with 64 % (n=64) of cases and the most commonly used drugs were Cephalosporins and Carbapenems (p value=0.00511). Indwelling foley’s catheter was present in 30% (n=30) of

patients ,out of these 30 patients who had indwelling foley’s catheter and developed significant candiduria, about 22 of them had history of number of catheter days of >5 days (p=0.0105),3% (n=3)cases were post COVID patients and many other risk factors.

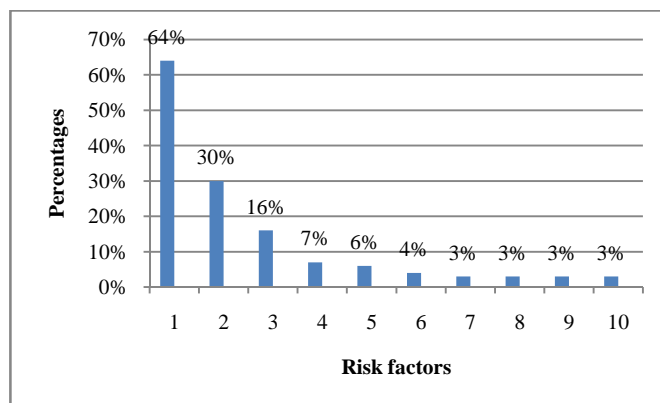


Figure 1 In the Bar chart diagram, 1-Use of broad-spectrum antibiotics ,2-indwelling foley’s catheter ,3-Diabetes with or without complications, 4-ICU patients ,5-immunocompromised patients ,6-Urinary tract structural abnormality ,7-burn patients, 8-postCOVID patients, 9-pregnant patients, 10- Known case of previous abdominal surgeries.

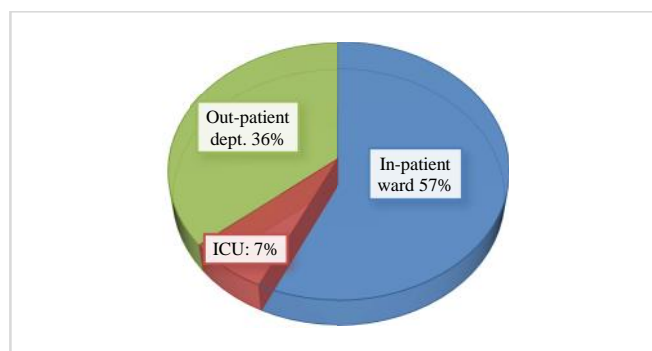


Figure 2 Percentages of patients with symptomatic significant candiduria obtained from In-patient wards, ICU and Out-patient departments.

Table 2 Out of 36 out-patients developing Candiduria, these 7 risk factors were found to be associated.

Risk factors :	Number :	Percentage
1.H/O Vulvovaginal candidiasis, treated with Fluconazole and Doxycycline	n= 11	30.6%
2.Chronically catheterized patients coming for routine OPD check-ups .	n= 10	27.8%
3.Uncontrolled diabetes mellitus	n= 7	19.4%
4.Immunocompromised patients on Chemotherapy or other immunosuppressants	n= 4	11.1%
5.Urinary tract structural abnormality	n= 2	5.5%
6.Post COVID patients	n= 1	2.8%
7.Pregnant patients	n= 1	2.8%
Total	36patients	

Significant pyuria was observed in 52% cases with significant candiduria, significant pyuria is defined as finding of 1 leucocyte per 7 high power fields which corresponds with 10^4 leucocytes per ml and any finding of clearly larger numbers than this [5] .

The most common *Candida species* involved was *Candida albicans* (48%),other species isolated were *Candida tropicalis* (45%),*Candida glabrata* (4%), *Candida parapsilosis* (2%) and *Candida guillermundii*. Antifungal susceptibility testing revealed an overall 87% susceptible to Voriconazole,65% susceptible to Fluconazole,19% susceptible to Itraconazole and 37% susceptible to AmphotericinB. One case of *Candida glabrata* and *Candida tropicalis* were susceptible dose

dependent to Voriconazole and another case of *Candida tropicalis* showed susceptible dose dependent to Itraconazole. The term susceptible dose dependent was described as a drug at usual dose is non-susceptible for an isolate but it can become susceptible either upon increasing dose of the drug or by increasing the dosing frequency^[6].

Table 3 Percentages (%) of drugs susceptible in each *Candida species*

<i>Candida species</i>	Voriconazole	Fluconazole	Itraconazole	Amphotericin B
<i>Candida albicans</i> (n=48)	n=41(85.4%)	n=32(66.6%)	n=8(16.6%)	n=22(45.8%)
<i>Candida tropicalis</i> (n=45)	n=40(88.8%)	n=30(66.6%)	n=8(17.7%)	n=14(31.1%)
<i>Candida glabrata</i> (n=4)	n=3(75%)	n=1(25%)	n=2(50%)	-----
<i>Candida parapsilosis</i> (n=2)	n=2(100%)	n=1(50%)	n=1(50%)	n=1(50%)
<i>Candida guilliermondii</i> (n=1)	n=1(100%)	n=1(100%)	-----	-----

About 30% patients with candiduria, eventually developed candidemia within 3-4 days as evident from culture reports. 90% of patients recovered upon treatment as per the antifungal susceptibility testing reports provided by our clinical microbiology laboratory, 3% died of urosepsis with multi-organ dysfunction syndrome (MODS) and rest died due to other causes.

Statistical analysis

The data obtained were analyzed with the statistical tool R. Fisher’s exact test /one way chi-square test was used for comparative analysis. The tests performed were evaluated at a confidence level of 95% and a p-value of <=0.05 was considered significant. Tests were performed for every factor which were found to be present in patients who developed significant candiduria. On analysis, it was found that for factors like, use of broad spectrum antimicrobials was strongly associated with the risk of developing candiduria, with a p-value =0.00511(p<0.05). Also when analysis of association of presence of number of catheter days >5 days with development of candiduria was done, p value =0.0105 (p<0.05) was found, suggesting strong association between the number of catheter days >5 days with risk of development of significant candiduria. However, for all other risk factors which were present, statistically significant association was not found so, they may or may not be contributory.

DISCUSSION

Candiduria is a common hospital acquired infection and various studies reveal Candiduria as the third most common organisms isolated from urine in hospitalized patients^[2]. During the study period , a total of 100 patients with symptoms of urinary tract infections showing significant candiduria , showed an age preponderance between 41-60 years , predominantly female patients .These results corroborates with another study by S.K. Chaudhary *et al*^[7]. This observation could be due to increased prevalence of risk factors like diabetes mellitus, benign prostatic hyperplasia ,immunosuppression due to multiple causes such as steroid therapy or chemotherapy in this age group or in higher age groups . Female preponderance to candiduria is mainly due to the shorter length of female urethra leading to an increased risk of UTIs.Candiduria was observed in 57% of in-patient wards , 7% ICU patients and 36% outpatients . Multiple risk factors has been found among such patients such as patients with history of use of broad spectrum antimicrobial drugs ,presence of indwelling foley’s catheter among which most of them had

a number of catheter days as >5 days, mixed thermal burns ,patients with prolonged ICU stay, immunocompromised patients ,patients with previous abdominal surgeries, few has urinary tract structural abnormality, diabetic patients especially with some complications like diabetic ketoacidosis, HONC, hyperglycemic hyperosmolar syndrome (HHS), etc., few patients had post COVID status. Increased risk of candiduria in broad spectrum antimicrobial usage is because of altered commensal flora. Similar results were found in a study conducted by M Weinberger *et al*^[8]. The increased risk of development of candiduria by the use of indwelling foley’s catheter was mainly attributed to the capability of *Candida species* to cause biofilm formation. Similar results were found in a study by Goetz, L., Howard M, CIPHERD.*et al* ^[9]. Especially inpatients who’s foley’s catheter been placed for >5 days, were classified as cases of CAUTI (Catheter associated urinary tract infection) as per CDC definition, which defines it is an UTI where an indwelling urinary catheter was in place for >2 calendar days on the date of event , with day of device placement being Day 1^[10] . Increased risk of development of candiduria in post COVID patients can be attributed to the use of steroids in treatment which suppresses immune system and hence predisposes to several opportunistic infections^[11]. So , Corticosteroids should be used judiciously in COVID19^[12]. Other studies have shown the virus SARSCoV2 itself may lead to loss of Bcl-6 expressing T follicular helper cells and germinal centers in COVID 19 disease , leading to weakening of immune system -COVID associated immune amnesia^[13] . Post COVID development of different spectrum of Candida infections have been studied by Amir Arastehfar *et al* showed an increased incidence of candida infections among post COVID patients ^[14]. Pregnancy related symptomatic candiduria was observed in 3 patients, one of them presented with puerperal sepsis, the 2nd patient was a case of placenta previa and the 3rd patient had IUFD with sepsis .The development of symptomatic candiduria in pregnancy can be attributed to the immunologic changes of pregnancy leading to a state of increased susceptibility to certain pathogens , though pregnant women are not immunosuppressed in classic sense^[15]. However a significantly higher percentage of pregnant women having community acquired candiduria was seen in a study by Jack D. Sobel *et al* ^[16]. Presence of a sexually transmitted disease like vulvovaginal candidiasis, which on sexual intercourse promotes migration of Candida infection into bladder leading to cystitis^[17]. Also, in our study it was found that patients with such sexually transmitted disease were prescribed Fluconazole and Doxycycline (a broad-spectrum antibiotic) which might have further increased the risk of developing candiduria .Urinary structural abnormality such as bladder outlet obstruction ,congenital malformations and presence of urinary stones may hamper the natural flow of urine and hence increases urinary stasis in bladder leading to an increased risk of urinary tract infections . In our study, 52% cases of significant candiduria was associated with significant pyuria .Which is in contrary to a study by Dinooop k.p.*et al*, who showed presence of 22.7% patients with significant pyuria among all patients with significant candiduria^[2]. In our study, about 30% patients with candiduria showed development of urosepsis or candidemia within 3-4 days .However, most of them had associated risk factors though initially presented with mild symptoms of urinary tract infection. So, from our study we can derive that detection of significant candiduria in symptomatic patients can be an early indicator of an

underlying sepsis or impending sepsis caused by *Candida species*. Most of the isolates were *Candida albicans* and least commonly found was *Candida guilliermondii*. These findings also corroborates with a study by Siobhan A Turner *et al* which also showed *Candida albicans* as the most commonly isolated species^[18]. Most of the isolates were susceptible to Voriconazole and Itraconazole was found to be least sensitive. Similar findings were seen in another study by Yashvanth *Ret al.*, in which the susceptibilities of Voriconazole was found to be 72.72% and Fluconazole was 66.66%, however, the Amphotericin B susceptibility was much higher in this study as compared to our study^[19]. From a 52 year old lady who had symptom of lower abdominal pain, a highly resistant *Candida albicans* was isolated which was resistant to all the 4 antifungal agents used in our study, later on diagnosed with cystitis with probable pyelonephritis upon imaging and was treated successfully with Caspofungin. As the urine concentrations achieved by echinocandin antifungal agents are low, drugs from this class are excluded from consideration when candiduria treatment is selected^[20]. Though IDSA (Infectious Disease Society Of America) recommends Echinocandins as the first choice of drug for candidemia, this drug is not recommended in Candiduria^[21]. So, in our study Caspofungin was not included. As of now, we do not recommend any antifungal prophylaxis in patients with symptoms of urinary tract infections with or without risk factors, as all the antifungal drugs are toxic, may require therapeutic drug monitoring^[22] and inappropriate and inadequate use of antifungal agents may lead to an increased risk of emergence of drug resistance, as inappropriate use of antifungals forces the fungi to evolve against selective pressure^[23]. Also as asymptomatic candiduria is a common nosocomial phenomenon i.e. common in hospitalized patients, antifungal prophylaxis will lead to their overuse^[24] hence predisposing the patient to unnecessary side effects and drug resistance development.

Limitation: Lack of genomic characterization of the resistant isolates by correlation with MIC of antifungals.

CONCLUSION

In our study, *Candida albicans* was most commonly isolated and there is an increasing trend in the non-albicans candida infections. Voriconazole was mostly susceptible among the isolates and Itraconazole was least susceptible, which implies Itraconazole is not an appropriate choice of drug for treating patients with significant candiduria. From the study we can also conclude that candiduria in symptomatic patients can be an early indicator of underlying sepsis or impending sepsis. So, we recommend routine screening for candiduria in all patients with symptoms of urinary tract infections including high risk patients, even if they have mild symptoms.

Declaration: Part of this study has been presented as a oral poster at the MYCOCON 2021 Conference organized by FISF (Fungal Infection Study Forum).

(Abstract available as poster at mycocon2021.webconvents.com.)

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How to cite this article:

Sharmila Gupta *et al* (2021) 'Clinicomycological Profile Of Candiduria In Symptomatic Patients In A Tertiary Care Hospital In Eastern India', *International Journal of Current Advanced Research*, 10(11), pp. 25462-25466.
DOI: <http://dx.doi.org/10.24327/ijcar.2021.25466.5084>
