Ann Ibd. Pg. Med 2025. Vol.23, No.2 75-82

DETERMINANTS OF CANDIDURIA AMONG HOSPITALIZED PATIENTS WITH URINARY TRACT INFECTIONS AT A TERTIARY HOSPITAL IN SOUTHWESTERN NIGERIA

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Submission Date: 12th Apr., 2025
Date of Acceptance: 24th July, 2025
Publication Date: 31st Aug., 2025

ABSTRACT

***Background*: Candiduria, though often innocuous, may be an indication of invasive or disseminated *Candida* infection necessitating further investigation and therapeutic intervention. This study determined the prevalence of candiduria, the species of *Candida* and factors that predict the presence of candiduria among hospitalized patients with urinary tract infections (UTI).**

***Methods*: A cross-sectional study was conducted on 220 consenting hospitalized adult patients with UTI at the University College Hospital, Ibadan, Oyo State from April 2020 - January 2021. Urine samples were examined microscopically, cultured on supplemented Sabouraud dextrose agar and *Candida* species were identified by microscopy, germ tube test and CHROMagar Candida. Chi-square test was used to identify factors associated with candiduria.**

***Results*: The age range of participants was 18-80 years (mean 44.5±19 years) while the male to female ratio was 1:1.4. About 80% had a history of recent antibiotics, 26% were on catheter, and 3.2% were known diabetics. The prevalence of candiduria was 16.4% and the most common species of *Candida* was *C. albicans* (83%), while the others were *C. krusei*. Candiduria was significantly higher ($p<0.05$) among patients with history of antibiotic use, indwelling urinary catheter, prolonged catheterization and surgical procedures while the elderly age, long duration of admission, and male gender had higher prevalence, but no statistically significant associations.**

***Conclusion*; Candiduria among this population is high and associated mostly with antibiotics use, catheterization, long duration of catheter use and surgical procedures. In addition to limiting antibiotic consumption, urethral catheterization and its duration, we recommend that patients with UTI who are at high risk of developing candiduria should be assessed for its presence to identify those who will benefit from treatment.**

Keywords: Candidiasis, Candida infection, Healthcare associated infections, Fungal infections, Nosocomial infections

INTRODUCTION

Candiduria, defined as the presence of *Candida* spp in urine, is an increasingly common pathology in hospitalized patients.[1] *Candida* is a fungal yeast cell which is found as normal microbiota on the skin and many mucosal surfaces including the gastrointestinal and genitourinary tracts of humans. However, it may transition from this commensal form to an opportunistic pathogen causing local mucosal infections and sometimes, systemic infections with spread to all major organs such as the kidneys.[2] The presence of this fungus in urine may result from colonization of an indwelling urinary catheter or urine sample contamination.[3] It may however be an indicator of a more serious problem such as underlying genitourinary pathology with symptomatic cystitis or a disseminated candida infection or candidemia.[4,5] The source of Candida species may be ascension to the urinary tract through a focus of colonization in the periurethral area or antegrade infection of the urinary tract through the bloodstream route.[5] *Candida* spp readily causes clinical urinary tract infections (UTI) via the hematogenous route, and may also reach the bloodstream from urinary tract albeit infrequently.[6]

Patients with candiduria are often asymptomatic and yeasts may be observed as a chance finding on

urinalysis or urine microscopy and culture. However, some patients, accounting for 5-15% of reported cases, present with symptoms suggestive of UTI.[7] These patients have symptomatic cystitis or pyelonephritis with presentations such as suprapubic discomfort, flank pain, dysuria, haematuria, oliguria and stranguria, often indistinguishable from bacterial genitourinary infections.[7] Candida pyelonephritis may present with fever and candiduria as the only initial indicators of systemic candidiasis in affected patients.[8,9] Thus, the finding of candiduria may be the only pointer to invasive and/or disseminated candida infection.[1,4] Furthermore, in 1-8% of patients with candiduria, an ascending Candida infection may result in candidaemia with associated poor prognosis.[10.11]

Although *C. albicans* is usually the most isolated species causing UTI, the non-albicans Candida, including *C. glabrata, C. krusei (Pichia kudriavzevii), C. tropicalis, C. parapsilosis* and *C. auris* have also been implicated as causative agents.[9] Candida species identification is crucial as cases due to non-albicans species have been increasing and are characterized by high resistance to antifungal agents, especially fluconazole and higher mortality rate.[3,12]

The finding of Candida in urine often represents a diagnostic and therapeutic challenge thus candiduria is one of the most contentious issues in patient management. Controversies exist regarding the indication for treatment of candiduria and even the appropriate treatment options. [7,13] Optimal patient management is marred on one hand by the frequent dismissal of many cases of candiduria as an insignificant finding and on the other hand by overtreatment of patients. [14,15] However, candiduria should be carefully considered, especially in hospitalized patients who have a high risk of candiduria and invasive candidiasis. [3,9]

Previous studies have reported the most common risk factors for candiduria as advanced age, female sex, pregnancy, diabetes mellitus, recent use of antibiotics previous surgery, use of immunosuppressive therapy, prolonged hospitalization, urinary tract abnormalities and urinary tract instrumentation.[8,12] Candiduria is an underlying factor associated with morbidity and mortality among hospitalized patients with immune system compromise and underlying chronic illnesses such as Human Immunodeficiency Virus (HIV) disease, diabetes and renal disease [4,8,12] Infections due to *Candida* spp have increased in the last two decades and are among the principal causes of nosocomial infections.[16] When systemic, these infections can be life threatening particularly among immunosuppressed individuals such as patients undergoing chemotherapy and radiotherapy, Advanced HIV Disease (AHD) and Acquired Immunodeficiency Syndrome (AIDS) patients, organ transplants recipients and patients with chronic morbidities.[17] As the population of immuno-compromised patients continues to increase globally due to improved medical facilities, higher rates of invasive procedures and immune compromising therapies infections, the risk of infection such as Candida UTI and potential systemic dissemination become considerable.[9,16]

There are limited studies in our environment on candiduria and the role of fungal pathogens in hospitalized patients with urinary tract infections. The aim of this study was to determine the prevalence of candiduria among hospitalized patients with Urinary Tract Infections in University College Hospital, Ibadan, Oyo State. We also identified the species of Candida causing candiduria and detected the factors associated with candiduria among these hospitalized patients.

MATERIALS AND METHODS

Study design and population

This descriptive cross-sectional study was carried out at the University College Hospital (UCH), a foremost tertiary health centre which is located in Ibadan North Local government of Oyo State, Nigeria. This 1000-bed capacity hospital serves as a referral centre for the management of both adults and children within the geographical area and beyond. About 75% of the hospital wards are dedicated to the adult population. The study population comprised adult in-patients at the University College Hospital, Ibadan with suspected or diagnosed UTI. Data collection took place from April 2020- January 2021. The minimum sample size was calculated as 213 using the formular for cross-sectional studies and a 16.5% prevalence of candiduria reported in a previous study by Zarei-Mahmoudabadi et al.[12] Inclusion criteria were all adult inpatients aged 18 years and above with a clinical diagnosis of urinary tract infections while patients on antifungal agents were excluded. All consecutive, eligible and consenting hospitalized patients with UTIs were recruited until the required number was obtained.

Ethical considerations

The study was approved by the University of Ibadan/ University College Hospital Ibadan, Ethics Committee with approval number UI/EC/20/0028. Permission was also obtained from the UCH management before data collection. Before recruitment into the study, informed consent was obtained from eligible patients or the care-givers of patients who were too ill to provide informed consent.

Data collection and laboratory processing

An interviewer-administered questionnaire was used to obtain information from hospitalized patients or patients' relatives and nurses where the patient was critically ill and/or unconscious.. The questionnaire was designed to obtain information on sociodemographic such as age and sex and clinical characteristics such as duration of admission, antibiotics use and catheterization.

About 10ml of appropriate urine sample either clean voided mid-stream or catheter specimen urine was collected with the assistance of the nurse on each ward. The samples were aseptically transferred to a sterile universal bottle and immediately sent to the Medical Microbiology laboratory for processing.

Urine sample processing and identification of isolates were done following standard microbiological process for macroscopy, microscopy, and culture. For microscopy the urine specimen was centrifuged at 2000 rpm for 5 minutes and urine sediments examined under high power field. Direct microscopic examination was done, looking for pus cells, blood cells, casts, crystal and yeast cells. A leucocyte count > 5 per high power field was considered significant. Urine samples with pyuria and yeast cells identified on wet mount were well mixed and cultured on Sabouraud dextrose agar and incubated 35^{0}C up to 48 hours. Candida growth was presumptively identified as colonies with white to cream coloured, smooth, glabrous appearance.

Colony counts corresponding to 10^3 CFU\ml or more of catheter specimen and 10^4 or more CFU\ml of midstream urine sample considered as significant. [5] The isolated *Candida* species were identified using Gram stain morphology, germ tube test and Candida CHROMagar appearance.

Data analysis

Data obtained was entered on Microsoft Excel and screened for errors and completeness. Analysis was done using IBM-SPSS version 25 software. Results were presented in tables as frequency counts, and percentage. Chi-square test was used to investigate the association between candiduria and patient demographic and clinical variables. Identified factors were considered statistically significant at $p<0.05$

RESULTS

Demographic characteristics of the participants

A total of 220 hospitalized patients who met the inclusion criteria for participation in the study were screened for candiduria. The ages of participants ranged from 18 to 80 years with a mean age of 44.5±19 years. Eighteen (8.2%) of the participants were below 20 years, 39.5% were between 20-40 years, 25.9% were between 41-60 years and 26.3% were 61 years and above respectively. Majority (57.7%) of the respondents were female and were mostly married (73.2%).. Two percent had no formal education, 57% primary, 7.3% secondary and 35% had tertiary education. Table 1 shows the demographic and clinical characteristics of participants.

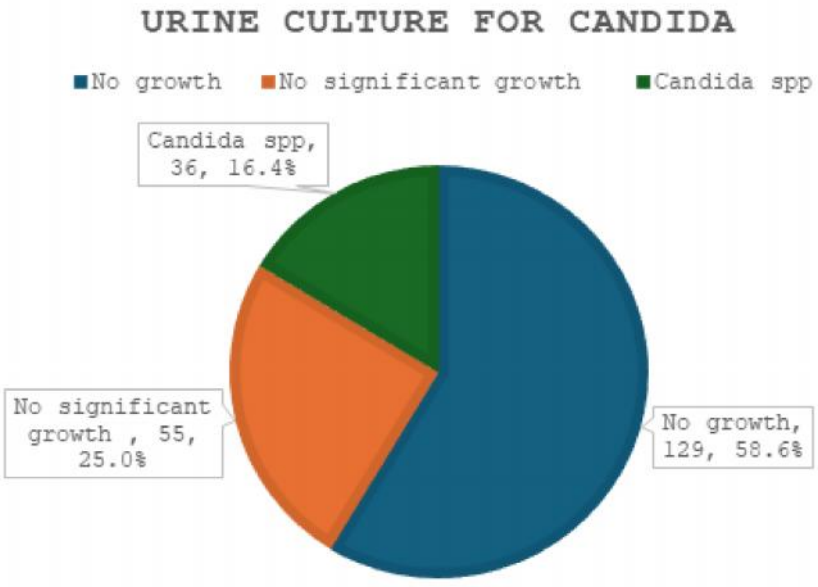

Figure 1: Prevalence of Candida species

** Significant candiduria- colony counts corresponding to ≥10^3 CFU\ml of catheter specimen and ≥10^4 CFU\ml of midstream urine sample*

Prevalence of candiduria

Of the 220 participants recruited, 36 had significant candiduria, giving a candiduria prevalence of 16.4%. Another 55 (25%) of them had candiduria which was non-significant and fungal culture for the remaining 129 (58.6%) yielded no growth (Figure 1). Among the 36 *Candida* species isolated, 30 (83.3%) were *Candida albicans* while the remaining 6 (16.7%) were *C. krusei (Pichia kudriavzevii)*.

Table 1: Demographic and clinical characteristics of participants

Characteristic	Candiduria Yes n(%)	No n(%)	Total
Sex			
Male	17(18.3)	76(81.7)	93(42.3)
Female	19(15)	108(85.)	127(57.7)
Age			
<20 yrs	1(5.5)	17(94.4)	18 (8.2)
20-40 yrs	16 (18.4)	71 (81.6)	87 (39.5)
41-60 years	8 (14.0)	49 (86.0)	57 (25.9)
≥ 61 years	11(19.0)	47(81)	58 (26.3)
Duration of admission			
<14 days	9(13.6)	57(86.4)	66(30)
2-3weeks	16(18)	73(82)	89(40.5)
>3 weeks	11(16.9)	54(83.1)	65(29.5)
History of antibiotics			
Yes	34(19.5)	140(80.5)	174(79.1)
No	2(4.3)	44(95.7)	46(20.9)
History of UTI			
Yes	11(16.2)	57(85.7)	68(30.9)
No	25(16.5)	127(83.5)	152(69.1)
History of Fungal Infection			
Yes	1(14.3)	6(85.7)	7(3.2)
No	35(16.4)	178(83.6)	213(96.8)
History of diabetes			
Yes	1(14.3)	6(85.7)	7(3.2)
No	35(16.4)	178(83.6)	213(96.8)
History of surgical procedures			
Yes	19(30.2)	44(69.8)	63(28.6)
No	17(10.9)	140(89.1)	157(71.4)
History of chemotherapy			
Yes	0(0.0)	1(100)	1(0.5)
No	36(16.4)	184(83.6)	219(99.5)
History of catheterization			
Yes	20(34.5)	38(65.5)	58(26.3)
No	16(9.9)	146(90.1)	162(73.6)
Duration of catheterization (n=58)			
<14days	8(24.2)	25(75.8)	33 (56.9)
2-3 Weeks	7(36.8)	12(63.2)	19 (32.8)
>3 weeks	5(83.3)	1(16.7)	6 (10.3)

Clinical characteristics of all study participants

As shown in Table 1, only a small proportion, accounting for 3.2% of participants were known diabetics. the highest proportion of participants (40.5%) were on admission for 2-3 weeks before the onset of UTI symptoms, while those on admission for less than 2 weeks accounted for 30% of participants. Most participants had received antibiotics (79.1%) and 28.6% had undergone any surgical procedure in the current admission. About a quarter of the patients had history of catheterization and most (56.9%) were on it for less than 14 days. Sixty-eight (30.9%) had a prior episode of UTI and only seven participants (3.2%) had a prior history of any fungal infection.

Demographic and clinical characteristics associated with candiduria.

There was a higher prevalence of candiduria among the male population (18.3% vs 15%) and the older age group >60 years (19% vs 15.4%). Those who had a longer duration of admission ≥14 days, history of

Table 2: Demographic and clinical factors associated with candiduria among patients with urinary tract infections

Characteristic	Candiduria				p-value
	Yes n(%)	No n(%)	Total	X^2	
Sex				0.432	0.511
Male	17 (18.3)	76(81.7)	93(42.3)		
Female	19 (15)	108(85.)	127(57.7)		
Age				0.39	0.532
Younger	25 (15.4)	137 (84.6)	162 (73.6)		
Old	11(19)	47(81)	58 (26.4)		
Duration of admission				0.51	0.474
<14 days	9(13.6)	57(86.4)	66(30)		
≥14 days	27(17.5)	127(82.5)	154(70)		
History of antibiotics				6.14	**0.013**
Yes	34(19.5)	140(80.5)	174(79.1)		
No	2(4.3)	44(95.7)	46(20.9)		
History of UTI				0.05	0.959
Yes	11(16.2)	57(85.7)	68(30.9)		
No	25(16.5)	127(83.5)	152(69.1)		
History of Fungal Infection				0.02	0.879
Yes	1(14.3)	6(85.7)	7(3.2)		
No	35(16.4)	178(83.6)	213(96.8)		
History of Diabetes				0.02	0.879
Yes	1(14.3)	6(85.7)	7(3.2)		
No	35(16.4)	178(83.6)	213(96.8)		
History of surgical procedures				10.9	**<0.001**
Yes	19(30.2)	44(69.8)	63(28.6)		
No	17(10.9)	140(89.1)	157(71.4)		
History of chemotherapy				0.19	0.66
Yes	0(0.0)	1(100)	1(0.5)		
No	36(16.4)	184(83.6)	219(99.5)		
History of Catheterization				18.89	**<0.001**
Yes	20(34.5)	38(65.5)	58(26.3)		
No	16(9.9)	146(90.1)	162(73.6)		
Duration of Catheterization (n=58)				7.92	**0.019**
<14days	8(24.2)	25(75.8)	33 (56.9)		
2-3 Weeks	7(36.8)	12(63.2)	19 (32.8)		
>3 weeks	5(83.3)	1(16.7)	6 (10.3)		

antibiotic use, presence of indwelling urinary catheters, longer duration of catheterization ≥14 days also had a higher prevalence of candiduria. On bivariate analysis, factors which were significantly associated with candiduria ($p<0.05$) were history of antibiotics use (p 0.044), presence of indwelling urinary catheters ($p<0.001$), longer duration of catheterization ≥14 days ($p=0.019$)and surgical procedures ($p<0.001$), No association was observed with age, sex, duration of admission, diabetes,, and prior history of UTI.

DISCUSSION

Candiduria is a common healthcare associated urinary tract infection and is reported to account for 10-30% of nosocomial urinary tract infections with a potential for systemic and bloodstream dissemination, particularly in critically ill patients.[7,12] An increase in the incidence of Candida UTI is also being reported as exemplified by Gajdacs *et al.* who observed a doubling in incidence of candiduria from 5.01 to 10.63% over a 10-year period among their study population.[5] Yismaw *et al.*, documented a similar observation from 0.9 to 2.0 per 1000 patients though the time frame was unspecified.[18] In this study, we found a high prevalence of 16.4% candiduria in our patient population similar to the prevalence of 16.5% reported by Zarei-Mahmoudabadi *et al.*[12] The much lower rates of 4.9% by Konje *et al.* and 9.2% by Fazeli *et al.* (2019) underscore the worrisome high burden of candiduria in our patient population.[19,20] A local study also on prevalence and susceptibility patterns of Candida in urine samples reported a slightly lower prevalence of 12.9%, although the authors did not assess probable risk factors.[21] *Candida albicans* was the predominant specie accounting for over 80% of isolates in our study. *Candida albicans* has remained the most common species

in most study findings. Similar studies from the United States, India and Iran, observed that *C. albicans* was predominant, representing about half to three quarters of the isolates while each of the non-albicans accounted for 2- 18% of the isolates. ,[4,22,23] However, a prominent rise in the prevalence of non-albicans species is being reported globally.[1,3,24]. In some studies, the non-albicans candida were the predominant specie particularly in patients with multiple morbidities or critically ill.[11,17,25] A previous study which showed an increase in the incidence of *C. glabrata* infection suggested that prolonged use of antifungal drugs such as the azoles might be responsible for this trend while others have alluded to its ability to efficiently adapt to urine osmolality, pH and other properties.[4,18] *Candida auris* is one of the most serious emerging non-albicans Candida pathogens and there are several reports of *C. auris* UTI. *Candida auris* dissemination into the bloodstream from a focus such as the urinary tract often results in severe consequences due to its virulence factors, multidrug resistance and potential for causing outbreaks, compounded by difficulty in identification using routine microbiological procedures.[26] Our study found *C. krusei* as the other Candida specie isolated making up 17% of the isolates. Of note is the characteristic intrinsic resistance of *C. krusei* to fluconazole, which is the usual first line of Candida treatment, particularly in resource limited setting as ours. Treatment failure could therefore result if adequate identification is not carried out to guide therapeutic options.

We noted a slightly higher prevalence of candiduria in the male population compared to the female. Though the association was not significant, this finding is contrary to the general higher preponderance for UTI in female population.[25] A probable reason for our finding could be that our population of men had other characteristics that promote the occurrence of candiduria. The highest prevalence of candiduria (19%) occurred within the age group of 61 years and above, inferring a higher risk of candiduria in the elderly individuals in our study population compared to other age groups. Physiologic and morphological changes that result in weakening of cellular immunity with advanced age puts the elderly population at great risk for developing candiduria.[27] In postmenopausal women, changes in the vaginal pH and incontinence from weakening of urethral support, can increase the risk of bacterial UTI, allowing for the fungal colonization and infection during antibiotics therapy.[28] This association, although it was not statistically significant in our study, is in consonance with other reports.

Candida has been reported as the second leading cause of catheter-associated UTI or colonization.[29] In agreement with this, we found a prevalence of 34.5% candiduria among patients who had been catheterized, and this was significantly higher than in patients without such history. Our finding is in keeping with other studies that have reported similar observations of fungal urinary tract infections occurring more frequently in patients with urinary catheters compared to those without it.[24,25] *Candida* is particularly proficient at adhering to indwelling medical devices such as catheters and implants. Such indwelling devices are commonly associated with formation of biofilms which protect the enclosed microorganisms including yeasts.[24] These biofilms therefore make Candida effectively resistant to antifungal agents including Amphotericin B and Fluconazole.[30] Furthermore, we observed that this risk was directly proportional to the duration of catheterization, increasing from 24% to 37% after two weeks while over 80% of patients on catheter for longer than three weeks had candiduria. Patients who have catheter in situ for long periods are thus at very high risk of candiduria. We also report a statistically significant association of candiduria with surgical procedures in index hospitalization. Surgeries, including both urological and non-urological surgical procedures, are recognized risk factors for candiduria.[4,31] Possible reasons for this higher risk could be the greater likelihood of catheterization and antibiotics therapy among patients undergoing surgery compared to other patients.

In the urinary tract, important factors which promote the transition of Candida from yeast to the pathologic hyphal or pseudo hyphal forms are acidic pH and proteinuria. Increased plasma glucose and acidosis from poorly controlled diabetes can create this environment making diabetes an important risk factor for candiduria and as reported by many studies.[11,17,32] Despite these observations, we could not demonstrate an association with diabetes in our study. We presume that this finding is due to the very low number of known diabetics among our study population. A study with a much larger population of diabetic patients is necessary to explore any association. In the index study patients with a history of antibiotics had a significantly higher prevalence of candiduria than those that did not have such history (19.4 vs 4.3%). The role of antibiotics in promoting fungal infections has been documented extensively and our result is in keeping with antibiotics use as an identified risk factor for candiduria.[4,32] From our study, patients with a history of antibiotics had over four times the risk of candiduria compared to those who did not.

It is well established that patients on prolonged hospital stay are more prone to healthcare associated infections which necessitate administration of antibiotics thus promoting overgrowth of fungi.[33] This is more common in tertiary care facilities, particularly in critically ill patients in the Intensive Care Unit (ICU) where the presence of candiduria is regarded as an indicator of increased risk of mortality.[4] In keeping with this observation our study reported a lower percentage of patients who had candiduria within two weeks of admission compared to those who had stayed for more than 2 weeks though the difference was not statistically significant.

One of the limitations of our study is the relatively small sample size thus limiting extensive data analysis and conclusions. We are also unable to generalize our findings to the paediatric population as the study purposively targeted adult population only. Further studies involving larger population size and involvement of children are indicated.

CONCLUSION

Candiduria among this population is high and associated mostly with catheterization and antibiotics use. Unnecessary antibiotic use should be avoided through appropriate antimicrobial stewardship processes. Furthermore, the direct relationship between the duration of catheter use, and candiduria emphasizes the importance of limiting catheterization and its duration. We recommend an assessment for candiduria in patients with UTI who have a high risk of candiduria to identify those who will benefit from treatment. Further studies are needed to fully understand the pathogenesis of candiduria and provide data to inform definitive treatment guidelines.

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