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Species distribution and antifungal susceptibility profile of *Candida spp* isolated from urine of hospitalized patients in Dschang District Hospital, Cameroon

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ABSTRACT

Candiduria refers to the presence of Candida species in urine, It is a common nosocomial infection afflicting the urinary tract. The aim of our study was to determine the prevalence of candiduria in hospitalized patients in Dschang District Hospital, and to evaluate the susceptibility patterns of *Candida spp* isolated from some commonly used antifungal drugs. Midstream urine samples were collected from 122 hospitalized patients at the Dschang District Hospital, then speciation of *Candida* was done based on colony colour on CHROMagar *Candida* medium. Antifungal susceptibility testing of the isolates was performed by the Broth dilution method. A total of 51 isolates of *Candida* species were recovered from 122 urine samples. *Candida albicans* was the most prevalent species 41.2% (21 isolates), followed by *C. parapsilosis* (27.5%), *C. glabrata* (17.6%), *C. krusei* (7.8%) and *C. tropicalis* (5.9%). Antifungal susceptibility test indicated that 100% and 96.1% of the *Candida* isolates were resistant to Amphotericin B and Nystatin respectively. Resistance varied depending on the species and the respective antifungal agents. We can conclude that candiduria is relatively common in hospitalized patients. The isolates were very resistant to polyenes (amphotericin B and nystatin) and most isolates were sensitive to azoles. Therefore, the species identification of *Candida* isolates along with their antifungal susceptibility pattern can help the clinicians in adequate treatment of the patients with candiduria.
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Keywords: Candiduria, *Candida* spp, Hospitalized patients, Antifungal susceptibility.

INTRODUCTION

Candiduria was previously uncommon and largely ignored. Nowadays, *Candida* species have become an increasingly important cause of infections in humans because of the use of invasive devices, immunosuppressive therapy, and broad spectrum antimicrobial agents (Kauffman, 2014; Oubayyou et al., 2016). Since 1980s, there has been a marked increase in opportunistic fungal infections involving the urinary tract, of which *Candida* species are the most prevalent (Wise et al., 2000; Mogtomo et al., 2016). Several studies

indicate that at least 10%–15% of hospital-acquired urinary tract infections (UTIs) are caused by *Candida* species and that the percentage of nosocomial UTIs due to *Candida* species increased from 22% for the period 1986-1989 to almost 40% for the period 1992-1997 (Richards et al., 2000; Kauffman et al., 2000; Olusegun-Joseph et al., 2016). Candiduria is the presence of *Candida* species in urine, particularly in hospitalized patients, especially those in the intensive care units (ICUs) who often have multiple predisposing factors which include; diabetes mellitus, indwelling urinary catheters, exposure to antimicrobial agents, cancer, long hospitalization, sex and age (Kauffman et al., 2011). Candiduria, when not properly diagnosed and treated, can lead to morbidity and mortality (Sangland and Odds, 2002). All *Candida* species are capable of causing UTIs and in many centers worldwide; non-*albicans Candida* (NAC) species have replaced *Candida albicans* as the predominant pathogen. NAC species appear better adapted to the urinary tract environment and are more resistant to antifungal drugs compared with *C. albicans* (Deorukhkar et al., 2014). A study carried out by Lohoue in Yaounde, on candiduria in human immunodeficiency virus (HIV) infected patients, notified that 38 (36.2%) out of 105 patients, comprising 25 females (65.8%) and 13 males (34.2%) had *Candida* species in their urine. *Candida albicans,* a saprophyte of human mucosae, was the most frequently isolated species. Some patients with candiduria were symptomatic, presenting one or several symptoms such as; fever, vulval pruritus, dysuria and severe burning sensation during (Lohoue et al., 2005). The clinical dilemma with fungal infection of the urinary tract is to distinguish between colonization and infection (Bukhary, 2008). The clinical context in this instance is invaluable in making therapeutics decisions. In the west region of Cameroon,

candiduria in hospitalized patients is not closely looked at in general practice, yet it can be the source of disseminated infection in immunosuppressed patients and individuals exposed to the risk factors. In the light of foregoing, we carried out the present study to determine the prevalence of *Candida* species involved UTIs, and their antifungal susceptibility pattern in hospitalized patients in Dschang District Hospital.

MATERIALS AND METHODS
Study design

After receiving an Ethics clearance from the Cameroon Bioethics Initiative (Reference number CBI/340/ERCC/CAMBIN), and an authorization to carry out the study in the hospital from the Director of Dschang District Hospital (Reference: 292/AR/MSP/DRO/DSD/HDD), informed consents were sought and signed by patients from whom the urine samples were collected. Patients were made to understand that the isolates obtained from their urine samples would be used for this study. The urine samples of patients who consented to participate in the study were analyzed for yeasts, at the Laboratory of Microbiology and Antimicrobial Substances (LAMAS) of the Biochemistry Department, University of Dschang. None of the patients used antifungal drugs during the sampling process.

Sample collection and mycological analysis

After cleaning the vulva region (in females) and the tip of the penis (in males) with a dakin solution (antiseptic), midstream urine samples were collected from patients into sterile urine containers in the morning, and maintained at 4 °C during transportation to the laboratory for analysis. One hundred microliters of each uncentrifuged urine sample was cultured on CHROMagar *Candida* (CHROMagar *Candida*®) supplemented with chloramphenicol in petri dishes and incubated

at 25 °C for 48 h. The number of colonies on each petri dish was counted and recorded based on colony colors.

Antifungal susceptibility test

The susceptibility of obtained isolates was tested with four commonly used antifungal agents, namely: fluconazole, nystatin, amphotericin B, and ketoconazole. The minimum inhibitory concentrations (MICs) were determined by means of the broth microdilution technique according to the protocol described by the National Committee for Clinical laboratory Standards (NCCLS, 2002). The number of colonies on each plate were counted and recorded based on colony colors. Since discrepancies in CFU (colony forming unit) criteria to diagnose candiduria have not yet been adequately addressed, the following CFU cut-offs were considered in this study: a quantitative culture with a colony count of ≥10,000 CFU/mL of urine was associated with infection while a colony count of <10,000 CFU/mL of urine was associated with colonization (Wise et al., 2000; Kauffman, 2014). Interpretive breakpoints established by the EUCAST (2008) and Thérèse et al. (2006) were used. They were as follows: ketoconazole: Sensitive (S) ≤ 0.125 μg/ml, Intermediate (I), 0.25–0.5 μg/ml, Resistant (R), ≥ 1 μg/ml; fluconazole (S) ≤ 8μg/ml, (I), 16-32 μg/ml, (R) ≥ 64 μg/ml; amphotericin B and nystatin (S) ≤ 1μg/ml, (I), 2-4 μg/ml, (R) ≥ 1 μg/ml.

RESULTS

In the present study, 122 hospitalized patients in Dschang District Hospital were sampled according to Laurentz formula, 51.6% (63) were females while 48.3% (59) were males. Their ages ranged from 2 to 60 years or more. Most of the hospitalized patients were more than 60 years old and the female gender was most represented. The prevalence of candiduria in the study population was 43.4% (51/122). There were 50.9% females and 40.1% males. We identified five different *Candida* species, namely *C. albicans, C. parapsilosis, C. glabrata, C. krusei* and *C. tropicalis,* present in the urine samples of the hospitalized patients group. *C. albicans* was the most prevalent species 41.2% (21 isolates), followed by *C. parapsilosis* (27.5%), *C. glabrata* (17.6%), *C. krusei* (7.8%) and *C. tropicalis* (5.9%) as shown in Figure 1. It also appears that the non-*albicans Candida* (NAC) species are emerging daily than the *C. albicans* species which has always remained the most prevalent. We had 58.2% of the NAC species against 41.2% of the *C. albicans* species. In our study, candiduria were also more prevalent in patients >60 years of age (27.45%) followed by; 21.57% aged 15- 30 years, 19.61% aged 46-60, 2-15 years and 11.76% of age 31-45 years (Figure 2).

According to the colony counts of the isolates, the *Candida* species isolated from the urine samples of these hospitalized patients were carried out following the standard protocol of colony forming unit per milliliter (CFU/mL of urine). We noticed a variation range of numbers with the different *Candida* species, *C. albicans* was the most prevalent in the range $<10^4$ CFU/mL of urine, seconded by *C. parapsilosis* and followed by *C. glabrata.* In the range of $>10^4$ CFU/mL of urine, *C. parapsilosis* was the most prevalent followed by *C. albicans* and *C. glabrata*. As shown in Figure 3. Regarding the risk factors' distribution in our study, the most prevalent risk factor was previous antibiotic therapy (32.1%), followed by age (18.9%) and diabetes mellitus (15.1%) as shown in Table 1. Concerning the distribution of hospitalized patients in the different departments as shown in Table 2, the majority of the hospitalized patients positive to candiduria were in the surgical ward (50%). *C albicans*, the most species isolated showed MICs values ranged

between 0.125 μg/mL and 2 μg/mL towards ketoconazole and fluconazole as shown in Table 3. All the isolates were very resistant to polyenes (100% of isolates for Amphotericin B and 96.1% of isolates Nystatin) and most isolates were sensitive to azoles with respective percentage of 30.7% for ketoconazole and 19.2% for fluconazole (Table 4). Only one isolate of *Candida tropicalis* was isolated and showed resistance to all the antifungal drugs tested.
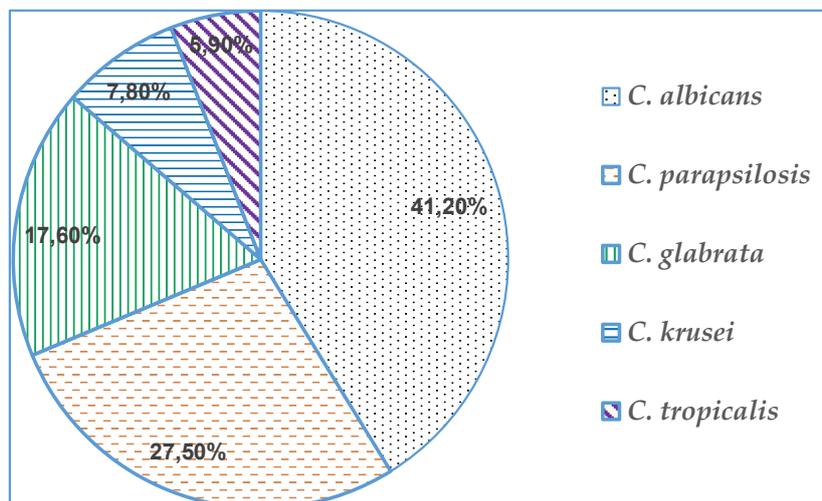

Figure 1: Distribution of *Candida* species identified.
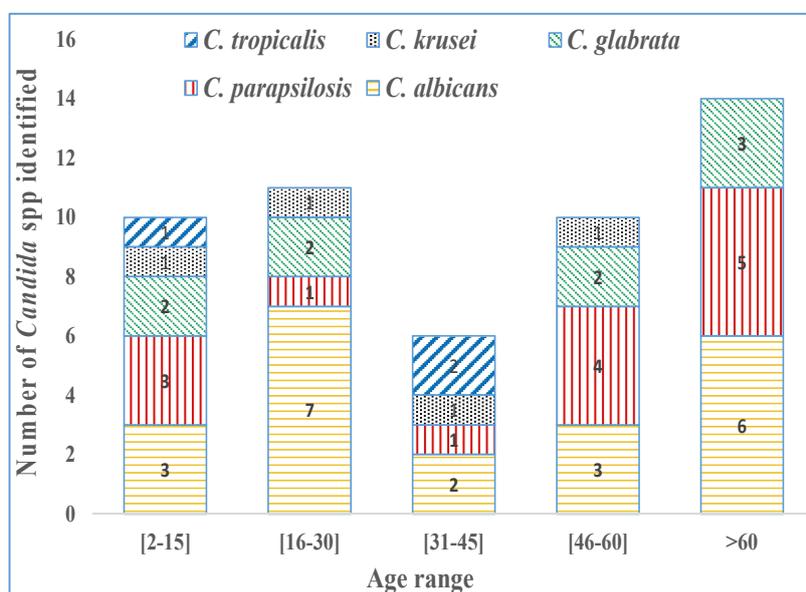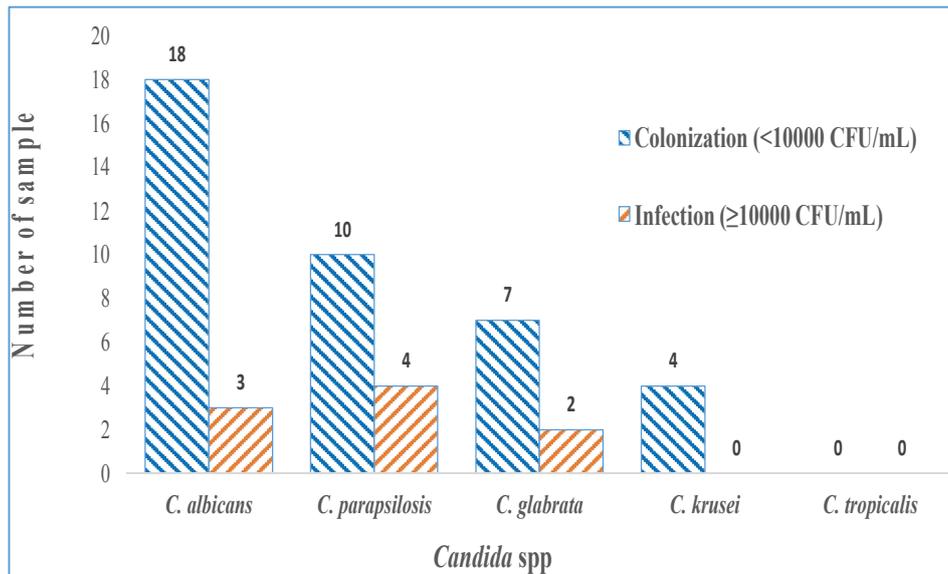

Figure 2: *Candida* species distribution with respect of range age.

Figure 3: *Candida* species distribution according to the colony count.

Table 1: Distribution of candiduria according to the risk factor.

Risk factors	Males	Females	Total
Antibiotic	8	9	17 (32.1%)
Age	6	4	10 (18.9%)
Diabetes mellitus	3	5	8 (15.1%)
Long hospitalization	2	4	6 (11.3%)
Indwelling urinary catheter	5	0	5 (9.4%)
Surgical operation	2	3	5 (9.4%)
HIV-AIDS	0	2	2 (3.8%)

Table 2: Distribution of candiduria in the hospital departments.

Departments	Total number of patients	Number of positive patients	Percentage
Male ward	41	17	41.4%
Female ward	37	18	48.6%
Pediatric	21	5	23.8%
Surgical ward	18	9	50%
Up standing	5	2	40%
Total	**122**	**51**	**41.8%**

Table 3: Minimum inhibitory concentration (MICs) values of antifungals tested on *Candida* spp isolates.

Antifungals		MIC(µg/mL)				
		Ca (n=8)	*Cp (n=7)*	*Cg (n=5)*	*Ck (n=5)*	*Ct (n=1)*
Ketoconazole	Range	0.125-2	0.125-4	34->256	1->256	>256
	GM	0.45	0.74	>12.12	>12.12	>256
Fluconazole	Range	0.125 -2	8-64	1->256	<0.125-2	>256
	GM	17.44	26.25	>111.43	<0.87	>256
Nystatin	Range	4->256	>256	>256	>256	>256
	GM	>14.67	>256	>256	>256	>256
Amphotericin B	Range	>256	>256	>256	>256	>256
	GM	>256	>256	>256	>256	>256

GM: Geometric mean, *Ca: Candida albicans*, *Cp: Candida parapsilosis*, *Cg: Candida glabrata*, *Ck: Candida krusei*, *Cd: Candida dubliniensis,* n=number of isolate tested.

Table 4: Antifungal susceptibility profiles of *Candida* spp identified against ketoconazole, fluconazole, nystatin and amphotericin B.

Antifungals		*Ca* (n=8)	*Cp* (n=7)	*Cg* (n=5)	*Ck* (n=5)	*Ct* (n=1)	Total
Ketoconazole	S	3 (37.7%)	2 (28.5%)	2 (40%)	1 (20%)	0 (0%)	8 (30.7%)
	I	2 (25%)	1 (14.2%)	0 (0%)	1 (20%)	0 (0%)	4 (15.3%)
	R	3 (37.7%)	4 (57.1%)	3(60%)	3 (60%)	1 (100%)	14 (53.8%)
Fluconazole	S	4 (50%)	1 (28.5%)	0 (0%)	0 (0%)	0 (0%)	5 (19.2%)
	I	2 (25%)	3 (42.8%)	2(40%)	2 (40%)	0 (0%)	9 (34.6%)
	R	2 (25%)	3 (42.8%)	3(60%)	3 (60%)	1 (100%)	11 (42.3%)
Nystatin	S	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	I	1(12.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.8%)
	R	7(87.5 %)	7 (100%)	5 (100%)	5 (100%)	1 (100%)	25 (96.1%)
Amphotericin B	S	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	I	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	R	8 (100%)	7 (100%)	5 (100%)	5 (100%)	1(100%)	26 (100%)

S: susceptible, I: intermediate, R: resistant, *Ca: Candida albicans*, *Ck: Candida krusei*, *Cg: Candida glabrata*, *Cp: Candida parapsilosis*, *Cd: Candida dubliniensis,* n=number of isolate tested.

DISCUSSION

This study identified five different species of *Candida* yeasts that cause infections among patients who are hospitalized in Dschang District Hospital. About 41.18% of the culture from sampled patients yielded different species of *Candida*, in which the non-*albicans Candida* were more prevalent than *Candida albicans*. However, several reports show that NAC species, especially *C. tropicalis*, *C. glabrata* and C. *parapsilosis* now predominate in many regions (Kaur et al., 2007). Our study reports a 58.82% prevalence of the non-*albicans* species and a 41.18% prevalence of a*lbicans* species as shown in Table 2, corroborating with the results of many similar previous studies, especially that of Jain et al. (2007). In

this study, candiduria was more prevalent in the age range greater than 60 years (27.7%) followed by 21.57% of age 15-30 years. According to this, candiduria was found to be more frequent in elderly patients. Similar observation was previously made by Hassaneen et al. (2014) who reported a highest percentage of positive cases of candiduria among those in the older age group. Several reports show that the frequency of candiduria in women is more than that in men (Kobayashi et al., 2012) and this corroborated with our study. Candiduria accounted for up to 10% of UTIs and has resulted in increased rate of mortality during the last decades, due to use of new medical instruments, surgery and transplantation (Nayman et al., 2011). According to Weinberger et al. (2003), prolonged hospitalization and long antibiotics use increase candiduria in patients. This correlates with our study in which candiduria was more prevalent in patients who were on antibiotic treatment. These results corroborated with those of Zarei-Mahmoudabadi et al. (2012) who found that he major predisposing factor associated with candiduria was prolonged antibiotic therapy (69.1%). However, there is little or no evidence that supports the fact that systemic antibiotics directly influence *Candida* species proliferation or virulence. It is likely that antibiotics contribute to the colonization by *Candida* species by suppressing endogenous bacterial flora, primarily in the gut and lower genital tract, and possibly, superficial areas adjacent to the urethral meatus (Fisher et al., 1995). The majority of the hospitalized patients positive to candiduria were in the surgical ward (50%). It has been reported that, the most common risk factors for candiduria is in hospitalized patients (Goetz et al., 2010). In this study, 82.35% of patients had colonization. However, 17.64% of diabetic patients had infection which could be due to their increased tissue glucose level, facilitating the

growth of *Candida*. Our finding is close to that reported by Seifi et al. (2013) who found an infection rate of 14.3% in children in Ahvaz.

Antifungal susceptibility profile of the isolates

Antifungal susceptibility of 26 *Candida* yeast isolates to fluconazole, ketoconazole, nystatin and amphotericin B was determined using the broth dilution method. The results showed that the susceptibility of 26 isolates of *Candida* species that were tested against frequently used antifungal drugs has various degrees. The isolates were very resistant to polyenes (amphotericin B and nystatin) and most isolates were sensitive to azoles (fluconazole and ketoconazole). *Candida albicans*, the most species isolated, showed some various degree of susceptibility against azole antifungals tested. Sensitivity to ketoconazole and fluconazole was 37.7%, and 50% respectively with respective geometric mean values of 0.45 µg/mL and 17.44 µg/mL. All the isolates were resistant to amphotericin B. Except for *C albicans* which revealed an intermediate susceptibility against nystatin, all other *Candida* species showed resistance. This observation is uncommon compared with almost all the previously reported studies that indicated some degree of sensitivity to amphotericin B. Although, in a study conducted by Ruan et al. (2008), the resistance was extremely high against amphotericin B in *C. krusei* strains (95%) and in *C. glabrata* strains (53%), in recent years, the low rates of amphotericin B resistance have been reported in the *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei* isolates (Metin et al., 2011; Taj-Aldeen et al., 2014).

Conclusion

In conclusion, the prevalence of candiduria in hospitalized patients at the

Dschang District Hospital was 41.8%, and *C albicans* was the most prevalent yeast isolated. All the isolates showed uncommon high percentage of resistance against polyenes antifungals (amphotericin B and nystatin) and most of the isolates were sensitive to azoles. Therefore, species definition and determination of antifungal susceptibility patterns are recommended for the proper management and treatment of patients at risk for candidiasis. Resistance to antifungal agents is an alarming sign for the emerging common nosocomial fungal infections.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

ISY, FAK and JPD conceived and designed the experiments; AND, IAE and CN performed the experiments; ISY, CN and IAE analyzed the data; AND and CN drafted the manuscript and JPD finalized the paper.

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