

Epidemiology of candiduria and *Candida* urinary tract infections in inpatients and outpatients: results from a 10-year retrospective survey

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Introduction The presence of *Candida* species in urine (candiduria) is a common clinical finding, which may frequently represent colonization or contamination of specimens, however, they may be etiological agents in urinary tract infections (UTIs) or be indicators of underlying pathology in the genitourinary system or disseminated candidaemia. *C. albicans* is the most frequently isolated species of the genus, however, an increase in the occurrence of non-*albicans* *Candida* species (NACS) has been reported, which may be attributable to frequent exposure to fluconazole.

Material and methods The aim of this study was to retrospectively assess and compare the prevalence of candiduria and UTIs caused by *Candida* spp. among inpatients and outpatients at a major clinical center in Hungary, during a 10-year period (2008–2017).

Results Candiduria was detected in 0.11–0.75% of positive samples from outpatients, while this number was significantly higher for inpatients, ranging between 3.49–10.63% ($p < 0.001$). Overall, *C. albicans* was the most frequently isolated species (65.22% in outpatients and 59.64% in inpatients), however, the presence of *C. glabrata* as a relevant etiologic agent (~20–30%) is also noteworthy, because there are corresponding therapeutic consequences.

Conclusions A pronounced female dominance (1.7–2.15-fold), advanced age (~70 years) and hospitalization of affected patients during candiduria is in line with the findings in literature.

Key Words: candida albicans ◊ candiduria ◊ epidemiology ◊ retrospective study
◊ underlying illness ◊ urinary tract infection ◊ yeast

INTRODUCTION

The genus *Candida* – under physiological conditions – exist as saprophytes, colonizing mucosal surfaces and the external genitalia of humans of either gender, but they are present abundantly near the urethral meatus of healthy women of childbearing age [1, 2, 3]. In voided specimens of urine from healthy individuals, *Candida* species can be found in detectable quantities in <1% of cases. However, in a primary care setting, they account for 5% of all positive urine culture results and 10% or more in tertiary-care hospitals and specialized centers [2]. The pres-

ence of *Candida* species in urine (i.e., candiduria), is a common clinical finding, particularly in hospitalized patients, with some reports indicating that as many as 90% of patients with *Candida* urinary tract infections (UTIs) were hospitalized and had a urinary catheter [1, 4, 5, 6]. In adult patients, candiduria may frequently represent colonization or contamination of the specimen, especially if the patient has no symptoms [7]. Nevertheless, clinicians should not dismiss this clinical finding haphazardly, because the presence of yeasts in the urine may very well be due to their etiological significance in UTIs or be indicative of or an underlying pathology in the

genitourinary system (e.g. vulvovaginal candidiasis) [8]. In addition, candiduria may serve as a marker of disseminated candidaemia, which is associated with a crude mortality of 30–40% [9, 10, 11]. Candiduria is defined as 10^4 – 10^5 CFU/ml of yeasts detected from urine, whereas a Candida UTI is mainly characterized by 10^5 < CFU/ml detected, which usually corresponds with the symptoms of the patient [1, 2]. Candida species may ascend to the urinary tract through a colonization focus, either near or directly at the urethra (retrograde infection route), however, they can enter the upper region of the urinary tract through the bloodstream (antegrade infection route) [2]. Risk factors of candiduria and Candida urinary tract infections are well established, and include the female sex, extremes of age, diabetes mellitus, prolonged hospitalization, intensive care unit (ICU) admission, recent use of broad-spectrum antibiotics or immunosuppressants, dysfunction of the bladder and urinary stasis, nephrolithiasis, transplantation, congenital or structural abnormalities of the urinary tract, catheterization and simultaneous bacteriuria or bacterial UTIs [12]. It has been established that HIV-positive women have higher rates of vaginal colonization with Candida, often non-*C. albicans* species [8]. In addition, several studies described the increased colonization levels of Candida species on almost all mucosal surfaces in HIV-positive patients, which (together with the general state of immunosuppression of the patient) will lead to higher levels of manifested Candida infections, including the genitourinary tract [8]. Yeasts generally have poor adherence to bladder mucosa and have no tropism regarding the tissues of the urinary system, therefore the importance of the abovementioned underlying factors (promoting obstruction in the urinary system) in the pathogenesis of candiduria (or funguria in general) is further highlighted [2].

The epidemiology of candiduria and Candida UTIs varies greatly by region, therefore the assessment of local data is essential to evaluate trends over time and to reflect on the national situation compared to international data. The aim of this study was to assess and compare the prevalence of candiduria and UTIs caused by different species of Candida spp. among inpatients and outpatients at the Albert Szent-Györgyi Clinical Center (Szeged, Hungary) retrospectively, during a 10-year study period.

MATERIALS AND METHODS

Study design

The Albert Szent-Györgyi Clinical Center is an 1,820-bed (1,465 active and 355 chronic beds, re-

spectively), primary and tertiary care university-affiliated (University of Szeged) teaching hospital, servicing an urban and rural population in the southeast region of Hungary of about 400,000 people [12]. Candiduria and Candida UTIs were identified retrospectively by reviewing the computerized microbiology records of the Institute of Clinical Microbiology. The data screening included samples taken at inpatient departments and outpatient clinics over a 10-year period (January 2008–December 2017). In addition, patient data was also collected, that were limited to demographic characteristics (age, sex, inpatient/outpatient status) and the indication for sample submission. An episode of candiduria was defined as isolation of Candida spp. from a urine sample of 10^5 CFU/ml or higher on at least one occasion [13]. Isolates were considered separate if they occurred more than 30 days apart or different Candida species were isolated.

Identification of isolates

A total of 10 μ L of each un-centrifuged and homogenized urine sample was cultured on UriSelect agar plates (Bio-Rad, Berkeley, CA, USA) with a calibrated loop, according to the manufacturer's instructions and incubated at $35 \pm 2^\circ\text{C}$ for 24 hours, aerobically. If the pathogen presented in a significant colony count of 10^5 or more CFU/ml and Candida spp. was suspected, a colony was inspected using microscopy (i.e. wet mount) and the plates were passed on for additional processing. Fungal isolates were identified based on colony morphology on Sabouraud Chloramphenicol Agar (Bio-Rad, Berkeley, CA, USA), germ tube production, micromorphology on BD Difco Rice Extract Agar (Becton Dickinson GmbH, Heidelberg, Germany) and BBL CHROMagar Candida (Becton Dickinson GmbH, Heidelberg, Germany). If identification was unsuccessful using phenotypic/biochemical methods, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) was used. Mass spectrometry was performed by the Microflex MALDI Biotyper (Bruker Daltonics, Germany) in positive linear mode across the *m/z* range of 2 to 20 kDa; for each spectrum, 240 laser shots at 60 Hz in groups of 40 shots per sampling area were collected. The MALDI Biotyper RTC 3.1 software (Bruker Daltonics, Germany) and the MALDI Biotyper Library 3.1 were used for spectrum analysis. Antifungal susceptibility testing is not routinely performed from urinary isolates. The following control strains were used for quality control purposes: *Candida albicans* ATCC 14053, *Candida gla-*

brata ATCC 90030, *Candida tropicalis* ATCC 13803, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 14243, *Trichophyton mentagrophytes* ATCC 9533, *Microsporium canis* ATCC 36299, *Cryptococcus neoformans* var. *neoformans* IFM 5844, *Cryptococcus neoformans* var. *gattii* IFM 5845.

Statistical analysis

Statistical analyses were performed with SPSS software version 24 (IBM SPSS Statistics for Windows 24.0, Armonk, NY, IBM Corp.), using the χ^2 -test and Student's t-test. P values below 0.05 were considered statistically significant.

RESULTS

Demographic characteristics, sample types

The median age was 72.01 years (range: 0.30–99.38) in the inpatient group with a female-to-male ratio of 2.15; while in the outpatient group, the median age was 69.74 years (range: 0.03–93.31) with a female-to-male ratio of 1.79. No statistically significant difference was observed between the patient characteristics ($p > 0.05$), however, a predominance of patients over 50 years of age could be noted in both patient groups (75.0% for inpatients and 84.25% for outpatients, respectively). Most (99.8%) of samples from outpatient clinics were voided (midstream) urine, while the majority (87.59%) from the inpatient departments were catheter-specimen urine, midstream urine (12.06%) and samples obtained through suprapubic bladder aspiration (0.3%) were less relevant.

Prevalence and distribution of *Candida* isolates from inpatient and outpatient urine samples

In the 10-year study period, the Institute of Clinical Microbiology received, on average, 2115 positive urine samples/year from outpatient clinics and 1933 positive samples/year from inpatient departments, where a significant urinary pathogen was isolated. Candiduria was detected in 0.11–0.75% of positive urine samples from outpatients, while this number was significantly higher for inpatients, ranging between 3.49–0.63% ($p < 0.001$) (Table 1).

In the outpatient group, urinary tract infection was the indication for sample submission in 19.56% of cases, whereas in the inpatient group, a suspected UTI or a urinary system-related pathology was noted in 6.08% and the suspicion of septicemia in 6.89% as the reason for sample submission. The distribution of species isolated during the study period is presented in Figure 1. The prevalence of *C. albicans* has remained relatively constant throughout the study period; there was no significant change in the ratio of isolation throughout the 10-year period ($p > 0.05$). Overall, *C. albicans* was isolated in 65.22% (outpatients) and 59.64% (inpatients), respectively. It is worth noting that the prevalence of NACS cannot be neglected (especially *C. glabrata* and *C. tropicalis*, accounting for ~20% of outpatient and ~30% of inpatient isolates), although there were no significant changes observed in their frequency of isolation ($p > 0.05$). In a small proportion of samples, *Candida* spp. was isolated together with another urinary tract pathogen (mainly *Escherichia coli* and *Enterococcus faecalis*) or two fungal isolates were present simultaneously (predominantly *C. albicans* with *C. glabrata*)

Table 1. Prevalence of *Candida* spp. in positive urine samples 2008–2017

Year	Outpatients		Inpatients	
	No. of positive urine samples	% of samples with <i>Candida</i> spp.	No. of positive urine samples	% of samples with <i>Candida</i> spp.
2008	1753	0.11%	1478	5.01%
2009	1798	0.22%	1546	3.49%
2010	1887	0.48%	1629	3.81%
2011	1862	0.25%	1818	4.24%
2012	1803	0.28%	1952	4.20%
2013	2005	0.40%	2013	5.51%
2014	2245	0.62%	2250	7.33%
2015	2596	0.65%	2312	6.36%
2016	2544	0.75%	2229	9.60%
2017	2657	0.49%	2098	10.63%
Overall	21 150	0.43% \pm 0.24%*	19 325	6.02% \pm 2.47%*

*represents the 10-year average and standard deviation

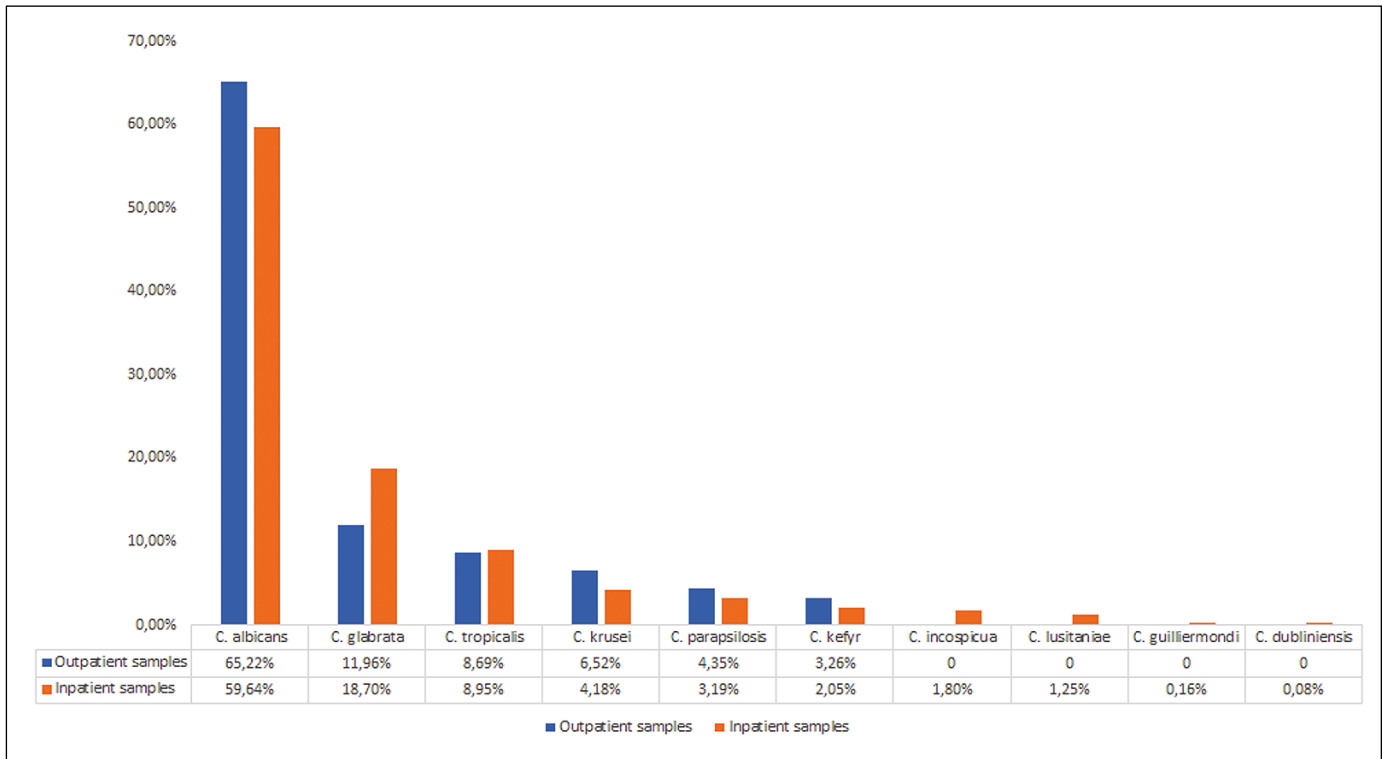


Figure 1. Distribution of *Candida* isolates form inpatient and outpatient samples 2008–2017.

[14]. The frequency of yeast-yeast or yeast-bacteria co-isolation was 4.28% for outpatients and 8.33% for inpatients ($p < 0.033$).

DISCUSSION

Urinary tract infections are a major cause of morbidity and present a considerable economic burden worldwide [15, 16]. The treatment of urinary tract infections (especially in settings where healthcare-related and human resources are scarce) may be based on epidemiological data and empiric antibiotic treatment [17]. This, however, carries the risk of not considering yeasts as probable causative agents of UTIs, which in turn will distort local epidemiological data and more importantly, may hinder the patient in receiving appropriate antimicrobial therapy [18]. Some routine laboratories do not perform the identification or even cultivation of yeasts from urine samples. Many publications indicate that *Candida albicans* is the most frequently isolated species however, an increase in the occurrence of non-*albicans* *Candida* species (NACS) has been reported [3, 18, 19, 20]. The drug of choice for proven *Candida* UTIs is usually fluconazole, because of the advantageous pharmacokinetic parameters (the drug is concentrated in the urine) of this antifungal agent [21]. In con-

trast, other azoles (e.g. itraconazole, voriconazole), flucytosine and amphotericin B are less favorable therapeutic options (both due to pharmacokinetics and adverse events associated with their use) and should be considered in refractory infections with fluconazole-resistant strains [22, 23]. This phenomenon may explain the rise in the isolation of fluconazole non-susceptible NACS (especially *C. glabrata*), which has been linked with prior exposure to fluconazole [19, 24]. Clinicians therefore need to be aware of the etiological role of NACS species (namely *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. guilliermondi*, *C. krusei* and *C. lusitaniae*) as there are therapeutic consequences corresponding with their isolation [17, 22, 26, 27].

Based on the results of this retrospective survey, the most prevalent isolate at our tertiary-care center remains *C. albicans*, however, a noteworthy difference could be observed in the number of different species (5 vs. 10 species) detected in the samples from inpatient and outpatient departments. Hospitalization, a pronounced female dominance (1.7–2.15-times higher) and the advanced age (~70 years) of many affected patients is in line with the findings in literature [3, 5, 6, 7, 12, 18, 27, 29]. The presence of *C. glabrata* as a relevant etiologic agent of urinary tract infections is noteworthy, mainly due to its increasing non-susceptibility to commonly used anti-

fungal agents (acquired resistance is also more and more frequent), most importantly fluconazole [25]. However, the frequency of its isolation was constant between 2008–2017, with no significant increasing tendencies. To the best of our knowledge this is the first and longest-spanning study reporting on the prevalence of candiduria (and UTIs caused by *Candida* spp. by proxy) in Hungary.

Based on our results, a positive urine sample was received by the Institute of Clinical Microbiology every three to four days, where significant growth of *Candida* spp. was detected. In these cases, the continuous communication between physicians and the diagnostic microbiology laboratory is crucial [12]. The role of the laboratory is to supply clinically relevant information in a precise and timely manner, which should be reciprocated by the feedback from the physicians, beginning from the submission of the sample, followed by information regarding the symptoms of the patient and the clinical picture. This way, the microbiologists can also consider the possibility of the isolated yeasts as contaminants or possible causative agents [2, 28, 29].

Some limitations of this study must be acknowledged. Firstly, the presence and nature of symptoms of the patients are unknown, which would be a critical parameter in the differentiation of contamination (although in these cases 10⁵ CFU/ml is rare [2]), colonization and true infection. In addition, due to the inability to access the medical records of the individual patients affected, the correlation between the existence of relevant risk underlying illnesses (e.g., Type 2 diabetes, recent courses of broad-spectrum antibiotics, iatrogenic or disease-related immunosuppression) and candiduria could not be assessed [28, 30]. Furthermore, antifungal susceptibility testing of the isolated *Candida* species was not performed, therefore no information

is presented regarding the resistance trends in the isolated fungal strains [28].

CONCLUSIONS

The aim of the present study was to highlight the incidence of candiduria in a tertiary-care teaching hospital over a long period of surveillance. Candiduria is most common in the nosocomial settings, i.e., in patients with indwelling urinary catheters, previous antibiotic use, abnormality of the genitourinary system, surgical intervention or immunosuppression (even diabetes mellitus); physicians tasked with the care of affected patients need to be aware of this phenomenon. In the majority of cases, candiduria is asymptomatic and antifungal therapy is not required. However, from the clinician's point of view, an individualized approach needs to drive therapeutic decisions. After the validation of candiduria by the microbiology laboratory, the physicians need to stratify by the presence/absence of relevant risk factors (renal functions, involvement of the genitourinary system, immune status). The precise (species-level) identification of *Candida* spp. may become necessary in complicated cases to aid the decision on antifungal therapy, and in addition to evaluate the response of the patient regarding the already administered antifungal drug.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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