Original Article

Candiduria: Prevalence, Identification of Isolated *Candida* Species and Trends in Antifungal Susceptibility in Hospitalized Patients

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Abstract

Background: Urinary tract candidiasis is known as the most frequent nosocomial fungal infection worldwide. Some of the predisposing factors of candiduria are extensive use of broad-spectrum anti-fungal agents, diabetes mellitus, indwelling urinary catheter, corticosteroids and, immunosuppressive drugs. There are some antifungal agents available for the treatment of candiduria. In recent years, resistance to antifungal agents has been increased. The aim of this study was to evaluate different *Candida* species (sp.) that cause candiduria and their susceptibility pattern to antifungal agents in patients admitted to educational hospitals.

Materials and Methods: Urine samples (n=200) were obtained; they were spread onto Sabouraud Dextrose Agar plates. Plates were incubated at 37°C. Only specimens were considered as candiduria, which have a colony count of $\geq 10^4$ CFU/mL colonies. Urine sediment was cultured in the CHROM agar *Candid*a medium and incubated at 35°C for 48h. The cultures were evaluated based on color. PCR-RFLP was performed for a definite identification of *Candida sp*. In vitro antifungal susceptibility test of the *Candida* isolates against amphotericin B, fluconazole and itraconazole was performed using the microdilution method, according to the standard CLSI guidelines, document M27-S3.

Results: Molecular findings confirmed the result of the morphological method. Candiduria rate was 11.5% among our patients. According to CHROM agar *Candid*a and PCR-RFLP, the most common species isolated was *C. albicans* (74%), followed by *C. glabrata* (26%). In vitro susceptibility tests of urinary *Candida* isolates to antifungals have been evaluated. All species were sensitive to amphotericin B. None of *C. glabrata* isolates were sensitive to fluconazole and itraconazole.

Conclusion: This study demonstrates the importance of *Candida* sp. in urine samples from hospitalized patients. It was concluded that *Candida* sp. obtained from candiduria in patients had excellent activity against Amphotericin B. Whereas, resistance against Itraconazole (21.7%) and especially Fluconazole (26%) was significant.

Keywords: Urinary tract infection, Candiduria, *Candida* sp, Antifungal susceptibility, PCR-RFLP

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Introduction

Among microorganisms that cause urinary tract infection (UTI), fungi are responsible for 10% of these infections[1]. The incidence of UTI has increased in recent years due to extensive use of broad-spectrum

anti-microbial agents, corticosteroids, immunosuppressive and cytotoxic drugs[2]. In addition, elderly age, diabetes mellitus and indwelling urinary catheter are some of UTI risk factors[3].

The majority of fungal infections of the urinary tract caused by *Candida* species (sp.)[4]. Although several species of *Candida* (especially, *C. albicans*) are normal flora of the skin and the gastrointestinal and genitourinary and respiratory tracts[5].

Candiduria is a general term for the presence of *Candida* sp. in urine. Candiduria may be related to colonization of *Candida* sp. in urinary tract. Also, invasive infections such as pyelonephritis/cystitis or disseminated candidiasis can cause candiduria[2].

In addition, candiduria was defined as the presence of *Candida* $>10^4$ CFU/mL (colony forming unit/mL of urine). Totally in Iran, the most common etiologic agents of candiduria are *C. albicans, C. glabrata, C. tropicalis, C. krusei, C. parapsilosis, C. kefyr* and *C. lusitaniae*[5].

The aim of this study was to evaluate different *Candida* sp. that cause candiduria in hospitalized patients, identify isolated *Candida* sp. (morphological and molecular) and their susceptibilities to antifungal agents.

Methods

This cross-sectional study was conducted from February 2018-April 2019 on 200 hospitalized patients with raging 15-80 years admitted to educational hospitals affiliated to Shahid Beheshti University of Medical Sciences (SBUMS), Tehran, Iran. The Ethical Committee of Shahid Beheshti University of Medical Sciences approved this study under the code: IR.SBMU.RETECH.REC.1396.342.

In this study, to examine patients regarding candiduria, about 10 mL of urine samples were obtained in sterile urine bottles. The urine samples were spread by the calibrated loop (0.01 mL) onto Sabouraud Dextrose Agar (SDA; Merck, Germany) plates. These plates were supplemented with 100µg/mL of chloramphenicol (Merck, Germany) for colony count. Plates were incubated at 37°C and read them 24 hours later. In this survey, the detection level for quantitative cultures was 100 CFU/mL (colony-forming unit/mL), represented by a single colony of yeast on a plate[6].

After the incubation period, the number of the *Candida* colonies was counted and only specimens were considered as candiduria, which have a colony count of $\geq 10^4$ CFU/mL colonies. The prepared suspension of urine sample was examined by direct microscopic examination after centrifugation (3000 rpm/3min). Then, 20µl of the suspension was cultured on CHROM agar *Candida* medium (bioMérieux, France). The culture media were incubated at 35°C for 48h and evaluated based on color. For each patient, the following data was recorded from the patient's profile: sex, age, antifungal therapy, underlying disease (Diabetes mellitus, malignancy, urinary catheter, steroid, and antimicrobial agents use), and duration of stay in the hospital.

Antifungal susceptibility testing: In vitro antifungal susceptibility test of the *Candida* isolates against some antifungals such as amphotericin B (AMB) (Sigma-Aldrich, USA.), fluconazole (FLU) (Sigma-Aldrich, USA.), and itraconazole (ITR) (Sigma-Aldrich, USA.) was performed. These tests were made using the microdilution method**,** according to the clinical and laboratory standards institute (CLSI, document M27-S3) guideline[7].

Reagent grade powder of FLU, ITR and AMB were obtained from their respective manufacturers. Stock solutions were prepared in water (for fluconazole) or dimethyl sulfoxide (DMSO) (for amphotericin B and itraconazole). Dilution of antifungal drugs was performed with RPMI 1640 medium (Invitrogen, USA) and buffered to pH 7.0 with 0.165M morpholine propane sulfonic acid buffer (MOPS) as described previously (Sigma, USA). The assay was conducted in 96-well round-bottom micro-titer plates. Cell suspensions were prepared in RPMI and were adjusted to give a final inoculum concentration of about 0.5×10^3-2.5×10^3 cells/mL. Then the plates were incubated at 35°C and read after 48 h. Then the minimum inhibitory concentrations (MICs) were determined and compared with a drug-free control. All tests were performed two times. Quality control isolates, *Candida parapsilosis* (ATCC 22019) were included in all runs[8]. MIC against AMB was ≤1µg/mL, which is considered as susceptible and >1µg/mL as resistant. In addition, regarding ITC, MICs ≤ 0.125 and ≥1µg/mL and for FLU, MICs ≤ 2 and ≥ 8µg/mL were considered as susceptible and resistant, respectively.

PCR-RFLP: All isolated strains sub cultured on Sabouraud Dextrose Agar medium (SDA; Merck, Germany) and genomic DNA were extracted using the phenol-chloroform method. Briefly, yeast cells were harvested and lysed adding 0.3g of glass beads (diameter, 0.45 to 0.52mm; Sigma, St. Louis, MO), 300µl of DNA lysis buffer (100mM Tris-HCl, pH 8.0, 2% Triton X-100, 1% sodium dodecyl sulfate, 1mM EDTA), and 300 µl of phenol-chloroform-isoamyl alcohol (PCI) (25:24:1). The mixture was then vortexed for 30 sec and centrifuged at 5,000 rpm for five minutes. The supernatant was collected, 300µl of chloroform was added, and vortexed for few seconds and centrifuged again; then 250µl of ethanol and 25µl of 3M sodium acetate (pH 5.2) were added to the obtained supernatant and incubated for 10 minutes at -20°C. The mixture was then centrifuged at 12,000 rpm for 12 minutes and the pellet was re-suspended in 100µl distilled water as purified DNA and stored at -20 °C until used[9,10].

PCR-RFLP was performed for a definite identification of species as described previously[9,10]. Briefly, PCR amplification was performed using the universal primers ITS1 (forward: 5′-TCCGTAGGTGAACCTGCGG-3′) and ITS4 (reverse: 5′-TCCTCCGCTTATTGATATGC-3′). PCR products were digested by *MspI* restriction enzyme and restriction fragments were separated by 1.8% agarose gel electrophoresis.

Statistical analysis: Statistical analyses were performed using SPSS software version 16.0. The findings were informed using descriptive statistics such as mean and standard deviation or frequency and percentage.

Results

Of the 200 urine samples, in the culture, 23 (11.5%) patients were yielded *Candida sp.* (19 urine samples from ICUs and 4 from other wards). They had a significant candiduria with a colony count of $\geq 10^4$ CFU/mL, however, no bacterial growth was present. The colony count was different from 10^4 to $\geq 10^6$ CFU/mL. It was present in 9 (39%) out of 88 male and 14 (61%) out of 112 female patients. The highest isolation rates of *Candida* sp. were found in age group between 41-60 years (Table 1). The mean age of the study population was 42.7±10.2 years (range 15–80 years).

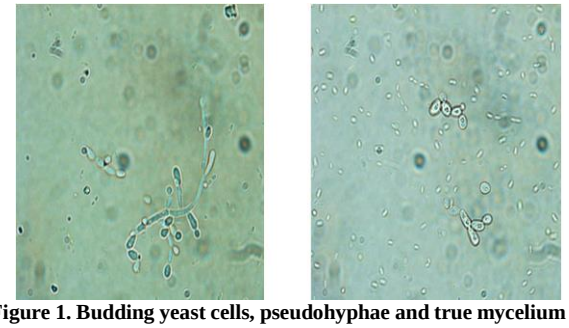

Figure 1. Budding yeast cells, pseudohyphae and true mycelium of *Candida albicans* (A), and Budding, small yeast cells of *Candida glabrata* (B), in direct examination of urine sediment (×400).

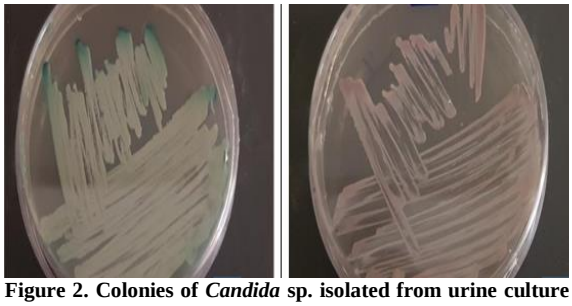

Figure 2. Colonies of *Candida* sp. isolated from urine culture on CHROM agar *Candida*. (A) Light green colonies of *Candida albicans*. (B) cream to white colonies of *Candida glabrata*.

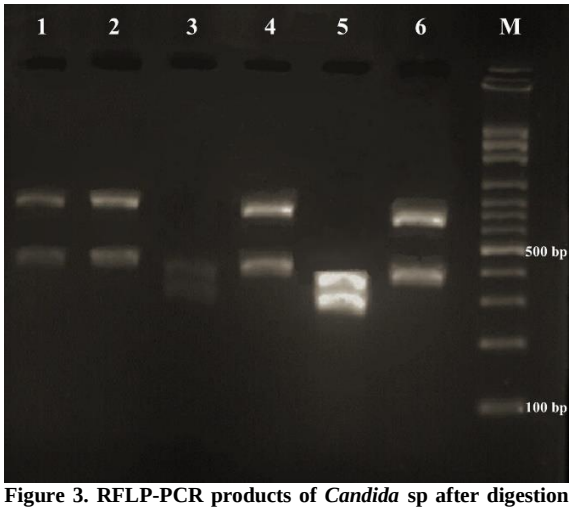

Figure 3. RFLP-PCR products of *Candida* sp after digestion with the enzyme *MspI*. Lane M is 100bp DNA size marker, Lane1 (1, 2, 4, 6) are *C. glabrata* (314 and 557 bp), Lane3 is *C. albicans* (238 and 297bp), Lane5 is *C. albicans* (ATCC 12261).

None of the patients received antifungal drugs for prophylaxis or treatment. The length of hospitalization before candiduria was higher than seven days for 83% (19/23) of the patients.

Underlying conditions in patients (n=23, 100%) were include: diabetes mellitus (n=21, 91%), urinary catheter (n=18, 78%), steroid and antibiotic use (n=11, 48%), and malignancy (n=8, 34%). The most common risk

Table 1: Age and Gender distribution of *Candida* isolates.

Age group (year)	1-20	21-40	41-60	>60	Total
Male	1	2	4	2	9 (39%)
Female	1	4	7	2	14 (61%)
Total	2	6	11	4	23 (100)

factors were diabetes mellitus (91%).

Direct examination showed ovoid shaped yeast cells, budding cells (3-15µm), pseudohyphae and true mycelium in the sediment of the urine (Figure 1).

The colonies were recognized based on the color of the colonies produced by the *Candida* sp. on the CHROMagar *Candida* incubated at 35 °C for 48h. Light green colonies were *C. albicans* and cream to white colonies were *C. glabrata* (Figure 2)[11].

Using PCR-RFLP method, the most common species isolated was *C. albicans* (n = 17, 74%), followed by *C. glabrata* (n = 6, 26%) (Table 2). Molecular findings confirmed the result of morphological method.

MIC ranges, MIC50/MIC90 values of antifungal agents for urinary *Candida* isolates are shown in Table 2.

Discussion

Candiduria is explained as the presence of more than 10^4 CFU/mL of the *Candida* sp. in the urinary system with different forms, asymptomatic form to clinical sepsis. This study had evaluated candiduria among 200 hospitalized patients admitted to educational hospitals of Shahid Beheshti University of Medical Sciences (SBUMS).To the best of our knowledge, this was the first report on evaluation the antifungal susceptibility pattern of *Candida* sp. isolated from urine against AMB, FLU, ITC by CLSI guideline. In Iran, there are only two studies on susceptibility pattern of *Candida* species obtained from patients with candiduria using other methods[12,13].

Epidemiological studies in Iran showed that the mean prevalence of candiduria was around 16.5%.

Table 2: In vitro susceptibilities of urinary *Candida* isolates to fluconazole, Itraconazole and amphotericin B.

Species (n)	Antifungal agents	Susceptible (n)	Intermediate (n)	Resistant (n)	Range (24 h) (µg/mL)	MIC50/MIC90 (24 h) (µg/mL)
C. albicans (17)	FLU	13	2	2	0.125-32	1/16
	ITC	7	8	2	0.0625-2	0.5/2
	AMB	17	-	-	0.25-0.5	0.25/0.5
C. glabrata (6)	FLU	-	2	4	4-32	16/32
	ITC	-	3	3	0.25-0.5	0.5/2
	AMB	6	-	-	0.25-0.5	0.5/0.5

Table 3: Overview of six reported articles of candiduria in Iran (2009-2018).

Number of references	**Publication year**	**Location**		**Frequency (among candiduria patients)**		**Frequency in wards**	**Identification method**	**Predisposing factor**	**Classification**	**Anti fungal therapy sensitivity ***	**Susceptibility method**
	***	City	Hospital or ward	Male	Female	Overall	***	Sorted respectively	Sorted respectively	***	
[19]	**2009**	Ahvaz	Golestan/ urology	65.8%	34.2%	15.6%	-Morphology -germ tube production	**Not mentioned**	*C.albicans* (65.8%) C.glabrata (21%) *C.tropicalis* (7.9%) *C.parapsilosis* (5.3%) *C.krusei* (2.6%)	**Not mentioned**	**Not mentioned**
[14]	**2011**	Zanjan	Valiasr/ mousavi/ ICU	44.8%	55.2%	26.4%	-direct microscopic examination	Age Urinary tract catheterization antibiotic therapy Diabetes mellitus	*C.albicans* (34.3%) *C.tropicalis*(31.4%) *C.glabrata* (20%) *C.lusitaniae* (5.7%) *C.kefyr* (5.7%) *C.parapsilosis* (2.9%)	**Not mentioned**	**Not mentioned**
[20]	**2012**	Ahvaz	Emam khomeini/ Golestan	50.5%	49.5%	16.5%	-Morphology -germ tube production	Antibiotic therapy	*C.albicans* (53.3%). *C.glabrata* (24.4%). *C.tropicalis* (3.7%). *C.krusei* (2.2%). Non-*candida sp*. (0.7%)	**Not mentioned**	**Not mentioned**
[26]	**2013**	Ahvaz	Educational hospitals	**Not mentioned**			Routine methods (not mentioned)	**Not mentioned**	*C.albicans* (62.3%) *C.glabrata* (26.8%) *C.tropicalis* (4.3%) *C.krusei* (1.1%) Other *candida sp* (4.3%)	Sensitive to econazole	**Disc diffusion**
[21]	**2014**	Tehran	ICUs/ urology	68%	32%	4.3%	-Morphology -germ tube production *	Antibiotic therapy	*C.albicans* (72%) NAC (28%)	**Not mentioned**	**Not mentioned**
[15]	**2015**	Ahvaz	ICU/ urology	46%	54%	41.7%	-Morphology -germ tube production	Not mentioned	*C.albicans* (46%) *C.glanrata* (24%) *C.tropicalis* (16%) *C.krusei* (14%)	Sensitive to Capsofungin posaconazole	**Serial dilution based on CLSI protocol**
[16]	**2016**	Isfahan	Not mentioned	5%	95%	2.5%	PCR-RFLP	Diabetes UTI Kidney stone	*C.glabrata* (41.3%) *C.albicans* (35%) *C.krusei* (10%) *C.parapsilosis* (6.3%) *C.kefyr* (6.3%) *C.tropicalis* (1.2%)	**Not mentioned**	**Not mentioned**

[17]	**2016**	Isfahan	Alzhara /khorshid	41.9%	59.1%	12.7%	PCR-RFLP	Renal transplant	*C.albicans* (44%) *C.glabrata* (26%) *C.tropicalis* (11%) *C.krusei* (8%) *C.parapsilosis* Complex (5%) Mixed infection (7%)	**Not mentioned**	**Not mentioned**
[18]	**2017**	Tehran	Labafinejad /nephrology	35.7%	64.3%	26.4%	PCR-RFLP	Not mentioned	*C.glabrata* (42.8%) *C.albicans* (24.2%) *C.krusei* (21.4%) *C.tropicalis* (7.2%) *C.parapsilosis* (7.2%)	**Not mentioned**	**Not mentioned**
[13]	**2018**	Mashhad	Diabetes care unit of health center	12.5%	87.5%	10%	MALDI TOF MS	Type 2 Diabetes	*C.albicans* (46.4%) *C.glabrata* (42.8%) *C.kefyr* (7.2%) *C.krusei* (3.6%)	**Not mentioned**	**Not mentioned**
Current study	2019	Tehran	Educational hospitals	44%	56%	11.5%	**- Morphology** PCR-RFLP	Diabetes mellitus Urinary tract catheterization antibiotic therapy Malignancies	*C.albicans* (74%) *C.glabrata* (26%)	**Sensitive to Amphotirici n B**	**Serial dilution based on CLSI protocol M27-S3**

The highest was in Qazvin (32.3%) and lowest in Khuzestan (5.2%) provineces[5,14]. Our finding showed candiduria in women (61%) was more than men (39%). This difference may be caused by the anatomical status of the urinary system in women, vaginal infections and its proximity to anus[15]. Our results support similar studies conducted in Iran that showed a higher rate of candiduria among females than males[12,15-19]. Although some studies indicated higher rate among males[5,20-22].

The most common predisposing factor among patients was diabetes mellitus (91%) followed by urinary catheters (78%). Because of the glycosuria caused by diabetes, urinary yeast growth increases. Consequently, diabetes may influence women by candiduria due to *Candida* colonization of the vulvovestibular zone[23].

The use of prolonged urinary catheters has been studied to be significant risk factors for candiduria. The colony counts more than 10^5 CFU/mL, are usually associated with prolonged urinary catheters[24].

Another risk factor was steroid and antibiotic use. It seems that prolonged antibiotic use facilitates colonization by *Candida* sp. and this contribution may suppress endogenous bacterial flora[1]. The effect of the use of steroid and antibiotic has been documented in the literature[25,26].

In the present study, *C. albicans* was the most common (74%) isolated species from urine samples followed by *C. glabrata* (26%). In similar studies reported in Iran, *C.albicans* was the most common cause of candiduria among all *Candida* sp.[12,13,15,16,18,20-22]. Whereas, some other studies were performed in Iran, identify *C. glabrata* as the most common cause of candiduria among patients[17,19].

Recently, *Candida non-albicans* was highly dominant in the urine, this tendency probably relates to the complex chemical composition of the urine (like pH)[26].

Candiduria may refer to colonization and does not need treatment, also UTI can lead to renal candidiasis and pyelonephritis [4].

The first step is the diagnosis of candidal UTI. Urine contamination or infection of the sample can be a problem. There is no standard definition for detecting candidal UTIs directly; therefore, the first positive urine culture was repeated to document an accuracy of results. UTI patients are

classified as either asymptomatic or symptomatic cas es.

In the case of symptomatic, antibiotic treatment was administered parallel with an antifungal drug like FLU. Symptomatic candiduria is seen in patients with cystitis, epididymorchitis, prostatitis, pyelonephritis, and renal candidiasis. For this reason, systemic treatment with antifungals is recommended in high-risk patients. However, the majority of people with candiduria are asymptomatic[27-29]. In this survey, asymptomatic candiduria is seen in all of the patients (n=23). Some studies have indicated that the mortality rate among candiduric patients was reported about 26% and candiduria among the critical patients can be a sign of disseminated infection, especially candidemia. Candidemia occurred among patients with asymptomatic candiduria in several studies[1,6,30].

In recent years, the prevalence of candiduria has increased among hospitalized patients. Due to the extensive use of antifungal agents in hospitals, resistant fungal strains have become a challenge for clinicians. In our study, we survey the susceptibility of *C. albicans* and *C. glabrata* to FLU, ITC and AMB. Due to safety, the pharmacokinetic and pharmacodynamic profile of FLU, it is a common choice for treatment of *Candida* UTIs[13,31,32].

AMB is another choice for Candiduria which is recommended only for infection is caused by FLU-resistant strains[33]. Due to the toxicity of AMB, consumption is limited for all clinical forms of candiduria[34,35]. In addition, ITC is antifungal medications used for a variety of fungal infections. We found that FLU and ITC resistance rates of *C. albicans* were 11.7%. All *Candida sp.* were sensitive to AMB. Zarei et al. reported that the most number of *C. albicans* were resistant to FLU and completely susceptible to ITC and AMB[13].

C. glabrata infections are often resistant to many azole antifungal agents, especially FLU; therefore, this infection is difficult to treat. Some similar works indicated that, compared to other *Candida sp.* (especially *C. albicans*) *C. glabrata* isolates tend to be associated with higher MICs of all azoles and are innately less susceptible to all antifungal agents including AMB[36,37].

In our study, relatively high levels of resistance to azole (58%) were found in isolates of *C. glabrata*. This species may be intrinsically resistant to FLU, thus urinary tract infections caused by *C. glabrata* are the most difficult to treat. Research has also demonstrated that different outcomes with *C. glabrata* may reflect the high doses of and prolonged therapy with FLU. It is suggested that susceptibility testing should be performed in this situation.

The result of our susceptibility test showed that none of *C. glabrata* species were sensitive to FLU and ITC. Interestingly, all *C. glabrata* were sensitive to AMB. In contrast to Zarei et al. that found 64% of this species were not sensitive to AMB. They reported that resistance rate of *C. glabrata* to ITC was 0%[20]. The increase of *C. glabrata*, due to the resistance to azoles brings up the importance of typing of all *Candida* sp. recovered in urine from patients.

Conclusion

Our observations indicate that candiduria prevalence was 11.5% among patients. The most common species isolated from urine samples was *C. albicans* followed by *C. glabrata*. Although, studies have been conducted on candiduria in the world, but there have been some articles on this issue in Iran (Table 3).

Further studies on a much larger scale needed to provide more information on various *Candida* sp. causing urinary tract infection and their antifungal susceptibility pattern in this region. Hence, information that is more comprehensive will help in an accurate treatment of candiduria.

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