



Candida Urinary Tract Infection Among ICU Patients in Isfahan, Iran

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Abstract

Background: Urinary tract infection (UTI) is a common disease in hospitalized patients with indwelling devices especially in the intensive care units (ICUs). *Candida* species are the etiologic agents of 20% - 25% of UTI in ICUs, and the most common organisms after *Escherichia coli*. Although fungal UTIs are clearly rare in comparison with bacterial UTIs, however there has been an increase in the prevalence of *Candida* species since 1980s. Despite *Candida albicans* being a main etiologic agent of fungal UTI, non-*albicans* *Candida* species (NACs) such as *C. krusei*, and *C. glabrata*, are repeatedly isolated from clinical samples. Identification of *Candida* to the species level is crucial due to expanding resistance of NACs to the antifungal agents.

Objectives: The present study aimed to identify the causative agents of fungal UTI among hospitalized patients at the ICU ward of Al-Zahra university hospital in Isfahan, Iran.

Methods: From March 2017 to October 2018, 100 ICU patients with positive urine cultures of *Candida* species were registered in Isfahan, Iran. All clinical isolates were sub-cultured on sabouraud dextrose agar, and CHROMagar *Candida* media and incubated at 37°C for 48 hours. Molecular identification was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique using specific primers.

Results: *Candida albicans* was the most prevalent species among clinical isolates (94%) followed by *Candida tropicalis* (4%), *Candida glabrata* (1%), and *Candida parapsilosis* (1%). Most patients belonged to the age range of 71 - 80. Diabetes mellitus and neutropenia were the main risk factors among patients.

Conclusions: Since *Candida albicans* was the most prevalent species in the present study, and due to its various sensitivities to antifungal agents, antifungal susceptibility testing for clinical isolates is recommended for better management of *Candida* UTI.

Keywords: *Candida*, Urinary Tract Infection, Intensive Care Units

1. Background

Candida species mainly *Candida albicans* are the causative agents of up to 20% - 25% of urinary tract infection (UTI) in intensive care units (ICUs), and the most common organisms after *Escherichia coli* (*E. coli*) (1). They can cause a range of infections from non-life threatening mucocutaneous diseases to life-threatening invasive and disseminated infections (2, 3). The entrance of *Candida* spp. to the urine (candiduria), is typically symptomless and has no features to indicate UTI (4). Candiduria is more common in hospitalized patients with indwelling devices and especially those in ICUs. Fungal UTIs are clearly rare in comparison with bacterial UTIs, however there has been an increase in the prevalence of *Candida* spp. causing UTIs since 1980s (5). *Candida* species present in the urinary tract via the climbing route, from the urethra to the bladder, and hematogenous dissemination by filtration of *Candida*

spp. in kidneys and excretion to the urine (6). Urinary tract instrumentation, prolonged hospitalized stay, widespread antibiotic consumption, extremes of age, corticosteroid therapy, organ transplantation, female gender, diabetes mellitus, and use of immunosuppressive agents are the most predisposing factors (7). *Candida albicans* is the most prevalent etiologic agent for UTI however non-*albicans* *Candida* species (NACs) such as *C. tropicalis*, *C. krusei*, *C. glabrata*, and *C. parapsilosis* are also isolated from UTIs (8-10).

2. Objectives

The aim of the present study was to identify the etiologic agents of *Candida* UTI among hospitalized patients at the ICU ward of Al-Zahra university hospital in Isfahan, Iran.

3. Methods

3.1. Inclusion Criteria

Patients with pyuria, and those patients who had antibacterial-resistant fever. The presence of blood and protein on urinalysis was a supporting sign of a *Candida* UTI only if yeasts alone were grown; without bacterial growth (4). In patients with indwelling catheters, colony counts ranged between 2×10^4 and $\geq 10^5$ colony-forming units (CFUs)/mL; and for those patients without indwelling catheters colony counts as low as 10^4 CFU/mL. For those patients who had an indwelling catheter, replacement of catheter with a new device was performed and then the second urine sample was collected. If there was growth in the next sample, we considered UTI for the patient (4, 10, 11).

3.2. Isolates

From March 2017 to October 2018, 5281 patients were hospitalized at the ICU ward of Al-Zahra university hospital in Isfahan, Iran. One hundred patients out of 5281 (1.9%) were diagnosed as *Candida* UTI. The clinical isolates were cultured on Sabouraud dextrose agar (Biolife, Italy), and incubated at 37°C for 48 hours.

3.3. Phenotypic Identification

The sediments of urine specimens were initially sub-cultured on chromogenic medium (CHROMagar, DIFCO; Becton Dickinson, France) and incubated at 30°C for 24 - 48 hours. Species identification was performed based on chromogenic reaction of *Candida* species. *Candida albicans*, *Candida tropicalis*, *Candida krusei*, and other species produce green, metallic blue, pink, and white to mauve colonies, respectively.

3.4. Molecular Identification

Genomic DNA of clinical isolates were extracted using the boiling method (12). Briefly, a loopful of fresh colonies were suspended in 150 μ L of double distilled water (DDW) and boiled for 20 minutes, then centrifuged for 5 minutes at 8000 rpm, finally the supernatant was used for polymerase chain reaction (PCR). The ITS1-5.8SrDNA-ITS2 region was amplified by a PCR mixture containing of 5 μ L of $10 \times$ reaction buffer, 1.5 mM $MgCl_2$, 0.4 mM dNTPs, 30 pmol of both ITS1 (5'-TCC GTA GGT GAA CCT GCG G-3') and ITS4 (5'-TCC TCC GCT TAT TGA TAT GC-3') primers, 2.5 U of Taq polymerase, and 3 μ L of DNA in a final volume of 50 μ L. The PCR cycling condition was: an initial denaturation phase at 94°C for 5 minutes, followed by 32 cycles of denaturation at 94°C for 30 seconds, annealing at 55°C for 45 seconds, and extension at 72°C for 1 minute, with a final extension phase

at 72°C for 7 minutes. In the second step, the *Hpa*II restriction enzyme (Fermentas, Vilnius, Lithuania) was applied to digest amplified products. Restriction fragment length polymorphism (RFLP) products were separated by gel electrophoresis on 2% agarose gel (containing 0.5 μ g/mL ethidium bromide) and photographed by Uvidoc (Clever Scientific Ltd, UK).

4. Results

Candida albicans was the most prevalent species among clinical isolates (94%) followed by *Candida tropicalis* (4%), *Candida glabrata* (1%), and *Candida parapsilosis* (1%) (Figure 1). Median age of patients was 61.8 (SD = 18.5). Male to female sex ratio was 40/60. The age range of (71 - 80) (24%) and (1 - 10) (1%) had the most and the least frequencies. All patients had urinary catheters. Forty four and 11 patients were diabetic and neutropenic, respectively. Two patients had undergone kidney transplantation. Hospitalization period was 2 - 40 days. Table 1 shows the characteristics of patients in the present study.

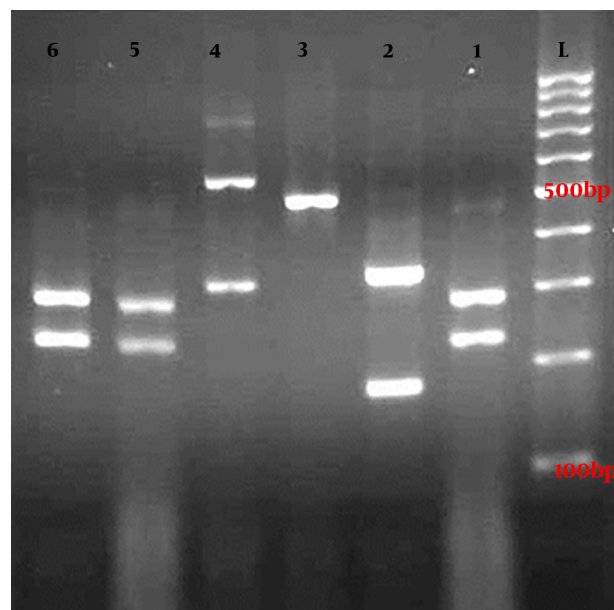


Figure 1. Gel electrophoresis of ITS-PCR amplicons of *Candida* species after digestion with *Msp*I restriction enzyme. Lanes 1, 5, and 6 are *C. albicans* (238 and 297 bp), lane 2 is *C. tropicalis* (184 and 340 bp), lane 3 is *C. parapsilosis* (520 bp), lane 4 is *C. glabrata* (314 and 557 bp), and lane L is a 100-bp DNA size marker.

5. Discussion

UTI is regularly found in patients with immunosuppressive conditions, long hospitalization, and who have

undergone surgical procedures. Alvarez-Lerma from Spain showed that 10% -15% urinary tract infections in the ICU patients are caused by the *Candida* species and 22% of critically ill patients hospitalized for more than seven days in ICUs revealed candiduria (13). During 1995 - 2001, there was 25,000 cases of candiduria per year in the United States (14). Diabetes mellitus is a formidable risk factor for the infection, since the mucous membranes in this group are more susceptible to UTI due to immune deficiencies (15). *Candida* colonization was elevated in the presence of nitrogenous compounds and acidic pH. In the present study, 44% of patients were diabetic as a major predisposing factor for UTI. The majority of UTI cases are catheter users (16). In accordance, all patients in the present investigation used urethral catheters. In agreement with our findings, *Candida albicans* is the most prevalent *Candida* species causing candiduria (17, 18), however there is a substantial trend to non-*albicans* *Candida* species (19, 20). A high number of cases of UTI due to the non-*albicans* species may be in connection with fluconazole consumption as a first line antifungal therapy because many *Candida* species are inherently resistant to fluconazole or susceptible only to high doses of this antifungal drug such as *Candida krusei* and *Candida glabrata* (1). The limitation of our study was the lack of determination of minimum inhibitory concentration (MIC) of the clinical isolates which is strongly recommended for further studies. Some studies introduce *Cryptococcus neoformans* and *Trichosporon asahii* as etiologic agents of UTI (21) but, *Candida* was the only fungus isolated from patients enrolled in the present investigation. A recurrent *Candida* UTI is a rare clinical manifestation and appears in diabetic patients or anatomical abnormalities of the urinary tract (22). Diabetes mellitus is a main risk factor for development of candidemia and is reported in nearly one third of all UTI patients (23). We followed up all patients especially diabetic patients (44%) and fortunately nobody presented systemic candidiasis in the present investigation. Similar to the present study, females usually have a higher chance for candiduria and UTI (24) in connection with vulvovaginal colonization by *Candida* species and their anatomy (6, 25), however, in many investigations males are the predominant population among UTI patients (11, 26). *Candida* species are isolated from 20-60% of UTI in neonatal intensive care units (NICU) and pediatric intensive care units (PICU) (27), but in the present study, the frequency of UTI among infants was only 1%. Since older individuals reveal natural modifications of the immune system, so longer hospitalization in intensive care units and use of urinary catheters was seen more commonly in this population (28, 29). Similar to most surveys in this field (6, 27), most patients in the present investigation were over 65 years old. The median absolute neutrophil count

(ANC) less than $1.5 \times 10^9/L$ is considered as neutropenia (30, 31). In the present study 11% of patients were neutropenic with the mid age of 65.2 years.

5.1. Conclusions

Patients with candiduria and UTI in ICU have increased mortality rates (13), so good management of patients depends on quick and precise intercessions. Since *Candida albicans* was a predominant species in the present study (94%), and it shows different sensitivities to antifungal drugs, determination of MIC for clinical isolates are recommended to determine the best choice for this potentially dangerous infection.

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Footnotes

Authors' Contribution: Study concept and design: Somayeh Haghighipour and Morteza Pourahmad. Acquisition of data: Mahta Noorbakhsh. Analysis and interpretation of data: Mahta Noorbakhsh and Rasoul Mohammadi. Drafting of the manuscript: Rasoul Mohammadi. Critical revision of the manuscript for important intellectual content: Somayeh Haghighipour and Rasoul Mohammadi. Statistical analysis: Mahta Noorbakhsh. Administrative, technical, and material support: Somayeh Haghighipour and Rasoul Mohammadi. Study supervision: Somayeh Haghighipour and Rasoul Mohammadi.

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Table 1. Details of Patients with UTI in the Present Study

No.	Gender	Age	Neutropenia	Diabetes Mellitus	Kidney Transplantation	Immunosuppressive Therapy	Antimicrobial Usage	Duration of Hospitalization (Day)	Candida spp.
1	Male	73	+	+	-	Azathioprine	+	14	<i>C. albicans</i>
2	Male	42	-	-	-	-	-	8	<i>C. albicans</i>
3	Male	72	+	+	-	Corticosteroid	+	5	<i>C. albicans</i>
4	Male	37	-	-	-	-	-	4	<i>C. albicans</i>
5	Female	73	-	+	-	-	+	6	<i>C. tropicalis</i>
6	Male	63	-	+	-	-	-	3	<i>C. albicans</i>
7	Female	32	-	-	-	-	-	3	<i>C. albicans</i>
8	Female	48	-	-	-	-	-	2	<i>C. albicans</i>
9	Male	75	-	+	-	-	+	13	<i>C. albicans</i>
10	Male	76	-	+	-	-	+	29	<i>C. albicans</i>
11	Female	42	-	-	-	-	-	2	<i>C. albicans</i>
12	Female	86	-	+	-	-	+	5	<i>C. albicans</i>
13	Female	22	-	-	-	-	-	8	<i>C. albicans</i>
14	Male	81	-	-	-	-	+	18	<i>C. albicans</i>
15	Male	73	-	+	-	-	-	2	<i>C. albicans</i>
16	Female	34	-	-	+	Tacrolimus	+	6	<i>C. albicans</i>
17	Male	36	-	-	-	-	-	39	<i>C. albicans</i>
18	Female	84	+	+	-	Azathioprine	+	6	<i>C. albicans</i>
19	Male	83	-	+	-	-	-	5	<i>C. albicans</i>
20	Female	70	-	-	-	-	-	5	<i>C. albicans</i>
21	Male	59	-	-	+	Tacrolimus	+	2	<i>C. albicans</i>
22	Female	51	-	+	-	-	-	6	<i>C. albicans</i>
23	Male	62	-	+	-	-	-	5	<i>C. albicans</i>
24	Male	36	-	-	-	-	+	9	<i>C. albicans</i>
25	Female	41	-	-	-	-	+	2	<i>C. albicans</i>
26	Female	60	-	-	-	-	-	4	<i>C. albicans</i>
27	Female	24	-	-	-	-	+	8	<i>C. albicans</i>
28	Male	73	-	-	-	-	-	9	<i>C. albicans</i>
29	Female	71	-	-	-	-	+	5	<i>C. albicans</i>
30	Male	65	-	+	-	-	+	15	<i>C. albicans</i>
31	Female	62	+	+	-	Trimethoprim-sulfamethoxazole	-	15	<i>C. albicans</i>
32	Female	77	-	-	-	-	+	6	<i>C. albicans</i>
33	Female	71	-	+	-	Corticosteroid	+	5	<i>C. albicans</i>
34	Female	27	-	-	-	Corticosteroid	-	6	<i>C. albicans</i>
35	Female	65	-	-	-	-	-	7	<i>C. tropicalis</i>
36	Female	55	-	+	-	-	+	2	<i>C. albicans</i>
37	Female	87	-	-	-	-	-	6	<i>C. albicans</i>
38	Male	61	-	-	-	-	+	4	<i>C. albicans</i>
39	Female	78	-	-	-	-	+	21	<i>C. albicans</i>
40	Female	88	-	+	-	-	+	4	<i>C. albicans</i>
41	Female	75	-	-	-	-	+	21	<i>C. albicans</i>
42	Female	82	-	-	-	-	-	23	<i>C. albicans</i>
43	Female	75	-	+	-	-	+	2	<i>C. albicans</i>
44	Male	79	+	+	-	Trimethoprim-sulfamethoxazole	-	3	<i>C. albicans</i>
45	Male	49	-	-	-	-	-	9	<i>C. albicans</i>
46	Female	80	+	+	-	Corticosteroid	-	21	<i>C. albicans</i>
47	Female	88	-	-	-	-	+	11	<i>C. albicans</i>
48	Female	76	-	+	-	-	+	24	<i>C. albicans</i>
49	Female	65	-	+	-	-	+	7	<i>C. albicans</i>
50	Female	74	-	+	-	Corticosteroid	-	9	<i>C. albicans</i>
51	Male	80	-	+	-	Corticosteroid	+	6	<i>C. albicans</i>
52	Female	61	-	-	-	-	+	12	<i>C. albicans</i>

53	Male	84	-	-	-	-	-	3	<i>C. albicans</i>
54	Female	90	-	-	-	-	-	30	<i>C. albicans</i>
55	Female	50	+	-	-	Trimethoprim-sulfamethoxazole	-	3	<i>C. tropicalis</i>
56	Male	59	-	+	-	-	-	9	<i>C. albicans</i>
57	Female	73	-	-	-	-	+	10	<i>C. albicans</i>
58	Male	47	-	-	-	-	-	15	<i>C. albicans</i>
59	Male	39	-	-	-	-	+	40	<i>C. albicans</i>
60	Male	63	+	-	-	Corticosteroid	+	35	<i>C. parapsilosis</i>
61	Male	77	-	+	-	-	-	15	<i>C. albicans</i>
62	Female	68	-	+	-	-	+	40	<i>C. albicans</i>
63	Female	57	-	+	-	-	-	32	<i>C. albicans</i>
64	Male	72	-	-	-	-	+	25	<i>C. glabrata</i>
65	Male	39	-	-	-	-	+	26	<i>C. albicans</i>
66	Female	56	+	-	-	Corticosteroid	-	10	<i>C. albicans</i>
67	Male	84	-	-	-	-	+	5	<i>C. albicans</i>
68	Male	69	-	-	-	-	-	7	<i>C. albicans</i>
69	Female	95	-	-	-	-	+	5	<i>C. albicans</i>
70	Female	55	-	+	-	Corticosteroid	+	25	<i>C. albicans</i>
71	Male	59	-	-	-	Corticosteroid	+	30	<i>C. albicans</i>
72	Female	73	-	+	-	-	-	6	<i>C. albicans</i>
73	Male	47	-	-	-	-	+	29	<i>C. albicans</i>
74	Female	55	+	+	-	Corticosteroid	+	23	<i>C. albicans</i>
75	Female	87	-	+	-	-	-	20	<i>C. albicans</i>
76	Male	61	-	-	-	-	+	10	<i>C. albicans</i>
77	Female	30	-	-	-	Corticosteroid	+	20	<i>C. tropicalis</i>
78	Female	74	-	+	-	-	-	16	<i>C. albicans</i>
79	Female	7	-	-	-	-	+	10	<i>C. albicans</i>
80	Male	43	-	+	-	-	+	27	<i>C. albicans</i>
81	Female	24	-	-	-	-	+	32	<i>C. albicans</i>
82	Male	70	-	+	-	-	-	15	<i>C. albicans</i>
83	Female	65	-	+	-	-	-	7	<i>C. albicans</i>
84	Female	69	-	+	-	-	+	10	<i>C. albicans</i>
85	Male	43	+	+	-	Corticosteroid	+	27	<i>C. albicans</i>
86	Female	38	-	-	-	-	-	8	<i>C. albicans</i>
87	Female	52	-	+	-	-	-	14	<i>C. albicans</i>
88	Female	54	-	-	-	-	+	18	<i>C. albicans</i>
89	Female	30	-	-	-	-	+	20	<i>C. albicans</i>
90	Male	59	-	+	-	-	+	20	<i>C. albicans</i>
91	Female	40	-	+	-	-	-	10	<i>C. albicans</i>
92	Female	64	-	-	-	-	-	11	<i>C. albicans</i>
93	Male	74	-	-	-	Corticosteroid	+	9	<i>C. albicans</i>
94	Female	68	-	-	-	-	-	5	<i>C. albicans</i>
95	Female	83	-	+	-	-	+	25	<i>C. albicans</i>
96	Female	58	-	-	-	Corticosteroid	-	15	<i>C. albicans</i>
97	Female	81	-	+	-	Corticosteroid	+	19	<i>C. albicans</i>
98	Female	32	-	-	-	-	-	6	<i>C. albicans</i>
99	Male	63	-	-	-	-	-	14	<i>C. albicans</i>
100	Male	69	-	+	-	-	+	7	<i>C. albicans</i>