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ORIGINAL ARTICLE

Candiduria in catheterized ICU patients: epidemiology, molecular identification, and antifungal susceptibility

Ali Ahmadi[1], Ebrahim Hazrati[2], Mahtab Noorifard[1], Zohreh Farahnejad[1,3*], Mojgan Mohammadimehr[1,4*]

[1]Infectious Disease Research Center, AJA University of Medical Sciences, Tehran, Iran
[2]Department of Anesthesiology and Critical Care and Trauma Research Center, AJA University of Medical Sciences, Tehran, Iran
[3]Department of Medical Mycology, AJA University of Medical Sciences, Tehran, Iran
[4]Department of Laboratory Sciences, AJA University of Medical Sciences, Tehran, Iran

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ABSTRACT

Background and Objectives: Candiduria related to urinary catheters is frequently encountered in patients hospitalized in intensive care units. The diagnosis and management of catheter-associated candiduria in hospitalized patients is frequently a gray area for both physicians and microbiologists because of the paucity of clinical and microbiological data.
Materials and Methods: This cross-sectional study aims to enhance the understanding of candiduria among adult ICU patients with urinary catheters across three hospitals in Tehran, Iran. Yeast identification was performed using a two-step multiplex PCR, and antifungal susceptibility testing was performed following the CLSI M27, 4th edition, recommendations.
Results: Among the 110 enrolled ICU patients, 38 (35%) had significant candiduria. A total of 45 yeast isolates were collected. The distribution was as follows: *Candida glabrata* (23/45; 51%), *C. albicans* (14/45; 31%), and *C. tropicalis* (4/45; 9%). These three species accounted for 91% of the isolates. Antifungal resistance was detected: six isolates (two *C. glabrata*, two *C. albicans*, one *C. krusei*, and one *C. tropicalis*) were fluconazole-resistant, and one *C. glabrata* isolate was resistant to itraconazole, voriconazole, and caspofungin. All isolated species were susceptible to amphotericin B. Symptomatic candiduria occurred in 29% of cases (11/38); only 55% (6/11) were treated, and of those, 50% (3/6) experienced fluconazole treatment failure. One symptomatic patient developed candidemia shortly after acquiring candiduria. The mortality rate was 21% (8/38), with no apparent difference in death rates between symptomatic and asymptomatic candiduric patients.
Conclusion: Our findings reveal that high fluconazole failure rates among patients with symptomatic candiduria are concerning. Furthermore, speciation and antifungal susceptibility testing are crucial, as they guide clinicians in selecting the most effective agent and improving case management.

Keywords: *Candida*; Urinary catheters; Drug resistance; Intensive care unit

*Corresponding authors: Zohreh Farahnejad, Ph.D, Infectious Disease Research Center, AJA University of Medical Sciences, Tehran, Iran; Department of Medical Mycology, AJA University of Medical Sciences, Tehran, Iran. Tel: +98-9122773149 Email: zfarahnejad@yahoo.com

Mojgan Mohammadimehr, Ph.D, Infectious Disease Research Center, AJA University of Medical Sciences, Tehran, Iran; Department of Laboratory Sciences, AJA University of Medical Sciences, Tehran, Iran. Tel: +98-9122593326 Email: mojganmehr20@yahoo.com

INTRODUCTION

Among critically ill patients, invasive fungal infections (IFIs) still represent a major clinical challenge, most notably in intensive care unit (ICU) settings (1, 2). Yeasts of the *Candida* genus are responsible for around 70% of all IFIs worldwide (3). Despite efforts to lower the incidence of urinary tract infections associated with catheters (which represent 95% of UTIs in the ICU), these infections continue to rank second among health-care-associated infections (HCAIs) in critically ill patients (4, 5).

Candiduria is commonly observed among catheterized ICU patients (6). In Iran, available studies report a candiduria prevalence of approximately 16.5%, with *Candida albicans* reported as the predominant isolate (58.53%), followed by *C. glabrata* (15.39%) and *C. tropicalis* (5%). Risk factors for candiduria include prolonged antibiotic therapy, urinary catheterization, and underlying conditions (7). Indwelling urinary catheters are the primary cause of catheter-associated candiduria (8).

Despite its rarity, candiduria has been linked to the development of candidemia. Furthermore, several studies have associated it with a high mortality rate (33%), particularly in ICU patients. Managing candiduria in hospitalized critical care patients therefore requires careful consideration (9). While patients with candiduria do not typically require antifungal treatment, the condition cannot be neglected entirely. In specific instances, it may be the sole indicator of underlying or imminent invasive candidemia and has been linked to considerable rates of morbidity and mortality (10). This is particularly applicable when risk factors such as immunosuppression, chronic diseases, extended hospital stays, long-term antibiotic usage, and catheterization are present (11).

Antifungals should only be administered to the following patients, according to the Infectious Diseases Society of America (IDSA) (12): neutropenic patients, those undergoing urologic manipulation, and newborns with exceptionally low birth weights. Management should be based on species identification; in practice, fluconazole (FLU) is typically administered to susceptible strains, while agents such as amphotericin B (AmB) or flucytosine are preferred for inherently resistant species, including *C. krusei* and *C. glabrata* (12). Despite existing treatment guidelines for candiduria, deviations in antifungal use—particularly of fluconazole (FLU)—have been observed in multicenter trials and may be associated with an increased thirty-day readmission rate (13).

These observations underscore the significance of implementing an all-encompassing antifungal stewardship program. Access to substantial clinical data is crucial for such a program, which could also help curb the rise of azole-resistant *Candida* species. The presence of *Candida* in urine is difficult to interpret. It could indicate anything from a blatant urinary tract infection (UTI) to mere colonization or contamination, or even an underlying, not-yet-manifest candidemia (14). At present, there is no approach with 100% sensitivity and specificity for distinguishing colonization from frank UTI. This quandary often arises when *Candida* species are cultured from the urine of a typical ICU patient who has an indwelling catheter. Unfortunately, research providing precise clinical and microbiological data on candiduria in catheterized patients is scarce. This clinic-microbiological study aimed to perform molecular identification and describe the antifungal susceptibility profiles of *Candida* isolates from catheterized ICU patients with candiduria at three tertiary hospitals in Tehran, Iran.

MATERIALS AND METHODS

Study design. This cross-sectional study comprised adult patients with urethral catheters admitted to the ICUs of three hospitals (Payambaran, Moheb Kowsar, and Imam Reza Hospitals) in Tehran, between January and July 2023. Patients were excluded if *Candida* was cultured from urine samples either prior to catheterization or within the first 48 hours post-catheter insertion. Demographic and clinical data were extracted from the hospitals' digitized medical records. Ethical clearance was obtained from the AJA University of Medical Sciences ethics committee (approval ID: IR.AJAUMS.REC.1401.166).

Diagnostic criteria. Asymptomatic candiduria was defined as *Candida* counts of at least 10^5 CFU/mL in two urine samples collected 24 hours apart, without accompanying urinary tract symptoms. Conversely, symptomatic candiduria was diagnosed in patients presenting with unexplained fever (≥38°C) alongside positive urine cultures (13). Confirmatory candidemia was defined based on positive *Candida* growth in blood cultures.

Candiduria treatment. Decisions regarding antifungal treatment were made by the attending ICU specialists, irrespective of the *Candida* species identified. Urinary catheter replacement or removal was systematically implemented in all patients with candiduria. Regardless of IDSA guidelines, patients who developed fever and suprapubic tenderness were additionally given fluconazole (FLU) at 100 mg daily for one week. Fluconazole treatment failure was defined as persistent candiduria, indicated by $\geq 10^5$ CFU/mL in two follow-up urine cultures after one week of therapy. In these cases, additional agents such as caspofungin (CAS) or amphotericin B (AMB) were added to the fluconazole regimen.

Yeast isolates and molecular identification. Urine specimens were inoculated onto chloramphenicol-supplemented Sabouraud dextrose agar plates (Merck, Germany) and incubated at 35°C for 24 to 48 hours. Positive cultures for candiduria were defined by colony counts $\geq 10^5$ CFU/mL of *Candida* species (13). Genomic DNA was extracted using a commercial silica-based column purification kit (DNP, Sinacolon, Iran). *Candida* species were identified via a two-step multiplex PCR protocol as previously described, distinguishing both common and uncommon pathogenic species (15, 16). Amplified PCR fragments were separated on 2% agarose gels pre-stained with GelRed (BioTium, USA) and documented using a gel imaging system.

Antifungal susceptibility testing. In line with the Clinical and Laboratory Standards Institute (CLSI) document M27, 4th edition, broth microdilution was used to perform antifungal susceptibility testing (AFST) for FLU, itraconazole (ITZ), AmB (each from Sigma-Aldrich, USA), CAS (Merck, USA), and voriconazole (VRZ; Pfizer, USA) (17). Dimethyl sulfoxide (DMSO) was used to dissolve the powders to create stock solutions for each drug, and further dilutions were made in RPMI buffered with 0.165 M MOPS (morpholine propane sulfonic acid; pH 7.0)–0.2% glucose, phenol red, and no bicarbonate, with final concentrations for FLU ranging from 0.125 to 64 µg/mL, for ITZ, AmB, VRZ from 0.031 to 16 µg/mL, and for CAS from 0.015 to 8 µg/mL. Minimum inhibitory concentrations (MICs) for all antifungal agents were determined visually after 24 hours of incubation at 35°C. For AmB, the MIC was defined as the lowest drug concentration that completely inhibited visible growth, whereas for azoles and CAS, a reduction of at least 50% in growth was used as the endpoint. MICs were interpreted using CLSI clinical breakpoints or epidemiological cutoff values (18). The *Candida* reference strains *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 were used as quality control isolates in each testing run.

Statistical analysis. Data were analyzed using SPSS version 24 (IBM, Chicago, IL, USA). Descriptive statistics are presented as mean ± standard deviation for continuous variables. Univariate and multivariate analyses were used to explore associations with demographic, clinical, and survival parameters. A P-value of <0.05 was considered statistically significant.

RESULTS

Patients' characteristics. In total, 110 ICU patients enrolled during the study period fulfilled the predefined inclusion criteria; among them, 38 individuals (35%) exhibited significant candiduria, defined by colony counts of $\geq 10^5$ CFU/mL. The median age of patients with candiduria was 62 years, with an age range of 19-100 years. No statistically significant difference was observed between male (46/110; 42%) and female (64/110; 58%) patients. Among the documented comorbid conditions, cardiovascular and vascular disorders represented the most commonly reported events (47%; 52/110), followed by diabetes (38%; 42/110) (Table 1). The majority of the patients with long-term indwelling urethral catheterization had a significantly higher prevalence of candiduria than those with short-term catheterization.

Clinical presentation and treatment outcomes. Asymptomatic and symptomatic candiduria were identified in 71% (27/38) and 29% (11/38) of patients, respectively. Antifungals were not administered to most patients. Fluconazole (FLU) was given to 11 patients: five of these were asymptomatic but had suprapubic tenderness (5/27; 19%), and six were symptomatic (6/11; 55%). All asymptomatic patients were effectively treated with catheter removal and FLU treatment. FLU treatment failure was observed among symptomatic patients (3/6; 50%), with one of them developing candidemia. FLU treatment failure occurred predominantly in cases due to *C. glabrata* (2/3) and, to a lesser extent, *C. albicans* (1/3). This case of can-

Table 1. Clinical data of patients recruited to the study

Characteristics	Patients without candiduria (n = 72)	Patients with candiduria (n = 38)	Value (P)
Age (mean ± SE)	58.5 ± 3.2	61.6 ± 2.1	0.16
Number of males (%)	28 (39%)	18 (47%)	0.14
Urine characteristics	Urine characteristics	Urine characteristics	Urine characteristics
White blood cells	40 (55%)	30 (79%)	0.04
Red blood cells	40 (55%)	28 (74%)	0.07
Pure yeast	-	32 (84%)	-
Mixed yeast	-	6 (16%)	-
Clinical signs and symptoms	Clinical signs and symptoms	Clinical signs and symptoms	Clinical signs and symptoms
Fever (>38°C)	15 (21%)	11 (29%)	0.6
Cloudy urine	20 (27%)	15 (39%)	0.1
Suprapubic tenderness	18 (25%)	13 (34%)	0.1
Underlying conditions	Underlying conditions	Underlying conditions	Underlying conditions
Surgery	41 (57%)	18 (47%)	0.6
Cardiovascular diseases	36 (50%)	16 (42%)	0.5
Diabetes	28 (39%)	14 (37%)	0.7
Abdominal complications	20 (27%)	15 (39%)	0.09
Cerebrospinal complications	20 (27%)	6 (16%)	0.8
Sepsis	15 (21%)	5 (13%)	0.5
Chronic lung diseases	14 (19%)	4 (11%)	0.7
Solid tumor	10 (14%)	2 (5%)	0.08
Dialysis	3 (4%)	2 (5%)	-
Antibiotic use	68 (94%)	36 (95%)	0.7
Hospitalization duration (mean ± SD)	20.6 ± 3.1	19.4 ± 2.5	0.8
Duration of catheterization (days)	Duration of catheterization (days)	Duration of catheterization (days)	Duration of catheterization (days)
2-14	40 (55%)	13 (34%)	0.04
15-30	29 (41%)	19 (50%)	0.07
>30	3 (4%)	6 (16%)	0.03
Outcome (death)	18 (25%)	8 (20%)	0.3

didemia in a 68-year-old man with a history of hypertension and a diagnosis of cerebrovascular accident (CVA) was diagnosed on the same day as candiduria, and both blood and urine cultures yielded *C. glabrata*. The patient died despite treatment with fluconazole (FLU, 100 mg/day for 7 days) and caspofungin (CAS, 200 mg/day for 7 days). Aside from *C. glabrata*, which was more frequently detected in symptomatic individuals, the distribution of *Candida* species was comparable between symptomatic and asymptomatic candiduria. No significant differences were found in survival rates or duration of hospitalization when comparing symptomatic and asymptomatic patients.

Yeast identification and co-isolation patterns. A total of 45 yeast isolates were obtained from the 38 candiduria patients. *C. glabrata* was the dominant species (23/45; 51%), followed by *C. albicans* (14/45; 31%) and *C. tropicalis* (4/45; 9%). Less frequent isolates included *C. dubliniensis* (n = 3, 7%), and *C. krusei* (n = 1, 2%). Mixed-species was identified in six cases, including *C. glabrata* + *C. albicans* (n = 3), *C. glabrata* + *C. tropicalis* (n = 1), *C. glabrata* + *C. dubliniensis* (n = 1), and *C. glabrata* + *C. albicans* + *C. dubliniensis* (n = 1). There were no statistically significant differences (P > 0.05) in mortality rate, metabolic or oncologic comorbidities, fever frequency, surgical background, or use of corticosteroids, antibiotics, and antifungals between *C. albicans* and NAC infections.

Antifungal susceptibility testing. Antifungal resistance varied depending on the species. Specifically, five *C. glabrata* isolates showed resistance against FLU (≥64 μg/mL; 2/23), one showed resistance to

ITZ (>4 µg/mL), one to VRZ (>0.5 µg/mL), and one to CAS (≥0.5 µg/mL). Three isolates demonstrated intermediate susceptibility to CAS at 0.25 µg/mL, and 21 were categorized as susceptible dose-dependent to FLU (≤32 µg/mL). Among *C. albicans* isolates, two were resistant to FLU (≥8 µg/mL; 2/14), one was susceptible dose-dependent (SDD) to FLU (4 µg/mL; 1/14), and two were susceptible dose-dependent (SDD) to ITZ (0.25–0.5 µg/mL; 2/14). One C. tropicalis isolate had resistance against FLU (≥8 µg/mL; 1/4). Apart from the inherent fluconazole resistance characteristic of *C. krusei*, neither *C. dubliniensis* nor *C. krusei* isolates exhibited resistance to the other antifungal drugs tested (Table 2).

DISCUSSION

The lack of awareness about the importance of candiduria in critically ill patients is comprehensible. This study clarifies this condition by detailing its clinical significance and associated risk factors. As the present data clearly show, most disregard candiduria as completely benign, but there is a strong school of thought that views it as a sign of hidden candidemia (19, 20).

This investigation evaluated candiduria in 110 catheterized ICU patients from three hospitals located in Tehran, Iran. It is challenging to assess the total incidence and prevalence of candiduria because different studies use different methodologies for collecting urine, there is disagreement on the microbiological definitions of candiduria, and patient characteristics vary. Our findings indicate that the incidence of candiduria is consistent with data reported internationally in multiple settings including Spain, India, and Brazil (31.5%-44.4%) (21-23), but higher than that in multicenter European countries (8.7-9.4%) (24). Approximately one-third of patients with candiduria were symptomatic, while the remaining two-thirds were asymptomatic. Consistent with previous research, we found that the most common risk factors associated with candiduria were diabetes, coronary and abdominal complications, and the use of antibiotics and corticosteroids (25, 26).

The most common species isolated from the urine of hospitalized patients are *C. albicans* (35-68%), *C. glabrata* (8-53%), and *C. tropicalis* (3-36%), according to most studies (26-28). Recently, several nations have seen a rise in the discovery of NAC species, including the introduction of multi-drug-resistant *C. auris*, which is responsible for hospital outbreaks, particularly in the ICU (29, 30). In this study, *C. glabrata* was the leading species isolated from candiduric patients, in line with earlier publications describing an increasing prevalence of *C. glabrata* in urinary *Candida* infections (9, 31). Moreover, the mixed growth of *C. glabrata* and other *Candida* species (i.e., *C. albicans*, *C. tropicalis*, and *C. dubliniensis*) was observed in six patients.

The rise of infections from NAC species poses the biggest threat to treating candidiasis, and it may be related to both the increased use of immunosuppressive medicines and the emergence of resistance to traditional antifungal therapies (32, 33). In this study, AmB and CAS were the most active antifungals against both *C. albicans* and NAC isolates, a finding consistent with most studies (9, 31, 34). Among *C. glabrata* strains, resistance rates were 9% to FLU, 4% to ITZ, 4% to VRZ, and 4% to CAS. In contrast, only 14% of *C. albicans* isolates were resistant to FLU. Previous investigations have shown that azole resistance in *C. glabrata* is multifactorial (35). Among other NAC isolates, azole resistance was found only in *C. tropicalis*, at a rate of 25%. Recent reports point to the emergence of NAC species—particularly *C. glabrata* and *C. tropicalis*—that can develop multidrug resistance (36).

Considering *C. krusei* is intrinsic to FLU resistance, these findings emphasize the significance of adhering to international guidelines and identifying isolates at the species level (36). Constraints in laboratory resources meant that, during the intervention period, *Candida* isolates were not routinely identified to the species level (37). This practice deviated from IDSA guidelines, as antifungal agents were administered regardless of the AFST results (12). Considering FLU's role as a primary therapy and the growing problem of FLU resistance among *Candida* species, notably *C. glabrata*, performing susceptibility testing becomes a key step in guiding appropriate antifungal therapy (38). Notably, FLU was administered to 19% of asymptomatic cases, yet nearly half of symptomatic patients (45%) remained untreated with it. Due to its high urinary concentration (39), 73% of patients who received FLU as first-line therapy had their candiduria cleared. In contrast to FLU, other azoles (e.g., ITZ, VRZ), and AmB are less favorable therapeutic options and should be considered in refractory infections caused by FLU-resistant strains

Table 2. Detailed antifungal susceptibility profile of *Candida* isolates recovered in our study.

Species (isolate no.)	Drug	Number of isolates (%)				MIC Range	MIC_{50}	MIC_{90}	GM	MICs (µg/ml)											
		S	SDD	I	R					≤0.031	0.063	0.125	0.25	0.5	1	2	4	8	16	32	≥64
C. glabrata (n = 23)	FLU	-	21 (91)	-	2 (9)	1 - ≥64	4	32	4.65						1	6	12		1	1	2
	ITZ	22 (96)	-	-	1 (4)	0.063 - 1	0.25	1	0.28		3	5	7	4	3			1			
	VRZ	22 (96)	-	-	1 (4)	≤0.031 - 0.5	0.031	0.125	0.06	13	6	2	1	1							
	AmB	23 (100)	-	-	-	≤0.031 - 1	0.125	0.5	0.16	1	4	8	7	2	1						
	CAS	19 (83)	-	3 (13)	1 (4)	≤0.031 - 0.5	0.125	0.25	0.11	3	6	10	3	1							
C. albicans (n = 14)	FLU	11 (79)	1 (7)	-	2 (14)	0.25 - 16	1	8	0.91				5	2	3	1	1	1	1		
	ITZ	12 (86)	2 (14)	-	-	≤0.031 - 0.25	0.063	0.25	0.08	4	5	3	2								
	VRZ	14 (100)	-	-	-	≤0.031 - 0.125	0.031	0.125	0.05	8	3	3									
	AmB	14 (100)	-	-	-	0.063 - 2	0.125	1	0.22		2	6	2	2	1	1					
	CAS	14 (100)	-	-	-	≤0.031 - 0.125	0.063	0.125	0.07	5	4	5									
C. tropicalis (n = 4)	FLU	3 (75)	-	-	1 (25)	0.25 - 8	NA	NA	NA				1	2				1			
	ITZ	4 (100)	-	-	-	0.063 - 0.25	NA	NA	NA		2	1	1								
	VRZ	4 (100)	-	-	-	≤0.031 - 0125	NA	NA	NA	2	1	1									
	AmB	4 (100)	-	-	-	0.25 - 0.5	NA	NA	NA				3	1							
	CAS	4 (100)	-	-	-	0.063 - 0.125	NA	NA	NA		2	2									
C. dubliniensis (n = 3)	FLU	3 (100)	-	-	-	0.125 - 0.25	NA	NA	NA			1	2								
	ITZ	3 (100)	-	-	-	0.063 - 0.125	NA	NA	NA		2	1									
	VRZ	3 (100)	-	-	-	0.063	NA	NA	NA		3										
	AmB	3 (100)	-	-	-	0.125 - 0.25	NA	NA	NA			2	1								
	CAS	3 (100)	-	-	-	0.125 - 0.25	NA	NA	NA		1	2									
C. krusei (n = 1)	FLU	*	*	*	*	8	NA	NA	NA									1			
	ITZ	1 (100)	-	-	-	0.25	NA	NA	NA				1								
	VRZ	1 (100)	-	-	-	0.25	NA	NA	NA				1								
	AmB	1 (100)	-	-	-	1	NA	NA	NA						1						
	CAS	1 (100)	-	-	-	0.125	NA	NA	NA			1									

Abbreviations: FLU, fluconazole; ITZ, itraconazole; VRZ, voriconazole; AmB, amphotericin B; CAS, caspofungin; S, susceptible; SDD, susceptible dose dependent; I, intermediate; R, resistant; NA, not available; GM, Geometric mean; *, Inherent resistance to fluconazole. Numbers in bold are modal values.

(40). Data from other investigations suggest that CAS may be effective in resolving candiduria caused by NAC organisms such as *C. glabrata*, despite the limited renal excretion of echinocandins into urine (41). Nevertheless, FLU therapy failed in a substantial fraction of treated symptomatic patients (50%; 3/6). In these cases, adding CAS and/or AmB to FLU led to resolution of candiduria in all but one patient.

Although relatively uncommon, candiduria may progress to candidemia, with reported rates ranging from 1.3% to 10% (26). In line with this, only one patient (2.6%) in our study developed candidemia and died. While the clinical relevance of candiduria is still unknown, it should be highlighted that blood samples from patients with candiduria were not analyzed in the majority of studies, which may have contributed to the low rate of concomitant candidemia (42). Clarifying whether simultaneous candidemia arises from the same strain as the urinary isolate requires the use of discriminatory genotyping techniques (42).

A key limitation of our study is its relatively small sample size (n=110), which may limit the generalizability of the findings to broader populations. Additionally, the research was conducted in Tehran, Iran, which may not reflect the epidemiology of candiduria in other geographic regions. To address these limitations, we recommend conducting larger, multicenter studies to validate our findings and further explore the risk factors associated with candiduria and its potential progression to candidemia. Establishing standardized diagnostic and management protocols for candiduria in ICU settings could improve patient outcomes and reduce antifungal treatment failures.

CONCLUSION

In conclusion, while candiduria is clinically relevant in catheterized ICU patients, there is often inconsistent adherence to standard treatment recommendations, a notable rate of therapeutic failure, and a frequent lack of species-level identification of isolates. In this study, *C. glabrata* was the predominant cause of candiduria. Given this species' rising antifungal resistance, its management poses a significant clinical challenge. Both discriminatory genotyping and antifungal susceptibility testing are essential, as they aid in identifying the infection source and guiding optimal antifungal therapy.

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