



Original Article

Concurrent candidemia and candiduria in intensive care unit patients: A retrospective evaluation

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Abstract

Objective: This study aimed to improve understanding of the management of such cases by evaluating risk factors in patients with concomitant candidemia and candiduria.

Methods: Microbial identification of clinical isolates at the species level was performed using the VITEK®2 automated system, and antifungal susceptibility was evaluated using the colorimetric microdilution method.

Results: The majority of patients with concurrent candiduria and candidemia were hospitalized in medical intensive care units. Prior antibiotic use was the most frequently observed predisposing factor. A total of 57 episodes of simultaneous candidemia and candiduria were identified. *Candida albicans* was the most frequently isolated species, whereas non-*albicans Candida* (NAC) accounted for 68.4% of cases. The majority of *Candida* isolates were pan-susceptible. Most isolates were susceptible to amphotericin B (7/11, 63.6%), except for *Candidozyma auris*. Fluconazole resistance was the most frequently identified resistance pattern, detected in all *C. auris* isolates (11/11, 100%) and in 3 isolates of the *C. parapsilosis* complex (3/10, 30%). Moreover, 2 isolates of the *C. parapsilosis* complex (2/10, 20%) exhibited resistance to voriconazole, whereas isolates of *C. albicans* and *C. tropicalis* remained susceptible. Additionally, 2 isolates of *C. albicans* (2/18, 11%) showed resistance to both anidulafungin and micafungin, and 1 isolate of *Nakaseomyces glabratus* (1/5, 20%) showed resistance to micafungin. Fluconazole was the most commonly used first-line antifungal agent. Mortality was higher among patients with *C. albicans* candidemia.

Conclusion: This study provides further insight into the association between candiduria and candidemia, offering valuable information to guide clinical practice.

Keywords: Antifungal treatment, invasive candidiasis, urinary tract infections, yeast.

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INTRODUCTION

The growing population of elderly and immunocompromised individuals has led to an increase in opportunistic fungal infections. *Candida* species, part of the normal urogenital microbial flora, are among the most common opportunistic fungal pathogens. Risk factors for urinary tract infections include extremes of age, female gender, poorly controlled diabetes, prolonged hospitalization, intensive care unit (ICU) admission, prior surgical procedures, genitourinary instrumentation, congenital or structural abnormalities of the urinary tract, and catheterization (1,2). Additionally, antibiotic use significantly contributes to the pathogenesis of candiduria, which often develops during or shortly after antibiotic therapy. Antibiotics suppress the endogenous microbial flora in the gastrointestinal and genital tracts, thereby increasing *Candida* colonization on mucosal surfaces. In the presence of a urinary catheter, *Candida* species adhering to the catheter may ascend into the urinary tract (3,4). Candiduria, defined as the isolation of *Candida* species from urine cultures, is uncommon in healthy individuals but frequently observed in hospitalized patients, particularly those in ICUs or with indwelling urinary catheters. Although candiduria is often considered a sign of colonization, it is important to distinguish it from true infection. While colonization may not require antifungal therapy, infection typically does. Therefore, determining the clinical significance of candiduria remains a challenge, especially among critically ill patients or those with multiple comorbidities. Evidence suggests that candiduria may also reflect an increased risk of disseminated candidiasis, particularly in high-risk groups such as those with prolonged hospitalization, antibiotic use, and invasive procedures (4–6). Candidemia, the presence of *Candida* spp. in the bloodstream, remains a significant public health concern due to its high mortality rates despite antifungal therapy. Regular epidemiological surveillance, including monitoring of fungal species distribution and antifungal susceptibility profiles, is essential for developing effective diagnostic and therapeutic strategies, containing resistant strains, ensuring appropriate antimicrobial selection, and formulating evidence-based empirical antifungal treatment guidelines (1). Among ICU patients, who constitute the highest-risk population for fungal infections, cutaneous and mucosal barriers are frequently disrupted due to surgical interventions, open wounds, endotracheal intubation, or intravascular catheters (7,8). Research has demonstrated that the risk of invasive fungal infection increases significantly following fungal colonization in ICU patients (8). The source of candidemia is critical for patient survival and should not be overlooked in epidemiological studies of invasive candidiasis. In our study, all patients with *Candida* isolated from urine cultures were included, regardless of colonization or infection. Candiduria is a predictor of candidemia; however, to the best of our knowledge, studies examining the concurrent occurrence of candidemia and candiduria are scarce.

In this study, we aimed to guide clinicians in establishing diagnosis and treatment protocols by evaluating species distribution, antifungal susceptibility patterns, and associated risk factors in patients with both candiduria and candidemia. This study also aims to contribute to the development of new treatment strategies and to enhance awareness of the necessity for careful management of these cases.

MATERIALS AND METHODS

This study was conducted in accordance with the Declaration of Helsinki, and ethics committee approval was obtained from the Gaziantep City Hospital Scientific Research and Publication Ethics Committee (decision no: 2024/13, date: 05.15.2024). This retrospective study was conducted between 2023 and 2024 at Gaziantep City Hospital, an 1875-bed tertiary care center in Gaziantep, Turkey. The study included patients from the

hospital's medical and surgical intensive care units, each with 259 beds. Cases with concurrent candiduria and candidemia were analyzed. Specifically, *Candida* spp. were isolated from both urine and blood culture samples of the same patient within a 0–10-day interval, and samples were processed in the Department of Microbiology Laboratory. Demographic and clinical data were retrieved from the hospital's electronic medical record system and the laboratory's computerized database. If the same strain was isolated multiple times from cultures of the same patient within a month, only the first isolate was included. However, isolates obtained more than one month apart from the same patient were considered a new episode. Urine and blood samples were collected under aseptic conditions and promptly transported to the laboratory. Blood culture specimens were immediately inoculated into the BacT/ALERT 3D automated microbial detection system (bioMérieux, France/USA) and monitored for five days. Positive samples underwent Gram staining prior to subculture onto blood agar, EMB agar, and chocolate agar. Samples showing yeast cells on Gram stain were additionally subcultured onto Sabouraud dextrose agar (SDA) and incubated at 37 °C for 24–48 h. Microbial identification at the species level was performed using the VITEK®2 automated system with the ID-YST card (bioMérieux, Marcy-l'Étoile, France), in combination with conventional phenotypic methods, including colony morphology on SDA, chlamydospore and/or blastospore formation, true and/or pseudohyphae development on cornmeal Tween 80 agar, and colony color on *Candida* CHROMagar (RTA, Turkey). Antifungal susceptibility was evaluated using the colorimetric microdilution method (Yeast MIC Plate Kit, Diagnostics). The lowest drug concentration causing a color change at the end of 24 h with $1.5\text{--}8 \times 10^3$ CFU/mL inoculum was defined as the MIC. MIC values were categorized as susceptible (S), dose-dependent susceptible/intermediate (S-DD/I), and resistant (R) according to EUCAST guidelines (9). Specific MIC breakpoints for anidulafungin, micafungin, voriconazole, fluconazole, and amphotericin B were applied according to EUCAST and CDC recommendations, with adjustments for *Candida auris* in the absence of established breakpoints. Quality control was performed using the *C. parapsilosis* complex strain (ATCC 22019), and all MIC readings were within EUCAST limits.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequencies (n) and percentages (%), while continuous variables were expressed as mean or range (minimum–maximum). The distribution of *Candida* isolates, antifungal susceptibility patterns, underlying comorbidities, risk factors, treatment characteristics, and mortality rates were evaluated using descriptive statistical methods. All analyses were conducted in accordance with the retrospective design of the study, employing a descriptive statistical approach.

RESULTS

During the study period, a total of 502 urine samples and 125 blood samples with confirmed fungal growth were retrospectively analyzed. We identified 57 episodes (11%) of candidemia occurring in patients with candiduria. Among the included patients, 58% were female and 42% were male, with a mean age of 63.5 years (range: 1–92 years). Fungal growth was most frequently observed in the 61–92 years (n=40, 70%) and 42–58 years (n=11, 19%) age groups. Most patients with concurrent candiduria and candidemia were hospitalized in medical intensive care units (46 patients), while 11 patients were in surgical ICUs. Among the identified comorbidities, hypertension was present in 39% of patients, diabetes mellitus in 35%, malignancy in 26%, and urinary tract disorders in 24%. Prior antibiotic use (70%) and total parenteral nutrition (15%) were the most frequently observed predisposing factors. Medical devices, including mechanical ventilation

and central venous catheters, were used in 53% of patients. A total of 57 episodes of simultaneous candidemia and candiduria were identified. The causative agents included *C. albicans* (18 cases, 31.6%), *Candidozyma auris* (formerly *Candida auris*) (11 cases, 19.3%), *C. parapsilosis* complex (10 cases, 17.5%), *C. tropicalis* (8 cases, 14.0%), *Nakaseomyces glabratus* (formerly *Candida glabrata*) (5 cases, 8.8%), and other yeast species (5 cases, 8.8%). Non-*albicans Candida* (NAC) species were responsible for 68.4% of cases (Table 1). The mycology laboratory does not routinely perform antifungal susceptibility testing on yeasts isolated from urine samples, except under extraordinary circumstances. Consequently, in this retrospective analysis, antifungal susceptibility results were available for only a few patients with yeast growth in urine samples. These data were excluded from the analysis, and only the antifungal susceptibility results of isolates obtained from blood cultures were presented. Antifungal susceptibility testing for anidulafungin (ANI), micafungin (MCF), voriconazole (VOR), fluconazole (FCZ), and amphotericin B (AmB) was performed on all clinical isolates from blood cultures. Most *Candida* isolates were pan-susceptible. All isolates, except *C. auris*, were susceptible to AmB. AmB resistance was observed in 7 *C. auris* isolates (7/11, 63.6%). Fluconazole resistance was detected in all *C. auris* isolates (11/11, 100%) and in 3 *C. parapsilosis* complex isolates (3/10, 30%). Additionally, 2 *C. parapsilosis* complex isolates (2/10, 20%) exhibited resistance to VOR, whereas *C. albicans* and *C. tropicalis* isolates remained susceptible. Two *C. albicans* isolates (2/18, 11%) demonstrated resistance to both anidulafungin and micafungin, and 1 *N. glabratus* isolate (1/5, 20%) showed resistance to micafungin. Details of MIC range, MIC₅₀, and MIC₉₀ are presented in Table 1. Antifungal treatment data were available for 33 patients with concurrent candiduria and candidemia. Fluconazole was the most commonly used first-line antifungal agent, administered to 24 patients (72.7%). Echinocandins, including micafungin in 6 patients and anidulafungin in 1 patient, were used in 7 patients (21.2%), while amphotericin B was administered to 2 patients (6.1%). Among the 57 episodes, simultaneous fungal growth in both blood and urine cultures was detected in 29 cases. In 18 of these 29 cases (62%), the same yeast species was identified in both samples. In 20 of the 57 episodes, fungal growth was initially detected in urine samples, followed by blood cultures approximately one week later; concordant yeast species were observed in 11 of these 20 cases (55%). In 8 of the 57 episodes, fungal growth was first detected in blood samples, followed by urine cultures approximately one week later. In 5 of these 8 cases (62.5%), the same yeast species was identified in both samples. The overall mortality rate among patients with *Candida* infections was 84.2% (48/57) (Table 2). Among the three most frequently isolated *Candida* species, *C. albicans* had a 30-day crude mortality rate of 33% and exhibited the highest mortality. Mortality rates for *C. auris* and *C. parapsilosis* complex were 27% and 12.5%, respectively.

DISCUSSION

The diagnosis of fungal infections remains challenging due to non-specific symptoms, delayed culture positivity, and the frequent coexistence of bacterial infections. Delayed antifungal treatment is directly associated with increased mortality; therefore, identifying risk factors is critical for initiating early therapy in intensive care unit (ICU) patients (10). For example, initiating antifungal treatment on the same day that *Candida* is detected in the bloodstream is associated with a mortality rate of 15.4%, whereas a three-day delay increases the rate to 41.4% (11). Effective management requires clinicians to understand the species distribution and antifungal susceptibility profiles of *Candida* isolates commonly recovered from blood cultures. This knowledge is essential for selecting appropriate antifungal agents and planning treatment strategies (9). In ICU patients, simultaneous analysis of candiduria and candidemia pathogens is crucial for guiding therapy. The presence of *Candida* in both blood and urine may indicate dissemination from a single portal of entry or represent two independent infectious events (12). Early identification of patients

Table 1. Minimal inhibitory concentration (MIC) results of *Candida* species according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

<i>Candida</i> species	No. of isolates	Antifungal agents	Range	MIC50	MIC90	S	I/DD-S	R
<i>C. albicans</i>	18	Anidulafungin	(0.004-0.25)	0.016	0.06	16 (87.5)		2 (12.5)
		Micafungin	(0.008-0.06)	0.016	0.06	16 (87.5)		2 (12.5)
		Voriconazole	(0.004-1)	0.004	0.12	18 (100)		
		Fluconazole	(0.06-2)	0.125	0.5	18 (100)		
		Amphotericin B	(0.12-1)	0.5	1	18 (100)		
<i>C. auris</i>	11	Anidulafungin	(0.008-0.5)	0.25	0.5	11 (100)		
		Micafungin	(0.008-0.5)	0.125	0.25	11 (100)		
		Voriconazole	(0.016-1)	1	1	NA		
		Fluconazole	(32-128)	128	128			11 (100)
		Amphotericin B	(1-8)	2	4	4		7 (63.6)
<i>C. parapsilosis</i> complex	10	Anidulafungin	(0.008-2)	0.5	1	10 (100)		
		Micafungin	(0.016-2)	1	2	10 (100)		
		Voriconazole	(0.004-1)	0.12	0.5	7 (70)	1 (10)	2 (20)
		Fluconazole	(0.05-16)	2	16	6 (60)	1 (10)	3 (30)
		Amphotericin B	(0.25-2)	0.5	1	10 (100)		
<i>C. tropicalis</i>	8	Anidulafungin	(0.004-0.064)	0.008	0.064			
		Micafungin	(0.004-0.064)	0.032	0.064			
		Voriconazole	(0.016-0.5)	0.12	0.125	7 (87.5)	1 (12.5)	
		Fluconazole	(0.25-2)	0.5	2			
		Amphotericin B	(0.25-1)	0.5	1	8 (100)		
<i>N. glabratus</i>	5	Anidulafungin	(0.006-0.016)	0.008	0.008	5 (100)		
		Micafungin	(0.008-8)	0.008	0.016	4 (80)		1 (20)
		Voriconazole	(0.016-0.5)	0.064	0.32	NA		
		Fluconazole	(4-32)	16	16		5 (100)	
		Amphotericin B	(0.25-1)	1	1	5 (100)		
Total	52*							

Abbreviations: R: Resistant, S: Susceptible, I/DD: Intermediate/dose-dependent susceptible, MIC50: Minimum inhibitory concentration for 50% of isolates, MIC90: Minimum inhibitory concentration for 90% of isolates, *C.auris*: *Candidozyma auris*, *N.glabratus*: *Nakaseomyces glabratus*, NA: Not Available

*Susceptibility rates did not include the two *C. kefyr*, three isolates of *C. guilliermondii*, *C. krusei*, *C. sphaerica* respectively.

Table 2. Characteristics of *Candida* isolates identified in 57 patients included in this study

	No of patients (%)	Same <i>Candida</i> species in urine and blood (n)	mortality (n)	Different <i>Candida</i> species in urine and blood (n)	mortality (n)	Total Mortality (%)
Urine culture positive before blood culture	20 (35.1)	11	10	9	8	18 (90.0)
Blood culture positive before urine culture	8 (14.0)	5	3	3	2	5 (62.5)
Both of them simultaneous positive	29 (50.9)	18	16	11	9	25 (86.2)
Total	57 (100.0)	34	29	23	19	48 (84.2)

at risk for candidemia may improve clinical decision-making and prevent unnecessary antifungal use. Urinary tract infections (UTIs) caused by *Candida* species are associated with a higher risk of developing candidemia, particularly in individuals with anatomic abnormalities of the urinary tract (11). Specifically, urinary colonization with *C. albicans*, *C. auris*, and *C. parapsilosis* complex may increase the risk of candidemia. Multiple colonization sites and high-density colonization have also been linked to a higher risk (5,13). In this study, 15 patients exhibited colonization with *Candida* at multiple anatomical sites: 10 in tracheal aspirate cultures, 3 in sputum cultures, 1 in a wound site, and 1 in peritoneal fluid. Previous studies suggest that urinary *Candida* infections may develop either as a primary infection preceding candidemia or as a secondary infection following candidemia, depending on host conditions and the virulence of the *Candida* species involved (2,5). For example, Nagata et al. reported a case of candidemia unresponsive to antifungal therapy that resolved only after surgical removal of a urethral foreign body present for ten years, highlighting the role of long-standing urinary sources in candidemia development (11). Observational studies indicate that urinary tract *Candida* infections are a common source of candidemia, accounting for up to 20.8% of cases. Vascular catheters are often the primary source, whereas the gastrointestinal tract is the most frequent overall source. Candidemia in these patients is frequently associated with urinary tract obstruction and stasis (14). In the present study, 22.8% of patients (13/57) had bladder catheters, and 24.6% (14/57) had urinary tract abnormalities, comparable to rates reported by Nagata (11). The incidence of candidemia among patients with candiduria has been reported between 1.3% and 10% in previous studies (2,3,14–16). In our study, the rate was slightly higher at 11% (57/502). Among all patients with positive urine cultures for *Candida*, 6.8% (34/502) had concurrent positive blood cultures with the same species. This aligns with Yapar et al. (15) but is higher than rates reported by Nagata et al. (11). Molecular studies of *Candida* isolates suggest that concurrent candiduria and candidemia may involve the same or different species. In one study, 11 patients with candidemia and candiduria showed different *Candida* species in 54.5% of cases and the same species in 45.5%, though not necessarily genetically related (17). In our study, the proportion of the same species in blood and urine samples was 60% (34/57), higher than previous reports. However, genetic analyses are necessary to establish a strong correlation between urinary and bloodstream infections. Diabetes mellitus and conditions causing urinary stasis, such as neurogenic

bladder, increase susceptibility to fungal infections (11). In this study, diabetes was the most common underlying condition, observed in 38.6% of patients with concurrent candiduria and candidemia. Broad-spectrum antibiotic therapy was identified as the most frequent risk factor (70.2%), consistent with prior studies (18). Regarding species distribution, non-*albicans Candida* (NAC) species were more prevalent than *C. albicans* among patients with concurrent infections, consistent with Ashraf et al. (19). Despite the rising prevalence of NAC, *C. albicans* remains the most commonly reported species in many studies (7,10,20). Predominant NAC species include *C. parapsilosis* complex, *N. glabratus*, *C. tropicalis*, *Pichia kudriavzevii* (formerly *C. krusei*), and *C. auris* (21). The prevalence of NAC varies geographically and is influenced by antifungal use, patient risk factors, and outbreaks (5).

In our study, *C. parapsilosis* complex was the second most frequently isolated species after *C. auris*, likely due to its ability to proliferate in parenteral nutrition solutions and form biofilms, facilitating colonization of intravascular devices and prosthetic materials (22). Healthcare worker hands and contaminated medical devices are important sources of *C. parapsilosis* complex in hospital environments (23). Similarly, *N. glabratus* was less frequent in our cohort (10%) compared to some reports (20–23%) (20). The emergence of *C. auris*, particularly in ICU patients, underscores the importance of timely empirical antifungal therapy. Inappropriate azole exposure may increase mortality, making echinocandins the preferred first-line therapy for invasive *C. auris* infections (9,23). In our cohort, fluconazole was most frequently used, likely reflecting empirical therapy practices, despite increasing azole resistance among NAC species (6). Resistance patterns observed in our study were consistent with global data: *C. albicans* and *C. tropicalis* isolates were fully susceptible to azoles and amphotericin B, while *C. auris* and some *C. parapsilosis* complex isolates exhibited resistance (10,15,22,26–27). Echinocandin resistance was rare, observed in only two isolates, indicating that these agents remain effective alternatives for azole-resistant infections. Mortality was highest among patients with *C. albicans* candidemia, contrasting with some reports linking NAC candidemia to higher mortality (20). Overall, invasive *Candida* infections remain a major cause of morbidity and mortality in immunocompromised patients, with reported mortality rates of 30–70% (10,1,20–23,26,28). Early antifungal therapy remains critical for reducing mortality (21).

Limitations: This study has several limitations. It is a single-center, retrospective analysis with a relatively small sample size, which may limit generalizability. Additionally, genetic relatedness of isolates from concurrent candidemia and candiduria was not investigated. Molecular analyses could clarify the role of hematogenous dissemination in these patients.

CONCLUSION

The present study demonstrated that *C. albicans*, *C. auris*, and members of the *C. parapsilosis* complex are the most frequently observed species in ICU patients with concurrent candiduria and candidemia. Underlying predisposing factors, along with multiple colonization sites in patients with candiduria, may increase the risk of invasive *Candida* infections. These findings highlight the importance of careful clinical management in this population. Furthermore, the present study provides valuable insights into the relationship between candiduria and candidemia, offering guidance for improved clinical decision-making.

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