ABSTRACT

Background and objectives: The finding of Candida species in urine is an usual finding and is called candiduria. There is an increase in the frequency of urinary tract infections (UTI) caused by Candida especially in critically ill patients. This study aimed to determine the epidemiological, clinical, and mycological characteristics of Candida urinary infections in intensive care unit (ICU).
and antifungal susceptibilities. **Methods:** Urine cultures of 394 ICU patients with clinical suspicion of UTI were evaluated. After 24-48 hours of incubation, colonies appeared to grow as yeast, were morphologically examined by Gram staining. *Candida* strains that grew $10^4 \geq$ CFU/mL in urine cultures were accepted as candiduria. The susceptibilities of the *Candida* strains to amphotericin B, itraconazole, fluconazole, voriconazole, flucytosine, and caspofungin were investigated with broth microdilution method. **Results:** The distribution of the isolated 100 urinary *Candida* strains were as, 54 *Candida albicans*, 34 *C. glabrata*, 7 *C. tropicalis*, 2 *C. kefyr*, 2 *C. lusitaniae*, and 1 as *C. parapsilosis*. Among 100 *Candida* species isolated in our study susceptibility rates of amphotericin B, fluconazole, caspofungin, fluconazole, itraconazole, and voriconazole were 100%, 100%, 91%, 23%, 13%, 25.8%, respectively. **Conclusion:** Accurate identification of *Candida* spp., as well as the investigating the antifungal susceptibility, will be beneficial in terms of the effectiveness of the treatment and the prevention of resistance development. **Keywords:** Candida. Urinary tract infection. Fluconazole. Amphotericin B.

**RESUMO**

**Justificativa e objetivos:** O achado de espécies de *Candida* na urina é um achado comum e é chamado de candidúria. Há um aumento na frequência de infecções do trato urinário (ITU) causadas por *Candida*, principalmente em pacientes críticos. Este estudo teve como objetivo determinar as características epidemiológicas, clínicas e micológicas das infecções urinárias por *Candida* em unidade de terapia intensiva (UTI) e a susceptibilidade aos antifúngicos. **Métodos:** Foram avaliadas culturas de urina de 394 pacientes de UTI com suspeita clínica de ITU. Após 24-48 horas de incubação, as colônias pareciam crescer como leveduras, foram morfologicamente examinadas por coloração de Gram. As cepas de *Candida* que cresceram $10^4$ UFC/mL em culturas de urina foram aceitas como candidúria. As suscetibilidades das cepas de *Candida* à anfotericina B, itraconazol, fluconazol, voriconazol, flucitosina e caspofungina foram investigadas com o método de microdiluição em caldo. **Resultados:** A distribuição das cepas 100 isoladas de *Candida* urinária foi de 54 *Candida albicans*, 34 *C. glabrata*, 7 *C. tropicalis*, 2 *C. kefyr*, 2 *C. lusitaniae* e 1 como *C. parapsilosis*. Entre 100 espécies de *Candida* isoladas em nosso estudo, as taxas de susceptibilidade de anfotericina B, fluconazol, caspofungina, fluconazol, itraconazol e voriconazol foram de 100%, 100%, 91%, 23%, 13%, 25.8%, respectivamente. **Conclusão:** A identificação precisa de *Candida* spp., bem como a investigação da susceptibilidade aos antifúngicos, será benéfica em termos de eficácia do tratamento e prevenção do desenvolvimento de resistência. **Palavras chave:** Candida. Infecções urinárias. Fluconazol. Anfotericina B.

**RESUMEN**

**Justificación y objetivos:** El hallazgo de especies de *Candida* en la orina es un hallazgo habitual y se denomina candiduria. Hay un aumento en la frecuencia de infecciones del tracto urinario (ITU) causadas por *Candida*, especialmente en pacientes críticamente enfermos. Este estudio tuvo como objetivo determinar las características epidemiológicas, clínicas y micológicas de las infecciones urinarias por *Candida* en la unidad de cuidados intensivos (UCI) y la susceptibilidad antifúngica. **Métodos:** Se evaluaron urocultivos de 394 pacientes de UCI con sospecha clínica de ITU. Después de 24-48 horas de incubación, las colonias parecían crecer como levadura, se examinaron morfológicamente mediante tinción de Gram. Las cepas de *Candida* que crecieron $10^4$ UFC/ml en urocultivos se aceptaron como candiduria. Las susceptibilidades de las cepas de Candida a la anfotericina B, itraconazol, fluconazol, voriconazol, flucitosina y caspofungina se investigaron con el método de microdilución en caldo. **Resultados:** La distribución de las cepas 100 urinarias aisladas de *Candida* fue de, 54 *C. albicans*, 34 *C. glabrata*, 7 *C. tropicalis*, 2 *C. kefyr*, 2 *C.
Candida esas islas en nuestro estudio, las tasas de susceptibilidad de anfotericina B, flucitosina, caspofungina, fluconazol, itraconazol y voriconazol fueron 100%, 100%, 91%, 23%, 13%, 25,8%, respectivamente. Conclusión: La identificación precisa de Candida spp., así como la investigación de la susceptibilidad antifúngica, será beneficosa en términos de la eficacia del tratamiento y la prevención del desarrollo de resistencias.

Palabras clave: Candida. Infecciones urinarias. Fluconazol. Anfotericina B

INTRODUCTION

Candida species are members of microbiota at various sites in the human body. However, they are capable of colonizing mucocutaneous tissues via attaching to the superficial mucosal cells and are accepted as opportunistic pathogens. The finding of Candida species in urine is a usual clinical situation and is called candiduria. In urine cultures, Candida albicans and non-albicans species are predominantly isolated among fungi, and in the last two decades, there was a remarkable increase in urinary tract infections (UTIs) caused by opportunistic fungi, especially among hospitalized patients which create considerable public health predicaments. Also, there is an increase in the frequency of UTIs caused by fungi, especially Candida species in critically ill patients.

Candida species may cause UTIs via both antegrade pathway by entering the upper urinary tract from the systemic circulation and retrograde pathway by ascending the urinary tract from a colonization site around the urethra. Several reports indicate that Candida species are responsible for at least 10-15% of nosocomial UTIs. UTIs caused by Candida is an emergent problematic issue for immunocompromised and critically ill patients, among the hospitalized patients, candiduria is a frequent finding particularly in intensive care units (ICUs) and in adult surgical ICUs candiduria more frequently go along with UTIs.

There are well defined independent risk factors for candiduria and Candida UTIs including; age >65 years, female sex, prolonged hospitalization, ICU admission, diabetes mellitus, disturbance in microbiome caused by broad-spectrum antimicrobials, female sex, total parenteral nutrition, bladder dysfunction, congenital abnormalities of the urinary tract, renal transplantation, urinary stasis, nephrolithiasis, concomitant bacteriuria, genitourinary tuberculosis, neutropenia, urinary tract instrumentation, chronic renal failure, mechanical ventilation and immunosuppressive therapy.
Even though *C. albicans* is often reported as the predominant species responsible for UTIs, all common *Candida* species can cause UTIs, and non-*albicans* species emerge with better adaptation to the urinary tract system because many studies worldwide stating that half of the candiduria isolates are non-albicans.\(^7\,^9\,^{12}\) Frequent use of antifungal prophylaxis and treatment results in infections with non-*albicans* species showing resistance to antifungals.\(^{13}\) An increase in non-*albicans* species appears as a significant problem due to decreased susceptibility of non-albicans species to antifungals, which may result in complexities or failures in the management of UTIs.\(^{14}\) This study aimed to determine the epidemiological, clinical, and mycological characteristics of *Candida* urinary infections in intensive care unit (ICU) patients and antifungal susceptibilities of *Candida* species.

**METHODS**

In our study, urine cultures of ICU patients were investigated duplicate samples and patients who were taking prior antifungal therapy were excluded. A total of 394 nonrepetitive patients with clinical suspicion of UTIs from anesthesiology and reanimation ICU (50.7%) and internal diseases ICU (49.3%) were evaluated. Since urinary catheterization is a standard practice in ICUs, all patients included in the study had an indwelling urinary catheter. The demographic information and laboratory findings of the patients including age, sex, length of stay, existence of concomitant bacteriuria, existence of concurrent candidemia and average days for detection of candiduria after admittance to the ICU were recorded. Urine samples were transferred with sterile urine containers and inoculated onto Sabouraud Dextrose Agar (SDA; Salubris, Turkey) medium. After 24-48 hours of incubation at 25 °C and 37 °C, colonies appeared to grow as yeast, were morphologically examined by Gram staining. *Candida* strains that grew 10\(^4\) ≥ CFU/mL in urine cultures were accepted as candiduria and included in our study.\(^{15}\,^{16}\)

For the identification of *Candida* species an automated identification system Phoenix (Becton Dickinson, Germany) and chromogenic agar (Chromagar; Salubris, Turkey), as well as classical methods like germ-tube formation was used. Color change of colonies at chromogenic
agar was observed after 48 hours of incubation; *C. albicans* was observed as green, *C. tropicalis* as blue, *C. glabrata*, and *C. kefyr* as pink-purple.

The susceptibilities of the *Candida* strains to amphotericin B, itraconazole, fluconazole, voriconazole, flucytosine, and caspofungin were investigated using the reference broth microdilution method in the Clinical and Laboratory Standards Institute (CLSI) M27-A3, M27-S3, and M27-S4. For both broth microdilution susceptibility experiments, caspofungin (Sigma, China), amphotericin B (Sigma, Israel), fluconazole (Sigma, USA), flucytosine (Sigma, UK), voriconazole (Sigma, USA), and itraconazole (Sigma, USA) were used as antifungals. Distilled water was used for fluconazole and flucytosine, DMSO (dimethyl sulfoxide) (Merck, USA) was used for water-insoluble caspofungin, amphotericin B, voriconazole, and itraconazole as a solvent. Stock solutions were prepared at 1280 μg/mL for fluconazole, 1600 μg/mL for amphotericin B, 1600 μg/mL for voriconazole, 1600 μg/mL for itraconazole, 1600 μg/mL for flucytosine, and 640 μg/mL for caspofungin. Prepared antifungal stock solutions were passed through a membrane filter, divided into 1 mL volumes, placed in sterile Eppendorf tubes, and stored at -80 °C until use. Amphotericin B was coated, protected from light.

An inoculum concentration adjusted to 1.5×10³±1.0×10³ cells/ml with using RPMI 1640 medium (Sigma, USA), were tested with two-folds increasing antifungal concentrations of amphotericin B (0.0313-16 μg/mL), flucytosine (0.125-64 μg/mL), itraconazole (0.0313-16 μg/mL), fluconazole (0.125-64 μg/mL), voriconazole (0.0313-16 μg/mL), caspofungin (0.015-8 μg/mL) by broth microdilution method. After incubation at 35 °C for 48 h (24 hours for caspofungin), minimum inhibitory concentrations (MICs) were defined as the lowest concentration that inhibited visual fungal growth compared with the drug-free controls. *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 strains were used for control.

Breakpoints for antifungal susceptibility were evaluated according to CLSI guidelines but, CLSI has not determined breakpoints for amphotericin. The isolates inhibited by amphotericin B at ≤1 μg/ml were considered susceptible, resistant isolates were defined as isolates with MIC >1 μg/ml. Also, since there is no new update in M27-S4 for *C. kefyr*, the values in M27-S3 were taken into consideration while evaluating the MIC breakpoints.

Also for *C. lusitaniae*, since there is
no update for M27-S4 fluconazole and voriconazole, the MIC breakpoints specified in M27-S3 were taken into consideration.

SPSS 16.0 (Statistical Package for Social Sciences) Package program was used for the analysis of the data obtained from the study. Mean, standard deviation, and percentage distributions were given as descriptive statistics. In addition, the Chi-Square test was used for the comparison of non-numerical variables. Mann Whitney-U test was used to compare binary variables with numerical data. The results obtained were evaluated at the 95% (P <0.05) significance level. In order to carry out this study, ethics committee approval was obtained from Gaziantep University Clinical Research Ethics Committee (Code:2016/298).

RESULTS

Urine samples from 394 ICU patients were examined; there was candiduria in 54 (13.7%) patients, candiduria and concomitant bacteriuria in 46 (11.6%) patients, bacteriuria in 69 (17.5%) patients, and 235 (59.6%) patients had negative urine cultures. A total of 100 Candida strains were evaluated. The distribution of the isolated urinary Candida strains were as, 54 C. albicans, 34 C. glabrata, 7 C. tropicalis, 2 C. kefyr, 2 C. lusitaniae, and 1 as C. parapsilosis. Concurrent candidemia was detected in 14 of patients with candiduria. The distribution of Candida species isolated from blood cultures was 10 (71.4%) C. albicans, 2 (14.2%) C. parapsilosis, 1 (7.1%) C. glabrata, and 1 (7.1%) C. lusitaniae.

Determined by broth microdilution; 91 Candida species were susceptible to caspofungin, 8 were moderately susceptible, and 1 was resistant, 23 Candida species were susceptible to fluconazole, 37 were dose-related susceptible, and 40 were resistant, 13 Candida species were susceptible to itraconazole, 18 were dose-dependent susceptible, and 69 were resistant. There were 17 (25.8%) voriconazole susceptible strains, 13 dose-dependent susceptible (19.7%) strains, and 36 (54.5%) resistant Candida strains (C. glabrata not included due to CLSI statement: current data are insufficient to demonstrate a correlation between in vitro susceptibility testing and clinical outcome). Among the 100 Candida strains examined, resistant strains against amphotericin B (≥2 µg/mL) and flucytosine (≥32 µg/mL) were not detected. MIC range, MIC$_{50}$, and MIC$_{90}$ values of
antifungal drugs for *Candida* species are given in Table 1. Also, detailed antifungal susceptibility results of different *Candida* species were given in Table 2.

Table 1. MIC ranges, MIC$_{50}$ and MIC$_{90}$ values of antifungals for different *Candida* species

| Species (n) | Antifungal | MIC range (μg/mL) | MIC$_{50}$ (μg/mL) | MIC$_{90}$ (μg/mL) |
|-------------|------------|-------------------|--------------------|--------------------|
|             |            |                   |                    |                    |
| *C. albicans* (54) | Amphotericin B | 0.125-1           | 0.5                | 1                  |
|             | Itraconazole | 0.06-16           | 2                  | 16                 |
|             | Voriconazole | 0.03-16           | 2                  | 16                 |
|             | Caspofungin  | 0.015-0.5         | 0.03               | 0.25               |
|             | Fluconazole  | 0.125-64          | 4                  | 64                 |
|             | Flucytosine  | 0.125-2           | 0.125              | 0.5                |
|             | Amphotericin B | 0.125-1         | 1                  | 1                  |
|             | Itraconazole | 0.03-16           | 8                  | 16                 |
|             | Voriconazole | 0.03-16           | 1                  | 16                 |
| *C. glabrata* (34) | Caspofungin  | 0.015-0.5         | 0.03               | 0.25               |
|             | Fluconazole  | 0.125-64          | 4                  | 64                 |
|             | Flucytosine  | 0.125-0.5         | 0.125              | 0.25               |
|             | Amphotericin B | 0.5-1            | 0.5                | 1                  |
|             | Itraconazole | 0.06-16           | 0.125              | 16                 |
|             | Voriconazole | 0.03-16           | 0.125              | 1                  |
| *C. tropicalis* (7)  | Caspofungin  | 0.03-0.125        | 0.06               | 0.06               |
|             | Fluconazole  | 1-32              | 8                  | 32                 |
|             | Flucytosine  | 0.125-0.5         | 0.125              | 0.5                |
|             | Amphotericin B | 0.5-1            | 0.5                | 1                  |
|             | Itraconazole | 1-16              | 1                  | 16                 |
Table 2. Antifungal susceptibility results of different *Candida* species

| Antifungal | *C. albicans* | *C. glabrata* | *C. tropicalis* | *C. lusitaniae* | *C. kefyr* | *C. parapsilosis* |
|------------|---------------|---------------|-----------------|-----------------|-----------|-----------------|
| Caspofungin | S 50 (92.6%)  | 29 (85.3%)    | 7 (100%)        | 2 (100%)        | 1 (100%)  | -               |
| I 4 (7.4%)  | 4 (11.8%)     | -             | -               | -               | -         | -               |
| R           | -             | 1 (2.9%)      | -               | -               | -         | -               |
| Fluconazole | S 18 (33.3%)  | -             | 3 (42.9%)       | 1 (50%)         | 1 (50%)   | -               |
| I 11 (20.4%)| 25 (73.5%)    | -             | 1 (50%)         | -               | -         | -               |
| R 25 (46.3%)| 9 (26.5%)     | 4 (57.1%)     | -               | 1 (50%)         | 1 (100%)  | -               |
| Voriconazole| S 9 (16.7%)   | 17 (97.6%)    | 4 (57.1%)       | 1 (50%)         | 2 (100%)  | 1 (100%)        |
| I 12 (22.2%)| 1             | 1 (14.3%)     | -               | -               | -         | -               |
| R 33 (61.1%)| 16 (2.4%)     | 2 (28.6%)     | 1 (50%)         | -               | -         | -               |
| Itraconazole| S 4 (7.4%)    | 4 (11.8%)     | 3 (42.9%)       | 1 (50%)         | -         | 1 (100%)        |
| I 12 (22.2%)| 5 (14.7%)     | 1 (14.2%)     | -               | -               | -         | -               |
| R 38 (70.4%)| 25 (73.5%)    | 3 (42.9%)     | 1 (50%)         | 2 (100%)        | -         | -               |
| Flucytosine | S 54 (100%)   | 34 (100%)     | 7 (100%)        | 2 (100%)        | 2 (100%)  | 1 (100%)        |
| I           | -             | -             | -               | -               | -         | -               |
| R           | -             | -             | -               | -               | -         | -               |
| Amphotericin B | S 54 (100%) | 34 (100%) | 7 (100%) | 2 (100%) | 2 (100%) | 1 (100%) |
In our study, 60 (60%) of the patients with candiduria were female and 40 (40%) were male. A significant difference was found between the two groups in terms of sex distribution (p=0.046). When *Candida* species were analyzed according to sex, *C. albicans* was higher (53.7%) among males and non-*albicans* species were higher (58.3%) among females. Non-albicans species were isolated more frequently in females and a statistically significant difference was found (p=0.002).

Of the 100 patients whose *Candida* strains were isolated, 9 were in the age range of 20-40, 16 were 41-60, and 75 were 61 and over. The length of stay of the patients in the ICUs was varying between 6 and 120 days (mean 33.8 days). After admittance to ICU, candiduria was detected (mean 9.7 days) within 1-9 days in 64 patients, 10-19 days in 23 patients, 20-29 days in 8 patients and >30 days in 22 patients. While the mortality rate was 41.1% among patients included in our study (n:349), the overall mortality rate among patients with candiduria was 69%, and among patients with both candiduria and candidemia was 92.8%. There was a significant difference in mortality rate between patients with candiduria and without candiduria (p <0.001). No significant difference was found between the causative agent of candiduria and the mortality rate.

**DISCUSSION**

The detection of candiduria manifests as a diagnostic and therapeutic challenge for all levels of health care settings and may be frustrating for physicians from primary care or infectious diseases, along with intensive medicine and surgery. Urinary *Candida* may be related to a number of conditions ranging from sample contamination to UTIs, including invasive candidiasis, therefore, require detailed analysis. Obtaining new urine samples and confirming whether candiduria persists, can usually help for differentiation of contamination from colonization or UTI. If there is growth in the second culture repeated, but the patient is asymptomatic, predisposing factors should be reviewed, the urinary catheter should be removed, and antibiotic therapy should...
be terminated. Urinary tract imaging is recommended in patients with diabetes mellitus and patients with known urinary tract abnormalities, it may be guiding for appropriate treatment.

In our study, female sex and advanced age were detected as risk factors for the development of candiduria. Although females are twice as likely to develop nosocomial candiduria when compared to males, possibly due to the anatomical differences of their genitals and vaginal colonization, females with candiduria was linked to a reduced risk of candidemia when compared to males. Candida species are more common in the urine of the elderly, especially after broad-spectrum antibiotic treatments, advanced age, normal physical changes, and/or various metabolic disorders or neoplastic diseases that cause disruption of the mucosal and cutaneous barriers and make the person vulnerable to Candida infections. Interestingly we did not find a correlation between long-stay in ICU and candiduria while 64% of our patients develop candiduria in 9 days after admittance to ICU, in a similar study from France, the time between admission to the ICU and the development of candiduria was reported as 17.2±1.1 days.

There are no defined standard diagnostic criteria for diagnosis of Candida UTIs and their differentiation of from asymptomatic candiduria, and differentiation of upper from lower UTIs. Also, there is no consensus in diagnostic evaluation colony counts(CFU/ml) and urine collection technique for neonatal candiduria unlike in bacteriuria. Although the clinical significance of candiduria is still contradictory, various researchers suggest that colony counts greater than \(10^3\)–\(10^4\)CFU/mL are more likely related to primary or disseminated candidiasis, rather than sample contamination or colonization.

Candiduria frequency among ICU patients increased in recent years, especially among patients requiring urinary instrumentation or receiving broad-spectrum antibiotics and risk of occurrence is as high as 22.89% in ICU patients. The finding of Candida in the urinary samples is associated with higher mortality, particularly in ICU patients with accompanying comorbidities. However, higher mortality rates in patients with candiduria are not often directly attributable to invasive candidiasis. Nevertheless, candiduria may be an indicator of severe underlying diseases. In a clinical study in-hospital mortality was 48.8% in patients with candiduria compared to 36.6% in those without candiduria (p <0.001), they also found significant differences for ICU mortality.
Researchers found, candiduria detected at any time in the surgical ICU was independently associated with mortality. Our study also revealed candiduria as an independent risk factor for mortality (p < 0.001). The incidence of concurrent candidemia is infrequent and has been encountered in 1-8% of patients with candiduria, even so, ICU patients constitute the high-risk group. Our results showing 14% candiduria with concurrent candidemia in ICU patients also indicate physicians should be more alarmed about invasive candidiasis in critically ill patients with candiduria. Long hospital-stay and malignancy are predictors for developing candidemia in patients with candiduria; however, the patient characteristics linked to concomitant candidemia in the presence of candiduria remain unknown.

Management of candiduria is still contradictory because the finding of Candida spp. in urinary specimens may indicate asymptomatic infection, lower UTI, upper UTI with a potential for ascending pyelonephritis, renal candidiasis leading to invasive and disseminated candidiasis, which not only results in considerable morbidity and mortality but also prolonged hospitalization and growing cost. Candiduria may be an indicator of disseminated candidiasis in neutropenic, low birth weight infants, patients undergoing urological procedures, and renal transplant recipients patient groups. Candiduria in critically ill patients whether symptomatic or not should initially be considered as a clue of disseminated candidiasis and antifungal drug prophylaxis appears to be warranted since the kidney is affected by disseminated candidiasis in 80% of patients. Detection of candiduria may be the only evidence that the patient has a serious infection. In these patients, systemic therapy with fluconazole or anotherazole derivative is recommended. An echinocandin, such as caspofungin, is selected if the patient has had recent exposure to fluconazole, which is the drug of choice. In the treatment of cystitis and pyelonephritis, oral fluconazole is used in susceptible strains, and flucytosine and amphotericin B are used in those with fluconazole resistance. Bladder irrigation with amphotericin B may be beneficial in cystitis caused by fluconazole-resistant strains such as C. glabrata and C. krusei. Voriconazole is stated as an effective antifungal that can be used in isolates resistant to fluconazole. However, a significant portion of fluconazole-resistant Candida isolates become resistant to voriconazole as well as itraconazole as a result of cross-resistance. The most important features of caspofungin are that it is effective against azole and amphotericin B resistant Candida strains. Since there is no cross-
resistance between azole antifungals, caspofungin can be a good option for Candida species resistant to azole antifungals.¹

Although C. albicans is the most prevalent species reported in urine culture, other species such as C. glabrata, C. parapsilosis, C. tropicalis, C. kefyr, C. lusitanae, C. guilhermondi, and C. dubliniensis can also be isolated.¹ The distribution of causative agents of Candida UTIs is shifting, non-albicans species are detected in more than half of the urinary samples, which also bring along antifungal resistance issues.⁷ These non-albicans Candida may not only show better adaptation to the kidney and collecting system but also more challenging to eradicate than C. albicans.⁹ The detection of candiduria in an ICU patient should be regarded as an indicator of poor prognosis and the accurate identification of Candida spp., as well as the investigating the antifungal susceptibility, will be beneficial in terms of the effectiveness of the treatment and the prevention of resistance development.

DECLARATIONS OF INTEREST

None.

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REFERENCES

1. Gajdács M, Dóczi I, Ábrók M, et al. Epidemiology of candiduria and Candida urinary tract infections in inpatients and outpatients: results from a 10-year retrospective survey. Cent European J Urol. 2019;72(2):209-214. https://doi.org/10.5173/ceju.2019.1909
2. Hollenbach E. To treat or not to treat--critically ill patients with candiduria. Mycoses. 2008;51(2):12-24. https://doi.org/10.1111/j.1439-0507.2008.01570.x
3. Kauffman CA, Vazquez JA, Sobel JD, et al. Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group. Clin Infect Dis. 2000;30(1):14-18. https://doi.org/10.1086/313583
4. Bougnoux ME, Kac G, Aegerter P, et al. Candidemia and candiduria in critically ill patients admitted to intensive care units in France: incidence, molecular diversity, management and outcome. Intensive Care Med. 2008;34(2):292-299. https://doi.org/10.1007/s00134-007-0865-y
5. Fisher JF, Sobel JD, Kauffman CA, et al. Candida urinary tract infections--treatment. Clin Infect Dis. 2011;52(Suppl 6):457-66. https://doi.org/10.1093/cid/cir112
6. Fisher JF. Candida urinary tract infections--epidemiology, pathogenesis, diagnosis, and treatment: executive summary. Clin Infect Dis. 2011;52(Suppl 6):429-32. https://doi.org/10.1093/cid/cir108
7. Kauffman CA. Candiduria. Clin Infect Dis. 2005;41:371–6. https://doi.org/10.1086/430918
8. Alvarez-Lerma F, Nolla-Salas J, León C, et al. Candiduria in critically ill patients admitted to intensive care medical units. Intensive Care Med. 2003;29(7):1069-1076. https://doi.org/10.1007/s00134-003-1807-y
9. Sobel JD, Fisher JF, Kauffman CA, et al. Candida urinary tract infections--epidemiology. Clin Infect Dis. 2011;52(Suppl 6):433-6. https://doi.org/10.1093/cid/cir109
10. Alfouzan WA. Epidemiological study on species identification and susceptibility profile of Candida in urine. Fungal Genom Biol. 2015;5:124. https://doi.org/10.4172/2165-8056.1000124
11. Achkar JM, Fries BC. Candida infections of the genitourinary tract. Clin Microbiol Rev. 2010;23(2):253-273. https://doi.org/10.1128/CMR.00076-09
12. Jamil S, Jamil N, Saad U, et al. Frequency of Candida albicans in Patients with Funguria. J Coll Physicians Surg Pak. 2016;26(2):113-116.
13. Sakamoto Y, Kawabe K, Suzuki T, et al. Species Distribution of Candidemia and Their Susceptibility in a Single Japanese University Hospital: Prior Micafungin Use Affects the Appearance of Candida parapsilosis and Elevation of Micafungin MICs in Non-parapsilosis Candida Species. J Fungi (Basel). 2021;7(8):596. https://doi.org/10.3390/jof7080596
14. He Z, Huo X, Lei D, et al. Management of candiduria in hospitalized patients: a single-center study on the implementation of IDSA guidelines and factors affecting clinical decisions. Eur J Clin Microbiol Infect Dis. 2021;40(1):59-65. https://doi.org/10.1007/s10096-020-03999-1
15. Denis B, Chopin D, Piron P, et al. Candiduria in kidney transplant recipients: Is antifungal therapy useful?. Mycoses, 2018;61(5):298-304. https://doi.org/10.1111/myc.12740
16. Sobel JD, Kauffman CA, McKinsey D. Candiduria: a randomized, double-blind study of treatment with fluconazole and placebo. The National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group. Clin Infect Dis. 2000;30(1):19-24. https://doi.org/10.1086/313580
17. Clinical and Laboratory Standards Institute (CLSI). Reference method for broth dilution antifungal susceptibility testing of yeasts; approved Standard-third edition. CLSI document M27-A3. Clinical and Laboratory Standards Institute, Wayne, Pennsylvania 2008.
18. Clinical and Laboratory Standards Institute (CLSI). Reference method for broth dilution antifungal susceptibility testing of yeasts; third informational supplement CLSI document M27-S3. Clinical and Laboratory Standards Institute, Wayne, Pennsylvania 2008.
19. Clinical and Laboratory Standards Institute (CLSI). Reference method for broth dilution antifungal susceptibility testing of yeasts; fourth informational supplement CLSI document M27-S4. Clinical and Laboratory Standards Institute, Wayne, Pennsylvania 2012.
20. Wang K, Hsueh K, Kronen R, et al. Creation and assessment of a clinical predictive model for candidaemia in patients with candiduria. Mycoses. 2019;62(7):554-561. https://doi.org/10.1111/myc.12917
21. García-Agudo L, Rodríguez-Iglesias M, Carranza-González R. Approach of clinicians to candiduria and related outcome in the elderly. J Mycol Med. 2018;28(3):428-432. https://doi.org/10.1016/j.jmycolmed.2018.05.011
22. He Z, Su C, Bi Y, et al. Evaluation of a Novel Laboratory Candiduria Screening Protocol in the Intensive Care Unit. Infect Drug Resist. 2021;14:489-496. https://doi.org/10.2147/IDR.S289885
23. He Z, Liu Y, Wang T, et al. Candiduria in hospitalized patients: an investigation with the Sysmex UF-1000i urine analyzer. PeerJ. 2019;7:e6935. https://doi.org/10.7717/peerj.6935
24. Aghili SR, Abastabar M, Soleimani A, Haghani I, Azizi S. High prevalence of asymptomatic nosocomial candiduria due to Candida glabrata among hospitalized patients with heart failure: a matter of some concern?. Curr Med Mycol. 2020;6(4):1-8. https://doi.org/10.18502/cmm.6.4.5327

Contribuições dos autores:
Fahriye Ekşi and Süleyman Ganidağlı was responsible for the organization and coordination and was the chief investigator. Ban Ali Hassan, Mehmet Erımez, Berna Kaya Uğur, and Hamit Yıldız performed the data analysis and developed the trial design. Mehmet Erımez and Fahriye Ekşi critically revised the manuscript for important intellectual content. All authors contributed to the writing of the final manuscript.
