Araştırma Makalesi/Original Article
Makale Dili "İngilizce"/Article Language "English"

Türk Hijyen ve Deneysel Biyoloji Dergisi

The epidemiology and antifungal susceptibility of *Candida* species isolated from patients in intensive care units of a research hospital

Araştırma hastanesinde yoğun bakım ünitelerindeki hastalardan izole edilen *Candida* türlerinin epidemiyolojisi ve antifungal duyarlılığı

Esma EREN[1] (ID), Hafize SAV[2] (ID), Zehra BEŞTEPE DURSUN[1] (ID)

ABSTRACT

Objective: Over the past two decades, *Candida* species have come to be regarded as important agents of nosocomial infection. In this study, we evaluated the epidemiology, antifungal susceptibility of *Candida* species isolated from adult and pediatric patients in intensive care units of a research hospital from 2015 to 2017.

Methods: A total of 279 yeast *Candida* isolates recovered from blood and other samples were identified to species by using conventional (germ tube formation, microscopic morphology in corn meal-Tween 80 agar and formation of clamydospore, presence of pseudohyphae, carbonhytrate fermentation and assimilation tests,ürease and nitrate test), and Phoenix (Becton Dickinson, ABD). Susceptibility of the same species to amphotericin B (AMB), fluconazole (FLC),voriconazole (VRC) and caspofungin (CAS)) were determined by E test method.

Results: The specimens were isolated from, urine 173 (62%), blood 76 (27.24%), wound 18 (6.45%), tissue culture 4 (1.43%), central venous catheter 3 (1.08%), respiratory tract 2 (0.72%), peritoneal fluid 2 (0.72%), pleural fluid 1 (0.36%). The most commonly isolated species was 185 (66.31%) *C. albicans* from the various clinical specimens

ÖZET

Amaç: *Candida* türleri son yirmi yılda nozokomiyal enfeksiyonların önemli ajanları olarak görülmeye başlanmıştır. Çalışmamızda hastanemizde 2015-2017 tarihleri arasında çocuk ve yetişkin hasta grubundan izole edilen *Candida* spp. türlerinin lokal epidemiyolojisi ve antifungal duyarlılığının belirlenmesi amaçlanmıştır.

Yöntem: Klinik örneklerden izole edilen toplam 279 *Candida* spp. türü ticari Phoenix (Becton Dickinson, ABD) ve konvansiyonel yöntem (germ tüp oluşumu, mısır unlu agarda mikroskobik morfoloji, klamidospor oluşumu, pseudohif bulunuşu, karbonhidrat fermantasyon ve asimilasyon testleri, üreaz testi, nitrat testi) ile tanımlanmıştır. İzole edilen türlerin flukonazol, vorikonazol, amfoterisin B, kaspofungin antifungal minimum inhibisyon konsantrasyonu (MIK) değerleri antifungal duyarlılığı E-test metodu ile belirlenmiştir.

Bulgular: Örneklerin dağılımı 173 (%62) idrar, 76 (%27,24) kan, 18 (%6,45) yara, 4 (%1,43) doku, 3 (%1,08) santral venöz kateter, 2 (%0,72) solunum yolu, 2 (%0,72) peritoneal sıvı, 1 (%0,36) plevral mayi olarak belirlenmiştir. Klinik örneklerden izole edilen *Candida* türleri 185 (%66,31) *C. albicans*, 33 (%11,83)

[1]Kayseri City Hospital, Department of Infectious Diseases and Clinical Microbiology, Kayseri
[2]Kayseri City Hospital, Department of Mycology, Kayseri

İletişim / Corresponding Author : Hafize SAV
Kayseri Şehir Hastanesi, Mikoloji bölümü, Kayseri - Türkiye
E-posta / E-mail : hafize.sav@hotmail.com

Geliş Tarihi / Received : 26.10.2020
Kabul Tarihi / Accepted : 23.03.2021

DOI ID : 10.5505/TurkHijyen.2022.34356

Eren E, Sav H, Beştepe Dursun Z. The epidemiology and antifungal susceptibility of *Candida* species isolated from patients in intensive care units of a research hospital. Turk Hij Den Biyol Derg, 2022; 79(1): 93 - 102

was followed by the species of 33 (11.83%) *C. parapsilosis*, 29 (10.39%) *C. glabrata*, 29 (10.39%), *C. tropicalis*, 2 (0.72%) *C. pelliculosa*, 1 (0.36%) *C. melibiosica*. *C. glabrata* was the most frequently isolated in elderly patients and *C. albicans* was the most frequently isolated in childhood. Various candida species have been isolated from the urine samples of 173 patients with candiduria. *C. albicans* was found to be the most common cause of candiduria (142 samples (82%)). Antifungal susceptibility test study was performed from 92 *Candida* isolates. For these species, the geometric mean minimum inhibitor concentration of each antifungal was calculated to be 2.2 µg/mL for FLC, 0.6 µg/mL for AMB, 0.6 µg/mL for CAS and 0.1 µg/mL for VRC. All *Candida* isolates were found susceptible to voriconazole. Seven isolates of 19 *C. glabrata* species were dose-dependent sensitivity and two isolates were determined to be resistant to fluconazole. Three isolates of 26 *C. parapsilosis* species were reported to be resistant to caspofungin.

Conclusion: *C. albicans* is the most common *Candida* species isolated from the clinical specimens we studied. Knowing the types and susceptibility of *Candida* strains will be an important factor in our choice of antifungal therapy.

Key Words: Antifungal susceptibility, *Candida* spp., epidemiology, intensive care unit

C. parapsilosis, 29 (%10,39) *C. glabrata*, 29 (%10,39) *C. tropicalis*, 2 (%,0,72) *C. pelliculosa*, 1 (% 0,36) *C. melibiosica* olarak tanımlanmıştır. Yaşlı hastalardan en sık *C. glabrata* türü, çocuk hastalardan en sık *C. albicans* türü izole edilmiştir. Kandidürisi olan 173 hastanın idrar örneğinde çeşitli kandida türleri izole edilmiştir. En sık (142 örnekte (%82)) kandidüri etkeni olarak *C. albicans* tespit edilmiştir. Klinisyen isteğine bağlı olarak 92 *Candida* izolatından antifungal çalışılmıştır. Bu türler için geometrik minimum inhibitor konsantrasyon değeri flukonazol için 2,2 µg/mL, amfoterisin B için 0,6 µg/mL, kaspofungin 0,6 µg/mL, vorikonazol 0,1 µg/mL olarak belirlenmiştir. İzolatların hepsi vorikonazol için duyarlı bulunmuştur. Flukonazol için 19 *C. glabrata* türünden yedi izolat doza bağlı duyarlı ve iki izolat dirençli olarak tespit edilimiştir. Kaspofungin için 26 *C. parapsilosis* türünün üçü dirençli olarak belirlenmiştir.

Sonuç: Çalıştığımız klinik örneklerden en sık izole edilen tür *C. albicans* türüdür. Kandida enfeksiyonlarının lokal epidemiyolojisini bilmek ampirik antifungal ajanların seçimi için gerekli bir bilgidir.

Anahtar Kelimeler: Antifungal duyarlılık, *Candida* spp., epidemiyoloji, yoğun bakım

INTRODUCTION

There are over 150 species of *Candida* spp. isolates in nature. While the isolation frequency of these species is changing, it is accepted that the most commonly isolated species are *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* (1). *Candida* species isolated from different age groups may vary. For example, *C. parapsilosis* isolated from the blood cultures of newborns is known as a predominant species (2, 3). The frequency of *C. glabrata* species is higher in adult and elderly patients (4). *C. tropicalis* is more frequently isolated in patients from non-neutropenic and haematological malignancies (5).

Nosocomial invasive infections caused by *Candida* spp. have been a major medical problem in intensive care units (ICUs). Infectious Diseases Society of America (IDSA) anti-fungal treatment protocols vary according to patients' age groups (6). These latest treatment protocols state that echinocandins are recommended as the first choice for suspected candidiasis. Fluconazole (FLC) is an acceptable alternative azole drug for non-neutropenic patients (those who have had no recent azole exposure and are not colonized with azole-resistant *Candida* species) in intensive

care. Despite new antifungal drugs, amphotericin B deoxycholate is recommended for neonates with disseminated candidiasis (7). In patients without neutropenia, initial antifungal treatment begins with FLC. This regimen can be used for infections caused due to *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. kefyr*, *C. dubliniensis*, *C. lusitaniae*, and *C. guilliermondi*. Caspofungin (CAS) is recommended for *C. glabrata* infections (6). *C. krusei* is intrinsically resistant to FLC and has a decreased susceptibility to other azoles. Echinocandins, VCZ or amphotericin B (AMB) are preferred antifungal regimens for *C. krusei* infection (8).

The aim of our study was to analyze the species distribution of *Candida* isolates from different clinical specimens and determine antifungal susceptibility to AMB, FLC, voriconazole (VRC) and CAS, by the E-test method.

MATERIAL and METHOD

Patients

This was a retrospective study of *Candida* infection in the ICUs of a 1200-bed research hospital in Turkey. The study was conducted according to the declaration of Helsinki. The patients were selected from patients who were hospitalized in ICUs between October 2015 and August 2017. A total of 279 non-repeat isolates of *Candida* isolates were obtained from 76 blood, 173 urine, 18 wounds, four tissue sample, three central venous catheters, two respiratory tracts, two peritoneal fluid, one pleural fluid of patients in adult and child intensive care unit of a research hospital. Candidemia was defined as the isolation of *Candida* spp. from blood cultures and other forms of invasive candidiasis (proven or probable) were defined according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria (9). In our study, all patients with asymptomatic candiduria had a urinary catheter. Candiduria refers to the laboratory finding of $>10^3$ colony-forming units (CFU) of *Candida* spp. per mL of urine. For suspicious infection potentially occurring nosocomially and out of the hospital, samples including wound, respiratory tract, peritoneal fluid, pleural fluid were cultured on SDA agar for fungal identification. The cut-off age value for elderly patients was taken as 65 years.

Mycological studies

Identification of each strain was performed by using conventional (germ tube formation, microscopic morphology in corn meal-Tween 80 agar) and automated methods, Phoenix (Becton Dickinson, ABD).

Antifungal Agents and Susceptibility Testing

All isolates were cultured by using SDA (Oxoid, Basingstoke, United Kingdom). These isolates were tested for susceptibility against FLC, CAS, VRC, and AMB with E test method. For the antifungal susceptibility testing RPMI 1640 (Sigma) medium was prepared. 4 g L-glutamine, 34.5 g morpholinepropanesulfonic acid, 20 g glucose, and 17 g Bacto agar (Becton Dickinson and Company, Sparks, MD, USA) were dissolved in 1 L deionized water and autoclaved at 121°C for 15 minutes. The inoculum suspensions were adjusted spectrophotometrically at 530 nm to match the turbidity of a 0.5 McFarland standard. Agar plates were inoculated with a cotton swab and allowed to dry for at least 15 min before the E-test strips were applied. E-test agar plates were incubated at 35°C and assessed at 48 h. Minimum inhibitory concentrations (MICs) of azole were detected as the lowest concentrations providing an 80% reduction in growth. MICs of AMB was determined as the lowest concentration inhibiting any growth. MICs were also determined by the E-test method according to the manufacturer's guidelines. E-test strips of FLC (0.016-256 µg/ml), VRC (0.002-32 µg/ml), AMB (0.002-32 µg/ml), and CAS (0.002-32 µg/ml) were placed perpendicular to each other on an RPMI plate. Quality control was performed in both tests in accordance with the CLSI (The Clinical & Laboratory Standards Institute) document M27-A3 using *C. krusei* ATTC 6258 and *C. parapsilosis* ATCC 22019.

RESULTS

Candida species were isolated from the clinical specimens of 279 patients, including 147 female and 132 male patients hospitalized in our ICUs. The mean age of the patients was found to be 65 years. The specimens were isolated from urine 173 (62%), blood 76 (27.24%), wound 18 (6.45%), tissue culture 4 (1.43%), central venous catheter 3 (1.08%), respiratory tract 2 (0.72%), peritoneal fluid 2 (0.72%), pleural fluid 1 (0.36%). The most commonly isolated species from various specimens of pediatric and adult patients was determined to be *C. albicans*. While 185 of 279 isolates (66.31%) were identified as *C. albicans*, the others were identified as 33 (11.83%) *C. parapsilosis*, 29 (10.39%) *C. glabrata*, 29 (10.39%) *C. tropicalis*, 2 (0.72%) *C. pelliculosa*, 1 (0.36%) *C. melibiosica*, respectively (Table 1). Considering all the specimens, the unit in which proliferation was observed most frequently was determined to be the anaesthesia intensive care unit. Simultaneously, the most commonly isolated species from all specimens in the pediatric intensive care unit (n = 11/17, 64.7%) were identified to be *C. albicans*. In the adult and pediatric intensive care units, 76 *Candida* species were isolated from the blood culture. Examining the blood culture isolates, the most commonly isolated species was 32 (42.2%) *C. albicans* species and it was followed by 26 (34.2%) *C. parapsilosis*, 11(14.4%) *C. glabrata*, 7 (9.2%) *C. tropicalis* species, respectively. Distribution of *Candida* species isolated from patients in intensive care unit was shown in Table 2. From the 142 of 173 urine specimens coming from the hospitalized patients of intensive care units in our hospital, *C. albicans*, (n = 15/173, 8.7%), *C. tropicalis*, (n = 11/173, 6.3%) *C. glabrata* (n = 2/173, 1.2%) *C. parapsilosis*, *C. pelliculosa* (n = 2/173 1.2%), *C. melibiosica* (n = 1/173, 0.6%) were isolated, respectively.

Table 1. Distribution of *Candida* species isolated from patients in intensive care

Department	*C. albicans*	*C. glabrata*	*C. melibiosica*	*C. parapsilosis*	*C. pelliculosa*	*C. tropicalis*	TOTAL
Anesthesia ICU	60	8	-	19	-	10	97
Brain surgery ICU	14	-	-	3	-	2	19
Pediatric ICU	11	1	-	3	-	2	17
Medical ICU	47	8	-	2	1	5	63
Chest diseases ICU	2	-	-	1	-	-	3
Surgical ICU	13	7	-	-	-	-	20
Cardiovascular surgery ICU	3	-	-	1	-	1	5
Cardiac ICU	8		1	1	1	1	12
Neurology ICU	21	4	-	2		4	31
Burn Unit	6	1	-	1		4	12
Total (Number%)	185(66.31%)	29(10.39%)	(0.36%)	33(11.83%)	2(0.72%)	29(10.39%)	279

ICU: Intensive Care Unit
-: Not growth

Table 2. Distribution of *Candida* species isolated from blood cultures in intensive care

Department	*C. albicans*	*C. glabrata*	*C. parapsilosis complex*	*C. tropicalis*	Total
Anesthesia ICU	10	2	17	4	33
Brain surgery ICU	1	-	2	-	3
Pediatric ICU	6	-	2	-	8
Medical ICU	7	4	1	3	15
Chest diseases ICU	1	-	-	-	1
Surgical ICU	2	4			6
Cardiovascular surgery ICU	-	-	1	-	1
Cardiac ICU	1	-	-	-	1
Neurology ICU	1	-	2	-	3
Burn Unit	3	1	1	-	5
Total	32	11	26	7	76

ICU: Intensive Care Unit

The antifungal sensitivity of 92 species of *Candida* species was evaluated by the E-test method. For these species, the geometric mean (GM) Minhibitor concentration of each antifungal was calculated to be 2.2 µg/mL for FLC, 0.6 µg/mL for AMB, 0.6 µg/mL for CAS and 0.1 µg/mL for VRC. The MIC 50 and MIC 90 values of the isolated *Candida* species against antifungals were presented in Table 3. No cross-resistance was encountered between FLC and VRC. Seven isolates of 19 *C. glabrata* species isolated from various clinical specimens had dose-dependent sensitivity to FLC and two isolates were determined to be resistant. Also, three isolates of 26 *C. parapsilosis* species were reported to be resistant to CAS.

Table 3. *In vitro* susceptibilities of the *Candida* isolates to four antifungal agents (µg/ml)

	AMB			CAS			FLC			VRC		
Species (Number)	MIC range	MIC50	MIC90	MIC range	MIC50	MIC90	MIC range	MIC50	MIC90	MIC range	MIC50	MIC90
C. albicans (20)	0.094-3	0.25	1	0.125-1.5	0.75	1	0.5-6	2	4	0.0012-2	0.38	0.75
C. parapsilosis (9)	0.125-2	0.5	1	0.19-1.5	0.75	1	1-48	3	4	0.125-0.5	0.25	0.38
C. glabrata (8)	0.125-6	0.25	0.75	0.125-1.5	0.75	1.5	2-24	8	24	0.064-2	0.75	1
C. tropicalis (3)	0.25-2	-	-	0.38-0.75	-	-	1-3	-	-	0.19-0.75	-	-
C. dubliniensis (1)	2	-	-	0.5	-	-	-	16	-	0.38-	-	-

AMB; Amphotericin b, CAS; Caspofungin, FLC; Fluconazole, VRC Voriconazol,
MIC: Minimal inhibitory concentration, GM; Geometric mean

DISCUSSION and CONCLUSION

The distribution of *Candida* species causing the fungal infection is changing gradually. *C. albicans* were reported to be most frequently isolated in Serbia (10), China (11). Australia (12) and Turkey (13, 14). However, non-albicans *Candida* species is the most commonly isolated fungal species in India (15) and Brazil (16). The differences in regional epidemiological data of these studies could not be explained completely, but it was considered that azole exposure of patients, underlying diseases and different applications in hospitals might have been the cause. In our study, the most commonly isolated species was *C. albicans* from the various clinical samples were followed by *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, *C. pelliculosa*, *C. melibiosica*, respectively. Also, 76 *Candida* species were isolated from the blood samples of the patients diagnosed with candidemia infection in our hospital during this period. Among these species, the most frequently isolated species was *C. albicans* and it was followed by the species of *C. parapsilosis*, *C. glabrata*, and *C. tropicalis*, respectively. Multicenter epidemiological data in conformance with our result are available (17, 18). According to our hospital data, *C. parapsilosis* was the second most commonly isolated species. *C. parapsilosis* is exogenous pathogenetic species and often isolated from the patients, especially those who use an intravascular device, in intensive care units (19). Also, since these species are frequently isolated from the hands of health care personnel working in the intensive care unit, we suggest that necessary precautions should be taken (20). *C. glabrata* species are the most commonly found species in critically ill elderly patients (21). When various clinical specimens obtained from all intensive care units were examined, 29 *C. glabrata* species were isolated and of these, 17 were isolated from the clinical samples of patients over 65 years of age. Candidemia cases are important among pediatric patients. Only six *C. albicans* and two *C. parapsilosis* species were isolated from our hospital's pediatric candidemia cases. According to changing candidemia epidemiologies depending on the region, such as Europe (22-24) and America (25, 26), *C. albicans* species are frequent while non-albicans species are most commonly isolated in Asian countries (27, 28). Examining the data from pediatric intensive care unit, the study had some limitations. The first of these was it was a single-centre study and the second was the clinical outcome could not be reflected, since it was a laboratory-based study.

The use of urinary catheters and wide-spectrum antibiotics for hospitalized patients in the intensive care unit may ause candiduria. Although the species isolated varies, they were often reported to be *C. albicans* (29, 30). *C. glabrata* and *C. tropicalis* species were reported as the second-and third-most common species, respectively (31,32). It is noted that the *C. parapsilosis* species attach to plastic materials owing to their extracellular polysaccharide or slime production (33). In this case, from the medical perspective, the prevalence of *C. parapsilosis* was expected to increase concerning the fact that urinary catheters used in intensive care units increase the risk for their colonization or infection. It must be noted that *C. parapsilosis* was isolated only in a 2% ratio, according to our results.

Antifungal sensitivity was determined with the E-test in some *Candida* species. The compatibility ratio of the E-test and broth microdilution was found to be high in various studies conducted (34, 35). The E-test method was also preferred because it was fast and had high repeatability. In a conducted study, when all *Candida* species were evaluated, VRC was sensitive at higher ratios than FLC (36). Further, in our study, no resistance to VRC was detected. In contrast, FLC resistance

was determined in two isolates in the iso-late of *C. glabrata* and dose-dependent resistance was detected in six isolates. The increase in the isolation frequency of *C. parapsilosis* species recently and its in-vitro resistance to CAS was presented in various studies (37, 38). Pfaller et al. (39) reported that the different MIC values shown by the *Candida* species to CAS were secondary to the biological differences among species. In our study, especially in the candidemia cases, the second most commonly isolated species was *C. parapsilosis*. A resistance to CAS was detected in three *C. parapsilosis* species from these isolates, while no resistance was observed among other species.

C. albicans species was revealed to occur at higher rates compared to non-albicans species in our study. The detection of the *C. parapsilosis* species as the second most com-mon species lead to the conclusion that hygienic conditions should be maintained in in-tensive care units. Moreover, the inability to isolate *C. krusei*, which has azole resistance, demonstrated that no substantial resistance pattern in our hospital. In conclusion, we propose that these data will be useful for the clinicians working in our hospital while selecting the antifungal agents for the treatment and prophylaxis of invasive fungal disease.

ETHICS COMITTEE APPROVAL

* This study does not require Ethics Committee Approval.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Whaley SG, Berkow EL, Rybak JM, Nishimoto AT, Barker KS, Rogers PD. Az-ole Antifungal Resistance in Candida albicans and Emerging Non-albicans Candida Species. Front Microbiol, 2017; 7: 2173

2. Caggiano G, Lovero G, De Giglio O, Barbuti G, Montagna O, Laforgia N, et al. Candidemia in the neonatal intensive care unit: a retrospective, observational survey and analysis of literature data. Biomed Res Int, 2017; 2017: 7901763.

3. Hoffmann-Santos HD, Paula CR, Yamamoto AC, Tadano T, Hahn RC. Six-year trend analysis of nosocomial candidemia and risk factors in two intensive care hospitals in Mato Grosso, midwest region of Brazil. Mycopathologia, 2013; 176 (5-6): 409-15.

4. Pfaller MA, Diekema DJ, Jones RN, Messer SA, Hollis RJ. Trends in antifungal susceptibility of Candida spp. isolated from pediatric and adult patients with bloodstream infections: SENTRY Antimicrobial Surveillance Program, 1997 to 2000. J Clin Microbiol, 2002; 40 (3): 852-6.

5. Garcia-Effron G, Kontoyiannis DP, Lewis RE, Perlin DS. Caspofungin-resistant Candida tropicalis strains causing breakthrough fungemia in patients at high risk for hematologic malignancies. Antimicrob Agents Chemother, 2008; 52 (11): 4181-83.

6. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis, 2016; 62 (4): e1-50.

7. Rowen JL, Tate JM. Management of neonatal candidiasis. Neona-tal Candidiasis Study Group. Pediatr Infect Dis J, 1998; 17 (11): 1007-11.

8. Antinori S, Milazzo L, Sollima S, Galli M, Corbellino M. Candidemia and invasive candidiasis in adults: A narrative review. Eur J Intern Med, 2016; 34: 21-28.

9. De Pauw B , Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG). Clin Infect Dis, 46 (12): 1813-21.

10. 1Arsic Arsenijevic VS, Otašević S, Dragana J, Minic P, Matijasevic J, Medić D, et al. Candida bloodstream infections in Serbia: First multicentre report of a national prospective observational survey in intensive care units. Mycoses, 2018; 61 (2): 70-8.

11. Guo LN, Xiao M, Cao B, Qu F, Zhan YL, Hu YJ, et al. Epidemiology and antifun-gal susceptibilities of yeast isolates causing invasive infections across urban Beijing, China. Future Microbiol, 2017; 12: 1075-1086.

12. Chapman B, Slavin M, Marriott D, Halliday C, Kidd S ,Arthur I, et al. Chang-ing epidemiology of candidemia in Australia. J Antimicrob Chemother, 2017; 72 (4): 1103-8.

13. Yeşilkaya A, Azap Ö, Aydın M, Akçil Ok M. Epidemiology, species distribution, clinical characteristics and mortality of candidemia in a tertiary care university hos-pital in Turkey, 2007-2014. Mycoses, 2017; 60 (7): 433-9.

14. Bilgi EA, Sav H, Zararsız G, Özakkaş F, Kiraz N. Distribution of Candida species isolated from blood cultures in a university hospital. Dicle Medi J, 2015;3 (42): 368-72.

15. Tak V, Mathur P, Varghese P, Gunjiyal J, Xess I, Misra MC. The epidemiological profile of candidemia at an Indian trauma care center. J Lab Physicians, 2014; 6 (2): 96-101.

16. Doi AM, Pignatari ACC, Edmond MB, Marra AR, Camargo LF, Siqueira RA, et al. Epidemiology and microbiologic characterization of nosocomial candidemia from a Brazilian National Surveillance Program. PLoS One, 2016; 11 (1): e0146909.

17. Falagas ME, Roussos N, Vardakas KZ. Relative frequency of albicans and the vari-ous non-albicans Candida spp. among candidemia isolates from inpatients in vari-ous parts of the world: a systematic review. Int J Infect Dis, 2010; 14 (11): e954-66.

18. Tortorano AM, Kibbler C, Peman J, Bernhardt H, Klingspor L, Grillot R.Candidemia in Europe: epidemiology and resistance. Int J Antimicrob Agents, 2006; 27 (5): 359-66.

19. Trofa D, Gácser A, Nosanchuk JD. Candida parapsilosis, an emerging fungal pathogen. Clin Microbiol Rev, 2008; 21 (4): 606-25.

20. Bonassoli LA, Bertoli M, Svidzinski TIE. High frequency of Candida parapsilosis on the hands of healthy hosts. J Hosp Infect, 2005; 59: 159-62.

21. Flevari A, Theodorakopoulou M, Velegraki A, Armaganidis A, Dimopoulos G.Treatment of invasive candidiasis in the elderly: a review. Clin Interv Aging, 2013; 8: 1199-208.

22. Lagrou K, Verhaegen J, Peetermans WE, De Rijdt T, Maertens J, Van Wijngaerden E. Fungemia at a tertiary care hospital: incidence, therapy, and distribution and an-tifungal susceptibility of causative species. Eur J Clin Microbiol Infect Dis, 2007; 26 (8): 541-7.

23. Lovero G, De Giglio O, Montagna O, Diella G, Divenuto F, Lopuzzo M, et al. Epi-demiology of candidemia in neonatal intensive care units: a persistent public health problem. Ann Ig, 2016; 28 (4): 282-7.

24. Feja KN, Wu F, Roberts K, Loughrey M, Nesin M, Larson E, et al. Risk factors for candidemia in critically ill infants: a matched case-control study. J Pediatr, 2005; 147 (2): 156–161.

25. Robinson JA, Pham HD, Bloom BT, Wittler RR. Risk factors for persistent can-didemia infection in a neonatal intensive care unit and its effect on mortality and length of hospitalization. J Perinatol, 2012; 32 (8): 621-5.

26. Benjamin DK Jr, Stoll BJ, Gantz MG, Walsh MC, Sánchez PJ, Das A et al. Neona-tal candidiasis: epidemiology, risk factors, and clinical judgment. Pediatrics, 2010; 126 (4): e865-73.

27. Rani R, Mohapatra NP, Mehta G, Randhawa VS. Changing trends of Candida species in neonatal septicaemia in a tertiary North Indian hospital. Indian J Med Microbiol, 2002; 1 (20): 42-4.

28. Fu J, Ding Y, Ba W, Wang L, Xu S, Qin P, et al. Epidemiology of Candida albi-cans and non-C. albicans of neonatal candidemia at a tertiary care hospital in west-ern China. BMC Infect Dis, 2017; 17: 329.

29. Alvarez-Lerma F, Nolla-Salas J, León C, Palomar M, Jordá R, Carrasco N,et al; EPCAN Study Group. Candiduria in critically ill patients admitted to intensive care medical units. Intensive Care Med, 2003; 29 (7): 1069-76.

30. Mishra M, Agrawal S, Raut S, Kurhade AM, Powar RM. Profile of yeasts isolated from urinary tracts of catheterized patients. J Clin Diagn Res, 2014; 8 (2): 44-6.

31. Lagrotteria D, Rotstein C, Lee CH. Treatment of candiduria with micafungin: a case series. Can J Infect Dis Med Microbiol, 2007; 18 (2): 149-50.

32. Achkar JM, Fries BC. Candida infections of the genitourinary tract. Clin Microbiol Rev, 2010; 23 (2): 253-73.

33. Ramage G, Saville SP, Thomas DP, Lopez-Ribot JL. Candida biofilms: an update. Eukaryot Cell, 2005; 4 (4): 633-8.

34. Arikan S, Gür D, Akova M. Comparison of E-test, microdilution and colorimetric dilution with reference broth macrodilution method for antifungal susceptibility testing of clinically significant Candida species isolated from immunocompromised patients. Mycoses, 1997; 40 (7-8): 291-6.

35. Alexander BD, Byrne TC, Smith KL, Hanson KE, Anstrom KJ, Perfect JR, et al. Comparative evaluation of Etest and sensititre yeastone panels against the Clinical and Laboratory Standards Institute M27-A2 reference broth microdilution method for testing Candida susceptibility to seven antifungal agents. J Clin Microbi-ol, 2007; 45 (3): 698-706.

36. Pfaller MA, Diekema DJ, Rinaldi MG, Barnes R, Hu B, Veselov AV, et al. Re-sults from the ARTEMIS DISK Global Antifungal Surveillance Study: a 6.5-Year analysis of susceptibilities of candida and other yeast species to fluconazole and voriconazole by standardized disk diffusion testing. J Clin Microbiol, 2005; 43 (12): 5848-59.

37. Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med, 2002; 347 (5): 2020-9.

38. Forrest GN, Weekes E, Johnson JK. Increasing incidence of Candida parapsilosis candidemia with caspofungin usage. J Infect, 2008; 56 (2): 126-9.

39. Pfaller MA, Messer SA, Boyken L, Rice C, Tendolkar S, Hollis RJ, et al. Further standardization of broth microdilution methodology for in vitro susceptibility testing of caspofungin against candida species by use of an international collection of more than 3,000 Clinical Isolates. J Clin Microbiol, 2004; 42 (7): 3117-9.