Int J Clin Exp Med 2018;11(9):9950-9957
www.ijcem.com /ISSN:1940-5901/IJCEM0070186

Original Article

Risk factors for mortality in cases of intensive care unit-acquired candidemia: a 5.5-year, single-center, retrospective study

Renyu Ding[1], Yangtao Ji[2], Baoyan Liu[1], Dongmei Zhao[1], Xiaojuan Zhang[1], Zhidan Zhang[1], Xiaochun Ma[1]

[1]*Intensive Care Unit,* [2]*Clinical Laboratory, The First Hospital of China Medical University, Shenyang, P.R. China*

Received December 1, 2017; Accepted May 14, 2018; Epub September 15, 2018; Published September 30, 2018

Abstract: Intensive care unit (ICU)-acquired candidemia is a potentially fatal complication. However, there are regional variations in the epidemiology of ICU-acquired candidemia. This study aimed to examine the epidemiology of *Candida* species infections and risk factors for related mortality among patients who were treated in the ICU at our center. This retrospective, single-center and observational study included consecutive patients with ICU-acquired candidemia between January 2010 and June 2015 at the First Hospital of China Medical University (Shenyang, Liaoning, China). Data were obtained regarding patients' clinical characteristics and the *Candida* species that were isolated from the patients' blood samples. Analyses were also performed to identify risk factors for mortality that were related to ICU-acquired candidemia. Seventy-two patients with ICU-acquired candidemia were included. The most common *Candida* species was *C. parapsilosis* (35/72, 48.6%). The overall rate of fluconazole resistance among all isolates was 11.1%. Independent risk factors for 30-day mortality among patients with ICU-acquired candidemia were previous corticosteroid use, abdominal surgery, septic shock, and the presence of *C. glabrata*. Our findings indicate that *C. glabrata* and previous corticosteroid use were potential risk factors for mortality related to ICU-acquired candidemia. However, our findings require validation in a larger and more comprehensive study.

Keywords: Candidemia, death, intensive care unit, mortality, mutual authentication analysis

Introduction

Candida species are the fourth leading cause of bloodstream infections (BSIs) among hospitalized patients, as well as the most common cause of invasive fungal infections in the intensive care unit (ICU) [1]. In the US, *Candida* species account for 12% of all hospital-acquired BSIs, with estimated mortality rates of 15-25% among adults and 10-15% among neonates [2, 3]. In addition, the mortality rate of candidemia can be even higher in developing countries. For example, Chakrabarti et al. reported a crude 30-day mortality rate of 44.7% among Indian patients with candidemia [4]. In addition, Ma et al. reported a 30-day mortality rate of 26% in China [5]. Moreover, *Candida* infections can prolong the duration of hospitalization [6] and increase the cost of medical care [7], which increases the financial burden of these infections. During recent decades, efforts have been made to alleviate the effects of ICU-acquired candidemia, although the variable epidemiology of candidemia in different countries makes it difficult for scientists and clinicians to develop a consistent and effective therapy for patients from different regions. Therefore, a better understanding of the microbial composition and risk factors for ICU-acquired candidemia in different countries is needed to effectively manage candidemia in different regions. Efforts to improve this understanding have helped improve the treatment of candidemia in developed countries [8]. Nevertheless, those efforts have been insufficient in China, and only a few studies during the last decade have explored the epidemiology of candidemia among the 189 million hospitalizations each year [9]. The present retrospective, single-center study aimed to evaluate the incidence, outcomes, and risk factors for candidemia-related mortality, as well as the *Candida* species and their resistance patterns.

Material and methods

Patient selection and data collection

This retrospective study evaluated data that were collected during a 5.5-year period (January 1, 2010 to June 30, 2015) in the 30-bed ICU of the First Hospital of China Medical University (Shenyang, Liaoning). A search of the microbiological laboratory database identified 78 patients with at least one blood culture that was positive for *Candida* species and a compatible clinical diagnosis. The medical records were searched by senior clinicians who were blinded to the study's purpose and design, and data were collected regarding the patients' clinicopathological characteristics (e.g., age, sex, comorbidities, and other risk factors for *Candida* infection). When multiple isolates were identified for a single patient, only the first isolate was considered in the analysis of risk factors for candidemia-related mortality. Patients with candidemia had been followed prospectively for 30 days after the diagnosis or until their hospital discharge, and outcomes were only considered for patients with ≥ 30 days of follow-up after the initial candidemia episode. The study's design was approved by the ethics committee of the First Hospital of China Medical University, and all methods complied with the provisions of the Declaration of Helsinki.

Candida species identification

Candida species were isolated from blood samples and identified using the Vitek2 system (bioMérieux) according to the manufacturer's instructions. Antifungal susceptibility testing was performed for each isolate using fluconazole, itraconazole, and amphotericin B. These tests were performed using the Sensitre Yeast One colorimetric plate (Trek Diagnostic System), according to the manufacturer's instructions.

Statistical analysis

Continuous data were reported as median and interquartile range. Categorical data were reported as number and percentage. The Wilcoxon signed rank test was used to analyze non-normally distributed variables. The Chi-square test and Fisher's exact test were used to analyze differences in categorical variables according to 30-day mortality. Covariates that were significant at a *P*-value of 0.1 in the univariate analyses, as well as factors that were related to 30-day mortality based on clinical experience, were included in multivariable regression models using a forward algorithm. Moreover, risk factors for 30-day mortality among patients with candidemia were validated in multivariable regression models using a backward algorithm (stepwise probability for entry: 0.05, probability for removal: 0.1). All tests were two-tailed and *P*-values of < 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS software (version 21.0; IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

The present study examined the records for 78 patients with candidemia, and the overall incidence of candidemia was 16.5 patients/1,000 ICU admissions. Six patients were excluded because they had been lost to follow-up, and 72 patients were included in this study. **Table 1** shows that 23 of the 72 patients died within 30 days (15 men and 8 women). Forty-nine patients underwent abdominal surgery within 30 days before the onset of candidemia. Sixty-three patients had a central venous catheter (CVC), which contributes to microbial infections in the ICU [10-12]. However, only 16 patients were judged to be infected by *Candida* species because of the CVC, based on the global criteria [13].

Previous use of broad-spectrum antibiotics and quinolones was recorded for 71 patients and 20 patients, respectively (**Table 1**). The most common comorbidities were solid tumors and diabetes mellitus. The median Acute Physiology and Chronic Health Evaluation index (APACHE) II score for all patients was 13.6, and patients who died had a higher score than survivors (**Table 1**). The Sequential Organ Failure Assessment (SOFA) score was also higher for patients who died. Thirty-six patients developed septic shock after their admission. Approximately 47% of patients had a lymphocyte count of $< 800/mm^3$ at the onset of their *Candida* BSI. A decreased lymphocyte count can reflect low immunity [14], although this factor did not influence the risk of mortality in the present study.

Table 1. Patient characteristics and univariate risk factors for 30-day mortality among 72 patients with candidemia

Factors	Patient status			Logistic regression analysis		Non-parametric analysis	
	Total, n (%)	Survived, n (%)	Died, n (%)	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (median, IQR)	62.5 (49.8, 77.0)	60.8 (48.5, 77.0)	66.0 (54.0, 78.0)	0.00 (0.00-0.01)	0.25	N/A	0.19
Male sex	45 (62.5)	30 (61.2)	15 (65.2)	1.19 (0.42-3.34)	0.74	1.19 (0.42-3.34)	0.74
Comorbidities							
Diabetes mellitus	19 (26.4)	17 (34.7)	2 (8.7)	0.18 (0.04-0.86)	0.03	0.18 (0.04-0.86)	0.02
Solid tumor	29 (40.3)	18 (36.7)	11 (47.8)	1.58 (0.58-4.32)	0.37	1.58 (0.58-4.31)	0.37
Risk factors for Candida infection							
Use of corticosteroids[b]	15 (20.8)	7 (14.3)	8 (34.8)	3.20 (0.99-10.3)	0.05	3.20 (0.99-10.3)	0.05
Abdominal surgery within 30 days	49 (68.1)	29 (59.2)	20 (87.0)	4.60 (1.20-17.6)	0.03	4.60 (1.20-17.6)	0.02
Total parenteral nutrition[c]	59 (81.9)	59 (81.9)	20 (87.0)	1.71 (0.42-6.92)	0.45	1.71 (0.42-6.92)	0.45
Presence of CVC[c]	63 (87.5)	42 (85.7)	21 (91.3)	1.75 (0.33-9.17)	0.51	1.75 (0.33-9.17)	0.50
Urinary catheter[c]	60 (83.3)	40 (81.6)	20 (87.0)	1.50 (0.37-6.16)	0.57	1.50 (0.37-6.16)	0.57
Mechanical ventilation[c]	55 (76.4)	36 (73.5)	19 (82.6)	1.72 (0.49-5.99)	0.40	1.72 (0.49-5.99)	0.40
Renal replacement therapy[b]	21 (29.2)	10 (20.4)	11 (47.8)	3.58 (1.22-10.5)	0.02	3.58 (1.22-10.5)	0.017
Prior use of broad-spectrum antibiotics[b]	71 (98.6)	48 (98.0)	23 (100.0)	N/A	N/A	N/A	N/A
Prior use of quinolones[b]	20 (27.8)	16 (32.7)	4 (17.4)	0.43 (0.13-1.49)	0.19	0.43 (0.13-1.49)	0.18
Lymphopenia at onset of *Candida* BSI (< 800/mm^3)	34 (47.2)	24 (49.0)	10 (43.5)	0.80 (0.30-2.17)	0.66	0.80 (0.30-2.17)	0.66
Illness severity							
APACHE II score (median, IQR)[a]	13.6 (9.00, 16.0)	12.6 (8.00, 16.0)	15.8 (13.0,16.0)	0.02 (0.00-0.03)	0.04	N/A	0.05
SOFA score (median, IQR)[a]	5.42 (3.00, 7.00)	5.42 (3.00, 7.00)	6.83 (4.00, 7.00)	0.03 (0.005-0.064)	0.024	N/A	0.11
Septic shock[b]	36 (50.0)	18 (36.7)	18 (78.3)	6.20 (1.97-19.6)	0.00	6.20 (1.97-19.6)	< 0.01
Candida species							0.16
C. parapsilosis	35 (48.6)	27 (55.1)	8 (34.8)	Reference	N/A	N/A	N/A
C. guilliermondii	18 (25.0)	12 (24.5)	6 (26.1)	1.69 (0.48-5.94)	0.42	N/A	N/A
C. albicans	11 (15.3)	6 (12.2)	5 (21.7)	2.81 (0.68-11.7)	0.16	N/A	N/A
C. glabrata	6 (8.3)	2 (4.1)	4 (17.4)	6.75 (1.04-43.9)	0.05	N/A	N/A
C. krusie	2 (2.8)	2 (4.1)	0 (0.0)	N/A	N/A	N/A	N/A
Treatment							0.25
None	11 (15.3)	7 (14.3)	4 (17.4)	Reference	N/A	N/A	N/A
Prophylaxis	20 (27.8)	11 (22.4)	9 (39.1)	1.43 (0.32-6.49)	0.64	N/A	N/A
Empirical	34 (47.2)	27 (55.1)	7 (30.4)	0.45 (0.10-2.00)	0.30	N/A	N/A
Definitive	7 (9.70)	4 (8.20)	3 (13.0)	1.31 (0.19-9.10)	0.783	N/A	N/A
Initial antifungal agents							0.931
None	11 (15.3)	7 (14.3)	4 (17.4)	Reference	N/A	N/A	N/A
Fluconazole	22 (30.6)	16 (32.7)	6 (26.1)	0.66 (0.14-3.08)	0.59	N/A	N/A
Voriconazole	7 (9.70)	5 (10.20)	2 (8.70)	0.70 (0.09-5.43)	0.73	N/A	N/A
Echinocandin	32 (44.4)	21 (42.9)	11 (47.8)	0.92 (0.22-3.83)	0.91	N/A	N/A

[a]The APACHE II and SOFA scores were recorded at the ICU admission. [b]The presence of corticosteroid use, renal replacement therapy, prior use of broad-spectrum antibiotics, prior use of quinolones, and/or septic shock was recorded from the admission to the onset of candidemia. [c]The presence of total parenteral nutrition, a CVC, a urinary catheter, and/or mechanical ventilation was recorded at the onset of candidemia. OR: odds ratio, CI: confidence interval, IQR: interquartile range, CVC: central venous catheter, BSI: bloodstream infection.

Table 2. In vitro resistance of the 72 clinical isolates to antifungal agents

Species	% of strains that were resistant (n)		
	Fluconazole	Itraconazole	Amphotericin B
C. parapsilosis (n = 35)	8.6 (3)	5.7 (2)	0 (0)
C. guiliermondii (n = 18)	11.1 (2)	11.1 (2)	0 (0)
C. albicans (n = 11)	9.1 (1)	0 (0)	0 (0)
C. glabrata (n = 6)	33.3 (2)	16.7 (1)	0 (0)
C. krusie (n = 2)	0 (0)	0 (0)	0 (0)
Total (n = 72)	11.1 (8)	6.9 (5)	0 (0)

Only the first isolate was considered in cases with multiple isolates.

Some patients received systemic treatment using fluconazole (22 patients), voriconazole (7 patients), or echinocandin (32 patients) (**Table 1**). Eleven patients did not receive antifungal therapy, and 3 patients died before their blood culture results became available. The remaining 8 patients underwent replacement of their CVC. Among the patients who received treatment, 20 received prophylactic treatment at a median time of 5 days before a positive blood culture result was available. Thirty-four patients received empirical treatment and 7 patients received definitive treatment. The median time to treatment after a positive blood culture result was available was 2 days (empirical therapy) and 7 days (definitive therapy) (**Table 1**).

Epidemiology and antifungal resistance of Candida species

We identified 11 *C. albicans* isolates and 61 isolates involving other *Candida* species. The most common *Candida* species was *C. parapsilosis* (35 isolates), followed by *C. guilliermondii* (18 isolates), *C. albicans* (11 isolates), *C. glabrata* (6 isolates), *C. tropicalis* (1 isolate), and *C. krusei* (1 isolate). The crude 30-day mortality rates were 22.9% for *C. parapsilosis*, 33.3% for *C. guilliermondii*, 45.5% for *C. albicans*, and 66.6% for *C. glabrata*, respectively.

The antifungal resistance rates were low (**Table 2**), with 11.1% of strains being resistant to fluconazole and 6.9% of strains being resistant to itraconazole. Resistance to fluconazole was observed in 33.3% of the *C. glabrata* isolates, 11.1% of the *C. guilliermondii* isolates, 9.1% of the *C. parapsilosis* isolates, and 8.6% of the *C. albicans* isolates. All *Candida* isolates were susceptible to amphotericin B.

Risk factors for 30-day mortality

Non-parametric testing revealed that 30-day mortality was significantly associated with diabetes mellitus ($P = 0.02$), corticosteroid use ($P = 0.05$), abdominal surgery ($P = 0.02$), renal replacement therapy ($P = 0.017$), a high APACHE II score ($P = 0.05$), and septic shock ($P < 0.001$) (**Table 1**). However, the univariate logistic analyses revealed different findings, as 30-day mortality was significantly associated with a high SOFA score ($P = 0.024$) and the presence of *C. glabrata* ($P = 0.05$). Thus, we performed multiple logistical regression analysis with or without SOFA score, which revealed that SOFA score did not significantly affect the regression results (data not shown). Therefore, the final multiple logistical regression analysis was performed using the forward algorithm without the SOFA score. The multivariable analysis revealed that the independent risk factors for 30-day mortality were abdominal surgery ($P < 0.001$), septic shock ($P < 0.001$), the presence of *C. albicans* ($P = 0.05$), and the presence of *C. glabrata* ($P = 0.04$) (**Table 3**).

Another multivariate logistical regression analysis using the backward algorithm was performed with all factors included. After 15 cycles of stepwise calculations, the results revealed that 30-day mortality was significantly associated with corticosteroid use ($P = 0.02$) but not the presence of *C. albicans* ($P = 0.09$) (**Table 3**). Thus, based on both analyses, the independent risk factors for 30-day mortality among patients with candidemia were corticosteroid use, abdominal surgery, septic shock, and the presence of *C. glabrata*.

Discussion

The present study revealed that the incidence of ICU-acquired candidemia at our center was 16.5 patients/1,000 ICU admissions, with a 30-day crude mortality rate of 31.9% (23/72). This mortality rate is relatively low, compared to results from Western countries (33.9-76.4%) [4], although it is similar to the reported rates from other Chinese tertiary centers (26.4-33.3%) [5], which suggests that population differences are responsible. The epidemiology of

Table 3. Multivariate logistic regression analyses of risk factors for 30-day mortality among 72 patients with *Candida* bloodstream infections

Factors	Algorithm (Forward)		Algorithm (Backward)	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Diabetes mellitus	0.13 (0.01-1.58)	0.11	0.87 (0.01-1.13)	0.06
Use of corticosteroids[b]	8.89 (0.77-105)	0.08	38.2 (1.73-847)	0.02
Abdominal surgery	23.4 (2.57-214)	< 0.01	84.7 (3.1-2,321)	0.01
Presence of CVC[c]	N/A	N/A	1,376 (0.55-3.4 × 10^6)	0.07
Renal replacement therapy	1.48 (0.21-10.2)	0.69	N/A	N/A
Prior use of quinolones	N/A	N/A	0.09 (0.01-1.56)	0.10
APACHE II score[a]	1.12 (0.93-1.35)	0.23	1.182 (0.95-1.46)	0.13
Septic shock	12.4 (2.23-69.5)	< 0.01	5.71 (0.99-33.0)	0.05
Candida species				
C. parapsilosis	Reference	N/A	Reference	N/A
C. guilliermondii	2.62 (0.36-18.9)	0.34	2.58 (0.32-20.7)	0.37
C. albicans	11.3 (0.96-131.9)	0.05	8.60 (0.72-103)	0.09
C. glabrata	37.5 (1.19-1,176)	0.04	136 (2.25-8,231)	0.02
C. krusie	0.00	1.00	0.00	1.00

[a]The APACHE II scores were recorded at the ICU admission. [b]The presence of corticosteroid use, renal replacement therapy, prior use of broad-spectrum antibiotics, prior use of quinolones, and/or septic shock was recorded from the ICU admission to the onset of candidemia. [c]The presence of a CVC was recorded at the onset of candidemia. OR: odds ratio, CI: confidence interval, CVC: central venous catheter.

candidemia has exhibited a shift towards non-*C. albicans* species in Europe [15], which is also reflected in our results (only 11 isolates from the 72 patients were *C. albicans*). The present study failed to detect a significant difference in the isolation of *C. albicans* and other *Candida* species when the patients were stratified according to previous antifungal exposure (data not shown). Interestingly, a large proportion of the non-*C. albicans* isolates were sensitive to fluconazole (88.5%, 54/61), which suggests that other factors influenced the high prevalence of other *Candida* species.

The most common isolate in the present study was *C. parapsilosis*, although previous reports have indicated that BSI isolates are typically *C. albicans* and *C. tropicalis* [16, 17]. Although rarely reported, *C. parapsilosis* has become an important cause of fungemia [18], and the prevalence of *C. parapsilosis* infection is closely associated with CVC use [10]. The present study revealed that 49% of patients with a CVC (31/63) were infected with *C. parapsilosis,* which supports that association. As there has been controversy regarding CVC use in the ICU based on the risk of microbial infection [10, 11], our hospital implemented a standard protocol for CVC use in 2010, which limited the risks that were associated with CVC use. The utility of this protocol is apparent in the fact that CVC use was not significantly associated with the risk of *Candida* infection or candidemia-related mortality. Interestingly, 49% of the patients with a CVC had been infected *C. parapsilosis*, although we did not detect a clear association between these two factors. However, the prevalence of *C. parapsilosis* was associated with the previous use of quinolones (60%), total parenteral nutrition (54%), and abdominal surgery (53%), which suggests that further investigations are needed to understand why *C. parapsilosis* was so commonly observed in this study.

Previous studies in Western countries indicated that *Candida* species that are associated with ICU-acquired candidemia tend to be resistant to fluconazole but sensitive to echinocandins [19]. Thus, the guidelines for managing ICU-acquired candidemia suggest that echinocandins be used as first-line therapy, given the high rate of resistance to fluconazole, although the specific treatment should be tailored to the local epidemiology of candidemia [19-21]. Interestingly, the present study revealed that the rate of fluconazole resistance was relatively low (11.1%), which may indicate that flucon-

azole remains effective for managing ICU-acquired candidemia in some regions. This possibility is supported by the absence of a significant difference in the mortality rates among patients in the present study who received fluconazole or echinocandins.

We performed mutual authentication using univariate and multivariate analyses, which revealed that 30-day mortality among patients with ICU-acquired candidemia was independently associated with corticosteroid use, abdominal surgery, septic shock, and the presence of *C. glabrata*. Previous studies have also revealed a close association between candidemia and the development of septic shock [22], which might partially reflect the contribution of septic shock to candidemia-related mortality. Furthermore, *C. glabrata* is relatively more resistant to fluconazole that most non-*C. albicans* species [5]. Although our results indicate that fluconazole may remain useful for managing ICU-acquired candidemia in our center, it is important to note that *C. glabrata* only accounted for 8.3% of the cases. Moreover, candidemia caused by *C. glabrata* is associated with a high mortality rate [23], which indicates that antifungal therapy must be carefully selected in centers with higher proportions of cases caused by *C. glabrata*. Previous studies have also indicated that candidemia is associated with corticosteroid use and abdominal surgery [24-26], which is supported by the relatively poor outcomes for those cases in the present study. Moreover, Ma et al. have also reported that abdominal surgery is associated with poor outcomes in cases of candidemia [5]. Other studies have indicated that corticosteroid use is a risk factor for mortality in candidemia cases [27, 28], although those studies only identified cases with corticosteroid administration at 15 or 30 days before the development of candidemia. In contrast, the present study examined corticosteroid administration at any time between the ICU admission and onset of candidemia. For example, 8 of the 15 patients who received corticosteroid treatment (200 mg/day of hydrocortisone) also had septic shock, which is associated with an inadequate response to fluid and vasopressor resuscitation [29]. Thus, there may be an association between corticosteroid administration and septic shock, although there was no significant difference in the incidence of septic shock between patients who did and did not receive corticosteroid treatment (53.3% *vs*. 49.1%). Previous studies have indicated that exogenous corticosteroids can decrease human immunity [30], which suggests that corticosteroid treatment influences candidemia-related mortality, as candidemia is associated with weak immunity [31]. Therefore, additional studies are needed to determine whether corticosteroids affect the prognosis of ICU-acquired candidemia.

The present study provides additional data regarding the epidemiology of *Candida* infections, and identified several risk factors (corticosteroid use, abdominal surgery, septic shock, and presence of *C. glabrata*) for 30-day mortality that was related to ICU-acquired candidemia in China. Non-*C. albicans* species were the most common isolates at our center, and these isolates had a low rate of resistance to fluconazole. Furthermore, no significant difference was detected in the mortality rates of patients who received fluconazole or echinocandins. However, these findings are limited by the small sample size, and our results should be validated using larger and more comprehensive studies.

Acknowledgements

We thank Hailong Wang (China Medical University) for providing advice regarding the statistical analysis. We also thank Editage (www.editage.cn) for English language editing.

Disclosure of conflict of interest

None.

Address correspondence to: Renyu Ding and Xiaochun Ma, Intensive Care Unit, The First Hospital of China Medical University, 155 Nanjing Bei Street, Shenyang 110001, Liaoning Province, P.R. China. Tel: (+86) 24-83282261; Fax: (+86) 24-83282631; E-mail: renyuding@126.com (RD); mxc2972@163.com (XM)

References

[1] Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004; 39: 309-17.

[2] Sipsas NV, Kontoyiannis DP. Invasive fungal infections in patients with cancer in the Intensive Care Unit. Int J Antimicrob Agents 2012; 39: 464-71.
[3] Panackal AA, Gribskov JL, Staab JF, Kirby KA, Rinaldi M, Marr KA. Clinical significance of azole antifungal drug cross-resistance in Candida glabrata. J Clin Microbiol 2006; 44: 1740-3.
[4] Chakrabarti A, Sood P, Rudramurthy SM, Chen S, Kaur H, Capoor M, Chhina D, Rao R, Eshwara VK, Xess I, Kindo AJ, Umabala P, Savio J, Patel A, Ray U, Mohan S, Iyer R, Chander J, Arora A, Sardana R, Roy I, Appalaraju B, Sharma A, Shetty A, Khanna N, Marak R, Biswas S, Das S, Harish BN, Joshi S, Mendiratta D. Incidence, characteristics and outcome of ICU-acquired candidemia in India. Intensive Care Med 2015; 41: 285-95.
[5] Ma CF, Li FQ, Shi LN, Hu YA, Wang Y, Huang M, Kong QQ. Surveillance study of species distribution, antifungal susceptibility and mortality of nosocomial candidemia in a tertiary care hospital in China. BMC Infect Dis 2013; 13: 337.
[6] Yenigün Koçak B, Kuloğlu F, Doğan Çelik A, Akata F. Evaluation of epidemiological characteristics and risk factors of candidemia in adult patients in a tertiary-care hospital. Mikrobiyol Bul 2011; 45: 489-503.
[7] Arnold HM, Micek ST, Shorr AF, Zilberberg MD, Labella AJ, Kothari S, Kollef MH. Hospital resource utilization and costs of inappropriate treatment of candidemia. Pharmacotherapy 2010; 30: 361-8.
[8] Zaoutis TE, Argon J, Chu J, Berlin JA, Walsh TJ, Feudtner C. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the united states: a propensity analysis. Clin Infect Dis 2005; 41: 1232-9.
[9] Li F, Wu L, Cao B, Zhang Y, Li X, Liu Y. Surveillance of the prevalence, antibiotic susceptibility, and genotypic characterization of invasive candidiasis in a teaching hospital in China between 2006 to 2011. BMC Infect Dis 2013; 13: 353.
[10] Levin AS, Costa SF, Mussi NS, Basso M, Sinto SI, Machado C, Geiger DC, Villares MC, Schreiber AZ, Barone AA, Branchini ML. Candida parapsilosis fungemia associated with implantable and semi-implantable central venous catheters and the hands of healthcare workers. Diagn Microbiol Infect Dis 1998; 30: 243-9.
[11] Frasca D, Dahyotfizelier C, Mimoz O. Prevention of central venous catheter-related infection in the intensive care unit. Crit Care 2010; 14: 212.
[12] Walz JM, Memtsoudis SG, Heard SO. Prevention of central venous catheter bloodstream infections. J Intensive Care Med 2010; 25: 131.
[13] O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, Lipsett PA, Masur H, Mermel LA, Pearson ML, Raad II, Randolph AG, Rupp ME and Saint S. Healthcare infection control practices advisory committee (HICPAC). CDC releases draft guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis 2011; 52: 32.
[14] Van Parijs L, Abbas AK. Homeostasis and self-tolerance in the immune system: turning lymphocytes off. Science 1998; 280: 243-8.
[15] Poikonen E, Lyytikäinen O, Anttila VJ, Koivula I, Lumio J, Kotilainen P, Syrjälä H, Ruutu P. Secular trend in candidemia and the use of fluconazole in Finland, 2004-2007. BMC Infect Dis 2010; 10: 312.
[16] Barchiesi F, Orsetti E, Gesuita R, Skrami E, Manso E. Epidemiology, clinical characteristics, and outcome of candidemia in a tertiary referral center in Italy from 2010 to 2014. Infection 2016; 44: 205-13.
[17] Voss A, le Noble JL, Verduyn Lunel FM, Foudraine NA, Meis JF. Candidemia in intensive care unit patients: risk factors for mortality. Infection 1997; 25: 8-11.
[18] Almirante B, Rodríguez D, Cuenca-Estrella M, Almela M, Sanchez F, Ayats J, Alonso-Tarres C, Rodriguez-Tudela JL, Pahissa A. Epidemiology, risk factors, and prognosis of Candida parapsilosis bloodstream infections: case-control population-based surveillance study of patients in Barcelona, Spain, from 2002 to 2003. J Clin Microbiol 2006; 44: 1681-5.
[19] Andes DR. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis 2012; 54: 1110.
[20] Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD; Infectious Diseases Society of America. Clinical practice guidelines for the management candidiasis: 2009 update by the infectious diseases society of America. Clin Infect Dis 2009; 48: 503-35.
[21] Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, Meersseman W, Akova M, Arendrup MC, Arikan-Akdagli S, Bille J, Castagnola E, Cuenca-Estrella M, Donnelly JP, Groll AH, Herbrecht R, Hope WW, Jensen HE, Lass-Flörl C, Petrikkos G, Richardson MD, Roilides E, Verweij PE, Viscoli C, Ullmann AJ; ESCMID Fungal Infection Study Group. ESCMID*

guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infec 2012; 18: 19-37.

[22] Bassetti M, Righi E, Ansaldi F, Merelli M, Trucchi C, De Pascale G, Diaz-Martin A, Luzzati R, Rosin C, Lagunes L, Trecarichi EM, Sanguinetti M, Posteraro B, Garnacho-Montero J, Sartor A, Rello J, Rocca GD, Antonelli M, Tumbarello M. A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. Intensive Care Med 2014; 40: 839-45.

[23] Pfaller MA, Diekema DJ. Twelve years of fluconazole in clinical practice: global trends in species distribution and fluconazole susceptibility of bloodstream isolates of Candida. Clin Microbiol Infect 2004; 10 Suppl 1: 11-23.

[24] Picazo JJ, Gonzálezromo F, Candel FJ. Candidemia in the critically ill patient. Int J Antimicrob Agents 2008; 32: S83-S5.

[25] Bouza E, Muñoz P. Epidemiology of candidemia in intensive care units. Int J Antimicrob Agents 2008; 32: S87.

[26] Horn DL, Ostrosky-Zeichner L, Morris MI, Ullmann AJ, Wu C, Buell DN, Kovanda LL, Cornely OA. Factors related to survival and treatment success in invasive candidiasis or candidemia: a pooled analysis of two large, prospective, micafungin trials. Eur J Clin Microbiol 2010; 29: 223-9.

[27] Colombo AL, Guimarães T, Sukienik T, Pasqualotto AC, Andreotti R, Queiroz-Telles F, Nouér SA, Nucci M. Prognostic factors and historical trends in the epidemiology of candidemia in critically ill patients: an analysis of five multicenter studies sequentially conducted over a 9-year period. Intensive Care Med 2014; 40: 1489.

[28] Kang SJ, Kim SE, Kim UJ, Jang HC, Park KH, Shin JH, Jung SI. Clinical characteristics and risk factors for mortality in adult patients with persistent candidemia. J Infect 2017; 75: 246-53.

[29] Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013; 39: 165-228.

[30] Butler WT, Rossen RD. Effects of corticosteroids on immunity in man. I. Decreased serum IgG concentration caused by 3 or 5 days of high doses of methylprednisolone. J Clin Invest 1973; 52: 2629-40.

[31] Talluri G, Marella VK, Shirazian D, Wise GJ. Immune response in patients with persistent candiduria and occult candidemia. J Urology 1999; 162: 1361-4.