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ORIGINAL PAPER

Risk factors and predictors of mortality of candidaemia among critically ill patients: role of antifungal prophylaxis in its development and in selection of non-*albicans* species

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Abstract
Purpose The aim of the present study is to identify risk factors for development and predictors of mortality of candidaemia among critically ill patients.
Methods A 1:7 case–control study was conducted during a 4-year period (2012–2015) in a Greek Intensive Care Unit (ICU). Candidaemia was confirmed by positive blood cultures. All yeasts were identified using API 20C AUX System or Vitek 2 Advanced Expert System. Epidemiologic data were collected from the ICU computerized database and patients' chart reviews.
Results Fifty-three patients developed candidaemia with non-*albicans* species being the predominant ones (33 patients, 62.3%). Multivariate analysis found that prior emergency surgery, malignancy, hospitalization during summer months, prior septic shock by KPC-producing *Klebsiella pneumoniae* and number of antibiotics administered were independently associated with candidaemia, while, prior administration of azole was a protective factor. Non-*albicans* candidaemia was associated with number of antibiotics administered and prior administration of echinocandin. Mortality of 14 days was 28.3% (15 patients) and was associated with SOFA score upon infection onset and septic shock, while, appropriate empirical antifungal treatment was associated with better survival.
Conclusions Prophylactic azole administration prevents development of candidaemia, while, echinocandin administration predisposes to non-*albicans* candidaemia. Empirical administration of an appropriate antifungal agent is associated with better survival.

Keywords *Candida albicans* · Septic shock · KPC-producing *Klebsiella pneumoniae* · Prophylaxis

Introduction

Candida species are a significant cause of healthcare associated infections, being the seventh most commonly isolated pathogen during a European point prevalence study [1]. Its incidence among patients hospitalized in Intensive Care Units (ICUs) is even higher, being the third most common isolated pathogen [2, 3]. This high incidence among ICU patients may be partially explained by the fact that critically ill patients accumulate more risk factors, such as, severe comorbidities, immunosuppression, parenteral nutrition, intravascular lines and prolonged antibacterial therapy [4–6].

Candidaemia is associated with high morbidity and considerable mortality among critically ill patients, with overall crude mortality rates being even higher among patients that develop septic shock [7, 8]. It is previously shown that appropriate empirical antifungal therapy and timing of initiation play an important role in survival [9, 10].

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Since early diagnosis of candidaemia remains a difficult task, prophylactic antifungal treatment, even though controversial, is a promising approach in ICU patients with high risk of candida infection [2, 11]. This approach is proposed by the ESCMID (European Society for Clinical Microbiology and Infectious Diseases) guidelines to prevent or delay the onset of candidaemia or invasive candidiasis [11]. Use of prophylactic antifungal treatment influences the epidemiology of *Candida* infection, with selection of non-susceptible species. Thus, an increase of non-susceptible species such as *C. glabrata* or *C. krusei* after fluconazole or *C. parapsilosis* after echinocandin administration is observed [4, 12–14].

The aim of this study was to identify risk factors for candidemia and factors associated with high mortality among ICU patients.

Materials and methods

We conducted a 1:7 case–control study in the ICU of the University General Hospital of Patras (UGHP), Greece, during a 4-year period (March 2012 to December 2015). The ICU comprises of 13 beds.

Cases were considered patients with candidaemia. Controls were patients without candidaemia. Matching parameters included Acute Physiology and Chronic Health Evaluation II (APACHE II) score upon admission (±3 points) and days at risk (±4 days; time from admission to BSI for cases and length of ICU stay for controls).

Two blood culture sets from peripheral sites and one from the central venous line, as well as, cultures from the suspected source (bronchial secretions, urine, pleural or peritoneal fluid, pus, catheter tip, etc.) were obtained from ICU patients with fever (≥38.0 °C) or clinical presentation suggestive of infection and sent off to the clinical laboratory of the Microbiology Department. In case of blood culture positivity (Bact/Alert 3D, Biomerieux, Marcy l'Etoile, France) they were further inoculated on Sabouraud dextrose agar. Plates were incubated at 37 °C for 96 h before assessed as negative. Yeast positive cultures were evaluated and *C. albicans* was identified when the germ tube test was positive. Germ tube negative yeasts suggest non-*albicans Candida* (NAC) species and were identified using the API 20C AUX System (Biomerieux, Marcy l'Etoile, France) or Vitek 2 YST card (Biomerieux). Antifungal susceptibility was determined by Etest (AB Biodisk, Solna, Sweden) on RPMI–2% glucose agar, and MICs of fluconazole, voriconazole, amphotericin B, caspofungin, anidulafungin and micafungin were evaluated according to EUCAST criteria [15].

Data regarding demographic characteristics, scores of severity of illness upon admission or infection onset [APACHE II, SAPS II (Simplified Acute Physiology Score II) and SOFA (Sequential Organ Failure Assessment) score], chronic illnesses, length of hospitalization, surgery, antibiotic and antifungal usage, catheters inserted, and prior bacterial infections were collected from ICU's computerized database (CriticusTM, University of Patras, Greece) and patients' chart reviews. Candidaemia was defined as at least one positive blood culture for *Candida* spp. and clinical symptoms consistent with bloodstream infection. Infection was categorized as sepsis or septic shock according to definition proposed by the Third International Consensus [16]. The date of collection of the first positive blood culture was defined as infection onset. Days at risk are defined as days of ICU hospitalization until onset of infection for patients with candidaemia or total length of stay for patients without candidaemia. According to ESCMID guidelines, prophylactic antifungal therapy was initiated in ventilated patients, hospitalized for at least 3 days, receiving antibiotics, having a central venous catheter and fulfilling at least one of the following criteria: parenteral nutrition, dialysis, major surgery, pancreatitis and/or immunosuppressant medication (including systemic corticosteroids) [11]. Appropriate antifungal treatment was defined as one that included an antifungal agent with in vitro activity against the infecting isolate, initiated within 72 h from the onset of infection, at an adequate dosage.

SPSS version 23.0 (SPSS, Chicago, IL, USA) software was used for data analysis. Categorical variables were analyzed using the Fisher exact test and continuous variables with Mann–Whitney *U* test. Backward stepwise multiple logistic regression analysis used all those variables from the univariate analysis with a $P < 0.1$. Factors contributing to multicollinearity were excluded from the multivariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association. All statistic tests were 2-tailed and $P < 0.05$ was considered statistically significant.

Results

During the study period, 1337 patients were admitted to the ICU. Fifty-three (4.0%) developed candidaemia during their stay corresponding to 2.6 per 1000 patient/days. NAC species predominated (33 patients, 62.3%) with *C. parapsilosis* being the most commonly isolated one (25, 47.2%) followed by *C. glabrata* (4, 7.5%) and *C. tropicalis* (4, 7.5%). *C. albicans* was the cause of 37.7% episodes of candidaemia (20 patients). Seventeen cases (32.1%) were attributed to primary candidaemia, 30 (56.6%) were catheter-related and six (11.3%) secondary to abdominal and urinary tract infections. Overall, 11 isolates were non-susceptible to fluconazole (five *C. albicans*, three *C. parapsilosis* and three *C. glabrata*), while, two *C. albicans* were resistant to voriconazole. Three

isolates were resistant to anidulafungin (two *C. parapsilosis* and one *C. albicans*), two to caspofungin (one *C. glabrata* and one *C. albicans*) and one *C. parapsilosis* to micafungin. All isolates were susceptible to amphotericin B.

The 53 patients that developed candidaemia were matched to 371 controls. Results of the univariate and multivariate analyses for candidaemia are depicted in Tables 1 and 2, respectively. Multivariate analysis found that hospitalization during summer months, prior emergency surgery, malignancy, number of antibiotics administered and prior septic shock due to KPC-producing *Klebsiella pneumoniae* (KPC-Kp) were independently associated with candidaemia (*C. albicans* and NAC), while, administration of an azole was a protective factor. *C. albicans* BSI was associated with chronic obstructive pulmonary disease and corticosteroid administration, while, azole administration was also a protective factor. NAC BSI was associated with hospitalization during summer months, tigecycline administration, echinocandin administration, and prior septic shock due to KPC-Kp. Azole use was also a protective factor. Multivariate analysis for differences among *C. albicans* and NAC BSI revealed that variables associated with candidaemia by NAC were the number of antibiotics, as well as, echinocandin administration.

Overall 14-day mortality was 28.3% (15 patients). Results of univariate analysis for predictors of mortality are shown in Table 3. Multivariate analysis found that SOFA score upon infection onset (*P* 0.019; OR 1.6, CI 1.1–2.3) and septic shock (*P* 0.028; OR 40.4, CI 1.5–1102.3) were associated with mortality, while appropriate empirical antifungal treatment (*P* 0.043; OR 0.041, CI 0.002–0.908) was associated with better survival.

Discussion

Candidaemia remains an important cause of ICU sepsis [2]. In the present study, 4% of all hospitalized patients developed a candidaemia, percentage that is higher to that reported in previous ones [6–8]. NAC predominated during the study period (62.3%). As previously shown, an abrupt epidemiologic change was observed in the ICU of UGHP from 2009 onwards, exhibiting increase in the incidence of candidaemia with a predominance of NAC [4, 17]. From 1998 to 2008, only 27 cases of candidaemia were reported in the ICU as compared to 16 cases (3%) from November 2009 to February 2012 corresponding to 1.9 cases per 1000 patient/days [4, 17]. In the present study the incidence is higher with 2.6 cases per 1000 patient/days. This epidemiologic change was attributed to dissemination of KPC-Kp in the ICU [4, 18]. During the study period, KPC-Kp was the predominant cause of sepsis and septic shock among patients with either candidaemia or without [18]. Bacterial infections in general have been shown to predispose to candidaemia [19], but in the present study only KPC-Kp septic shock was found to be associated to candidaemia. Bacterial septic shock leads to immune system dysregulation, resulting to increased predisposition for candidaemia [20, 21]. *C. albicans* BSI was associated with corticosteroid administration which also provokes immune system dysfunction.

In our study, the number of antibiotics administered was identified as a risk factor for candidaemia. It was also significantly higher among NAC as compared to *C. albicans* BSI. The effect of previous antibiotic administration to its development was shown previously [2, 4–6]. However, this is the first time that tigecycline is significantly associated with NAC. In a murine model, gut colonization by *C. albicans* was substantially increased when mice received tigecycline, but this increase was not associated with dissemination [22]. No data on humans exist on the effect of tigecycline in NAC colonization or infection.

Hospitalization during summer months was found to be independently associated with development of candidaemia, in general, and also of NAC BSI. An association was also found in a previous report from our setting, but data on the effect of seasonality in *Candida*'s infection are scarce [4]. *C. parapsilosis* ratio among critically ill patients with candidaemia was high (47.2%). Such percentages were shown previously in studies from Portugal and the Mediterranean area (Italy, Spain and Turkey), but not from northern European countries. However, the effect of higher temperatures on *C. parapsilosis* epidemiology has not been studied [23]. Another possible explanation may be the increased workload during summer months, contributing especially to dissemination of *C. parapsilosis*, since hands of healthcare workers constitute the predominant environmental source [24]. More studies are needed to assess the real role of seasonality in *Candida*'s epidemiology.

Even though antifungal prophylaxis in ICU patients remains controversial, ESCMID guidelines propose the use of fluconazole or caspofungin as appropriate therapies to prevent or even delay the time of invasive candidiasis development [4, 10, 11]. In the present study, more than half of patients received antifungals with fluconazole being the most commonly agent used. Azole prophylactic administration has an important protective effect, as proved by multivariate analyses, preventing the development of both *C. albicans* and NAC BSI, as previously shown [4]. An important finding in the present study is that administration of echinocandins constitutes a risk factor for non-*albicans* candidaemia development. As shown in previous studies, the use of fluconazole or echinocandins induces a shift in *Candida*'s epidemiology, with the former being responsible for fluconazole non-susceptible species selection (such as, *C. glabrata* or *C. krusei*). Echinocandin use is associated with increased *C. parapsilosis*

Table 1 Univariate analysis for *Candida* (*albicans* and non-*albicans*) isolation risk factors of Intensive Care Unit patients

Characteristics	No infection ($N = 371$)	Candidaemia			P^a	P^b	P^c	P^d
		C. albicans ($N = 20$)	*C.* non-*albicans* ($N = 33$)	All ($N = 53$)				
Days at risk[e]	19.9 ± 18.7	7.2 ± 4.2	26.7 ± 24.5	19.3 ± 21.6	0.837	0.003	0.054	<0.001
Demographics								
Age (years)	61.2 ± 16.9	58.9 ± 16.7	63.9 ± 18.1	62.0 ± 17.6	0.756	0.538	0.299	0.312
Male gender	251 (67.7%)	11 (55.0%)	18 (54.5%)	29 (54.7%)	0.087	0.328	0.129	1.000
Chronic diseases (number)	0.9 ± 1.0	0.9 ± 0.9	1.0 ± 0.9	1.0 ± 0.9	0.668	0.992	0.351	1.000
Diabetes mellitus	63 (17.0%)	1 (5.0%)	8 (24.8%)	9 (17.0%)	1.000	0.220	0.337	0.129
Chronic obstructive pulmonary disease	40 (10.8%)	5 (25.0%)	3 (9.1%)	8 (15.1%)	0.355	0.066	1.000	0.137
Chronic heart failure	49 (13.2%)	1 (5.0%)	2 (6.1%)	3 (5.7%)	0.176	0.491	0.408	1.000
Chronic renal failure requiring dialysis	20 (5.4%)	2 (10.0%)	0 (0.0%)	2 (3.8%)	1.000	0.312	0.392	0.138
Malignancy (solid organ or hematologic)	36 (9.7%)	5 (25.0%)	7 (21.2%)	12 (22.6%)	0.010	0.047	0.068	0.748
Corticosteroid use (within last month of ICU admission)	29 (7.8%)	1 (5.0%)	5 (15.2%)	6 (11.3%)	0.420	1.000	0.180	0.390
Obesity	85 (22.9%)	3 (15.0%)	8 (24.2%)	11 (20.8%)	0.861	0.584	0.831	0.503
Admission data								
APACHE II score upon admission	17.8 ± 7.0	17.5 ± 8.8	17.3 ± 5.9	17.4 ± 7.0	0.686	0.859	0.830	0.919
SAPS II upon admission	41.5 ± 11.6	44.6 ± 15.8	42.2 ± 8.5	43.1 ± 11.7	0.351	0.565	0.604	0.466
SOFA score upon admission	8.8 ± 3.3	10.1 ± 3.8	9.2 ± 3.4	9.5 ± 3.5	0.125	0.228	0.597	0.427
Previous emergency surgery	124 (33.4%)	7 (35.0%)	17 (51.5%)	24 (45.3%)	0.093	1.000	0.055	0.270
Previous abdominal surgery	64 (17.3%)	3 (15.8%)	9 (27.3%)	12 (23.1%)	0.334	1.000	0.159	0.499
Hospitalization data								
During summer months (June–July–August)	94 (25.3%)	7 (35.0%)	14 (42.4%)	21 (39.6%)	0.033	0.430	0.041	0.773
Tracheostomy	206 (55.5%)	8 (40.0%)	26 (78.8%)	34 (64.2%)	0.300	0.248	0.010	0.007
Presence of catheters[f]	181 (48.8%)	10 (50.0%)	22 (66.7%)	32(60.4%)	0.142	1.000	0.068	0.259
Presence of colostomy or abdominal catheter	57 (15.4%)	3 (15.0%)	10 (30.3%)	13 (24.5%)	0.112	1.000	0.046	0.325
Corticosteroid administration	202 (50.4%)	17 (85.0%)	23 (69.7%)	40 (75.5%)	0.004	0.009	0.102	0.325
Parenteral nutrition	124 (33.4%)	8 (40.0%)	20 (60.6%)	28 (52.8%)	0.009	0.628	0.004	0.168
Enteral nutrition	228 (61.5%)	9 (45.0%)	24 (72.7%)	33 (62.3%)	1.000	0.162	0.261	0.078
Colonization/infection data								
KPC-Kp infection[g]	78 (21.0%)	2 (10.0%)	15 (45.5%)	17 (32.1%)	0.079	0.391	0.004	0.014
KPC-Kp shock[g]	34 (9.2%)	2 (10.0%)	13 (39.4%)	15 (28.3%)	<0.001	0.705	<0.001	0.028
Sepsis (excluding KPC-Kp)[g]	68 (18.3%)	2 (10.0%)	4 (12.1%)	6 (11.3%)	0.249	0.549	0.481	1.000
Septic shock (excluding KPC-Kp)[g]	14 (3.8%)	1 (5.0%)	2 (6.1%)	3 (5.7%)	0.458	0.552	0.382	1.000
Antifungal administration	197 (53.1%)	5 (25.0%)	24 (72.7%)	29 (54.7%)	0.884	0.020	0.043	0.001
Azoles	137 (36.9%)	2 (10.0%)	7 (21.2%)	9 (17.0%)	0.005	0.015	0.088	0.456
Fluconazole	119 (32.1%)	2 (10.0%)	6 (18.2%)	8 (15.1%)	0.010	0.045	0.117	0.695
Voriconazole	10 (2.7%)	0 (0.0%)	1 (3.0%)	1 (1.9%)	1.000	1.000	1.000	1.000
Itraconazole	13 (3.5%)	0 (0.0%)	2 (6.1%)	2 (3.8%)	1.000	1.000	0.351	0.521
Echinocandins	92 (24.8%)	3 (15.0%)	21 (63.6%)	24 (45.3%)	0.003	0.427	<0.001	0.001
Anidulafungin	55 (14.8%)	3 (15.0%)	14 (42.4%)	17 (32.1%)	0.003	1.000	<0.001	0.067
Caspofungin	29 (7.8%)	0 (0.0%)	5 (15.2%)	5 (9.4%)	0.597	0.383	0.180	0.144
Micafungin	17 (4.6%)	0 (0.0%)	4 (12.1%)	4 (7.5%)	0.317	1.000	0.082	0.285
Liposomal amphotericin B	15 (4.0%)	0 (0.0%)	1 (3.0%)	1 (1.9%)	0.705	1.000	1.000	1.000
Number of antibiotics administered	3.6 ± 1.9	3.2 ± 1.3	5.6 ± 1.9	4.7 ± 2.0	<0.001	0.366	<0.001	<0.001
Carbapenems	309 (83.3%)	17 (85.0%)	29 (87.9%)	46 (86.8%)	0.691	1.000	0.628	1.000
Piperacillin/tazobactam	149 (40.2%)	3 (15.0%)	14 (42.4%)	17 (32.1%)	0.294	0.032	0.854	0.067

Table 1 (continued)

Characteristics	No infection ($N = 371$)	Candidaemia			P^a	P^b	P^c	P^d
		C. albicans ($N = 20$)	*C.* non-*albicans* ($N = 33$)	All ($N = 53$)				
3rd or 4th generation cephalosporins	41 (11.1%)	2 (10.0%)	13 (39.4%)	15 (28.3%)	0.002	1.000	<0.001	0.028
Quinolones	54 (14.6%)	3 (15.0%)	6 (18.2%)	9 (17.0%)	0.679	1.000	0.608	1.000
Tigecycline	50 (13.5%)	3 (15.0%)	15 (45.5%)	18 (34.0%)	<0.001	0.743	<0.001	0.036
Colistin	136 (36.7%)	4 (20.0%)	27 (81.8%)	31 (58.5%)	0.004	0.156	<0.001	<0.001
Aminoglycosides	118 (31.8%)	6 (30.0%)	18 (54.5%)	24 (45.3%)	0.062	1.000	0.012	0.097
Glycopeptides	292 (78.7%)	13 (65.0%)	31 (93.9%)	44 (83.0%)	0.588	0.166	0.040	0.019
Metronidazole	40 (10.8%)	2 (10.0%)	6 (18.2%)	8 (15.1%)	0.355	1.000	0.246	0.695
Linezolid	117 (31.5%)	8 (40.0%)	19 (57.6%)	27 (50.9%)	0.008	0.464	0.004	0.264
Mean antibiotic use per day	2.5 ± 0.9	2.2 ± 0.4	2.9 ± 0.6	2.7 ± 0.6	0.142	0.226	0.005	<0.001

Data are number (%) of patients or Mean ± SD

ICU Intensive Care Unit, *KPC-Kp* KPC-producing *K. pneumoniae*, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *SAPS II* Simplified Acute Physiology II Score, *SOFA* Sequential Organ Failure Assessment

[a] Comparison between patients with *Candida* spp. infection and patients with no infection

[b] Comparison between patients with *C. albicans* infection and patients with no infection

[c] Comparison between patients with *C.* non-*albicans* infection and patients with no infection

[d] Comparison between patients with *C.* non-*albicans* and *C. albicans* infection

[e] Days at risk are defined as days of ICU hospitalization until *Candida* spp. infection and total ICU days for patients without *Candida* infection

[f] All patients after ICU admission were intubated, mechanically ventilated and were continuously monitored with a central venous catheter, an arterial catheter, and a urinary catheter. This variable does not include the aforementioned catheters

[g] Identified prior to *Candida* spp. infection

Table 2 Multivariate analysis for candidaemia (by *C. albicans* and non-*albicans*) risk factors of Intensive Care Unit patients

Characteristics	*Candidaemia* vs. control		*C. albicans* BSI vs. control		*C.* non-*albicans* BSI vs. control		*C.* non-*albicans* BSI vs. *C. albicans* BSI	
	P	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)
Hospitalization during summer months	0.049	2.0 (1.0–3.8)	–	–	0.040	2.3 (1.0–5.1)	–	–
Prior emergency surgery	0.005	2.7 (1.3–5.4)	–	–	–	–	–	–
Malignancy (solid tumor or haematologic)	0.010	2.9 (1.3–6.6)	–	–	–	–	–	–
Chronic obstructive pulmonary disease	–	–	0.021	3.9 (1.2–12.6)	–	–	–	–
Corticosteroid administration	–	–	0.014	5.0 (1.4–17.9)	–	–	–	–
Numbers of antibiotics administered	<0.001	1.4 (1.2–1.7)	–	–	–	–	0.014	2.0 (1.1–3.3)
Tigecycline administration	–	–	–	–	0.015	3.2 (1.3–8.1)	–	–
Prior septic shock due to KPC-Kp	0.003	12.7 (2.4–69.0)	–	–	0.025	3.0 (1.1–7.6)	–	–
Azole administration	<0.001	0.180 (0.08–0.43)	0.013	0.14 (0.03–0.66)	0.022	0.32 (0.12–0.85)	–	–
Echinocandin administration	–	–	–	–	0.024	2.8 (1.1–7.0)	0.005	10.2 (2.0–52.0)

BSI bloodstream infection, *OR* odds ratio, *CI* confidence interval, *KPC-Kp* KPC-producing *K. pneumoniae*

isolation due to reduced susceptibility [4, 12–14]. The high use of echinocandins in our ICU may partially explain the predominance of *C. parapsilosis* among patients with candidaemia. Thus, even though antifungal prophylaxis is a promising approach in critically ill patients, more studies are required to define the optimal agent and to assess the risk for selection resistant isolates.

In accordance with previous studies, the 14-day mortality rate of candidaemia was 28.3% [7, 8]. Consistent with published results, the severity of infection (as depicted by SOFA score upon candidaemia onset) and development of septic

Table 3 Univariate analysis for predictors of mortality in patients with *Candida* spp. bloodstream infection (BSI) during Intensive Care Unit hospitalization

Characteristics	Survivors ($n = 38$)	Non-survivors ($n = 15$)	*P*
Demographics			
Age (years)	59.9 ± 18.0	67.4 ± 16.0	0.138
Male (gender)	25 (65.8%)	4 (26.7%)	0.015
Chronic diseases (number)	1.0 ± 0.9	0.9 ± 0.8	0.692
Diabetes mellitus	6 (15.8%)	3 (20.0%)	0.701
Chronic obstructive pulmonary disease	6 (15.8%)	2 (13.3%)	1.000
Chronic heart failure	3 (7.9%)	0 (0.0%)	0.550
Chronic renal failure	1 (2.6%)	1 (6.7%)	0.490
Malignancy	8 (21.1%)	4 (26.7%)	0.772
Corticosteroid use (within last month of ICU admission)	5 (13.2%)	1 (6.7%)	0.662
Obesity	9 (23.7%)	2 (13.3%)	0.482
Hospitalization data			
Infection during summer months (June–July–August)	13 (34.2%)	8 (53.3%)	0.227
APACHE II score upon admission	15.6 ± 6.9	21.3 ± 5.9	0.011
SAPS II upon admission	41.2 ± 11.7	47.7 ± 10.8	0.080
SOFA score upon admission	8.9 ± 3.3	11.1 ± 3.7	0.040
Prior emergency surgery	19 (50.0%)	5 (33.3%)	0.363
Prior abdominal surgery	7 (18.4%)	5 (33.3%)	0.286
Previous antifungal therapy	21 (55.3%)	8 (53.3%)	1.000
Infection data			
Septic shock	16 (42.1%)	14 (93.3%)	<0.001
SAPS II upon infection onset	41.2 ± 8.8	50.6 ± 12.2	0.008
SOFA score upon infection onset	7.9 ± 3.1	11.2 ± 3.3	0.003
Azole treatment	11 (28.9%)	2 (13.3%)	0.305
Echinocandin treatment	26 (68.4%)	8 (53.3%)	0.351
Liposomal amphotericin B treatment	0 (0.0%)	2 (13.3%)	0.076
Appropriate antifungal treatment	35 (92.1%)	10 (66.7%)	0.033
Corticosteroid administration	27 (71.1%)	13 (86.7%)	0.305
Microbiologic data			
Infection due to *C.* non-*albicans*	24 (63.2%)	9 (60.0%)	1.000
Primary BSI	13 (34.2%)	4 (26.7%)	0.748

Data are number (%) of patients or mean ± standard deviation

APACHE II Acute Physiology and Chronic Health Evaluation II, *SAPS II* Simplified Acute Physiology Score II, *SOFA* Sequential Organ Failure Assessment

shock were associated with increased mortality [9]. The administration of appropriate empirical antifungal therapy (within 72 h from candidaemia onset) independently reduced mortality. Early administration of appropriate antifungal on survival was proven in previous studies [9, 10, 13].

The present study has several limitations. First, it is a case–control study with relative small number of patients with candidaemia. Second, epidemiologic data may represent local epidemiology.

In conclusion, an increase of candidaemia incidence is observed in the ICU predominantly due to NAC, especially *C. parapsilosis*. Risk factors for development were prior septic shock by KPC-Kp, number of antibiotics administered and hospitalization during summer months. Administration of fluconazole prophylaxis prevents the development of candidaemia of either *albicans* or non-*albicans* species, while, the use of echinocandin predisposes to development of non-*albicans* candidaemia, mainly by *C. parapsilosis*. Mortality of candidaemia is influenced by the development of septic shock and appropriate antifungal treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard The study was approved by the Hospital Ethics Committee (HEC No: 571).

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