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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

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Take-home message: We observed that the mortality rate of candidemia in ICU patients decreased in recent years and that receipt of an echinocandin as primary therapy was associated with lower 30-day mortality.

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Abstract *Purpose:* To describe temporal trends in the epidemiology, clinical management and outcome of candidemia in intensive care unit (ICU) patients. *Methods:* This study was a retrospective analysis of 1,392 episodes of candidemia in 647 adult ICU patients from 22 Brazilian hospitals. The characteristics of candidemia in these ICU patients were compared in two periods (2003–2007, period 1; 2008–2012, period 2), and the predictors of 30-day mortality were assessed. *Results:* The proportion of patients who developed candidemia while in the ICU increased from 44 % in period 1 to 50.9 % in period 2 ($p = 0.01$). Prior exposure to fluconazole before candidemia (22.3 vs. 11.6 %, $p < 0.001$) and fungemia due to *Candida glabrata* (13.1 vs. 7.8 %, $p = 0.03$) were more frequent in period 2, as was the proportion of patients receiving an echinocandin as primary therapy (18.0 vs. 5.9 %, $p < 0.001$). The 30-day mortality rate decreased from 76.4 % in period 1 to 60.8 % in period 2 ($p < 0.001$). Predictors of 30-day mortality by multivariate analysis were older age, period 1, treatment with corticosteroids and higher APACHE II score, while treatment with an echinocandin were associated with a higher probability of survival. *Conclusions:* We found a clear change in the epidemiology and clinical management of candidemia in ICU patients over the 9-year period of the study. The use of echinocandins as primary therapy for candidemia appears to be associated with better outcomes.

Keywords Candidemia · Mortality · Antifungal therapy · Echinocandin · Invasive candidiasis

Introduction

Despite the best efforts of the medical community, the morbidity and mortality associated with candidemia remains elevated, with crude mortality rates of ≥40 % [1–3]. In addition, population-based studies conducted in the USA and Europe suggest that the incidence of candidemia has increased during the last decade [4–6]. Patients admitted to intensive care units (ICUs) are at high risk of developing candidemia, with recent

multicenter studies reporting that 30–40 % of candidemic patients were in ICUs at the time of the diagnosis. Delays in initiating antifungal therapy may increase mortality rates in patients with candidemia [7, 8]. Consequently, serious attempts have been directed to validating predictive guidelines based on risk factors and/or the presence of fungal biomarkers in order to assist clinicians in their decision to provide early antifungal therapy to patients at high risk [9–12].

In Latin America, overall mortality rates of patients with candidemia are usually higher than those observed in the Northern Hemisphere [13–15]. However, it should be noted that data on the epidemiology and prognostic factors associated with candidemia in patients admitted to ICUs in Latin America are scarce. Therefore, the main objective of this study was to evaluate historical trends in the epidemiology and clinical management of patients admitted to ICUs in tertiary care hospitals in Brazil, as well as to identify the prognostic factors of candidemia.

Patients and methods

Patient selection and data collection

This is a retrospective analysis of a collection of candidemia cases created by merging the databases of five prospective laboratory-based surveillance cohorts conducted in 22 tertiary care medical centers in Brazil between March 2003 and February 2012. Only tertiary care hospitals providing medical care in most medical specialties participated in these five studies, and they can be categorized as public hospitals ($n = 13$), which provide medical assistance to low-income patients, and private hospitals ($n = 9$), which are for-profit medical institutions that provide care mostly to patients covered by private insurance plans. These hospitals are representative of public and private reference medical centers located in 12 large cities in Brazil. In the first two cohorts, only patients from public hospitals were enrolled, while in the latter three cohort studies, the patients were from a mixture of public and private hospitals.

An investigator at each medical center was assigned the specific task of contacting the microbiology laboratory of the hospital on a weekly basis in order to collect clinical and epidemiological data of all incident cases of candidemia. This investigator was trained to record such data on a standard case report form using a dictionary of terms that included all definitions of underlying conditions and medical exposures collected during the study. The case report form, dictionary of terms and strategy for data collection were the same in all five surveillance studies. Patients were followed up to 30 days after the incident candidemia or death. A case of candidemia was defined as the incident isolation of *Candida* spp. from a blood culture. The date of the incident candidemia was defined as the date of the collection of the blood culture that became positive for *Candida* species. Candidemia occurring >30 days after the incident isolation was defined as a new case. Fever was defined as an axillary temperature of ≥37.8 °C and neutropenia as an absolute neutrophil count of <500/mm^3. Cardiac and lung diseases were considered if the patient presented any cardiac or lung condition requiring active treatment. Such conditions included (but were not restricted to) congestive heart failure, coronary arterial disease, hypertension and cardiac arrhythmias (cardiac diseases), as well as chronic obstructive pulmonary disease, asthma, emphysema, bronchiectasis or chronic pneumonia or interstitial disease of any etiology (lung disease). Renal failure was defined as any documented serum creatinine value of >1.5 g/dL.

With the exception of invasive medical procedures and antibiotic use, we considered all these manifestations documented up to 30 days before the date of the incident candidemia as conditions associated with candidemia. Data on central venous catheters, dialysis and antibiotic use were captured up to 15 days before the onset of candidemia. Data on surgery requiring general anesthesia was captured up to 3 months before candidemia. All medical records were reviewed and monitored by a central data collection system for the analysis of completeness and consistency. In cases of uncompleted or inconsistent clinical forms, queries were generated and sent back to the investigators for corrections or completion.

Yeast identification

All *Candida* bloodstream isolates were sent to a central laboratory (Special Mycology Laboratory, Escola Paulista de Medicina, UNIFESP) for further species identification based on the micromorphologic characteristics of the colonies and biochemical tests (ID 32C system; bioMérieux, Marcy l'Etoile, France).

Data analysis

For this analysis we excluded patients aged <18 years. We compared candidemia occurring in ICU patients versus non-ICU patients in terms of baseline characteristics, clinical manifestations, species distribution, treatment and outcome. In addition, we arbitrarily defined two 5-year periods (2003–2007, period 1; 2008–2012, period 2) and compared the epidemiological characteristics of ICU patients admitted in these two periods. Additional analyses included comparison of the epidemiology of candidemia in ICU patients from public versus private institutions. Finally, prognostic factors for ICU patients with candidemia were identified by comparing

patients who died versus those who survived for 30 days after the candidemia episode.

Categorical variables were analyzed using chi-square or Fisher's exact tests, as appropriate, and continuous variables were compared using the Wilcoxon test. A p value of <0.05 was considered to be statistically significant. Variables significant at $p < 0.1$ by univariate analysis were included in a multivariate model (backward and forward). Statistical analyses were performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL).

Results

A total of 1,392 episodes of candidemia were collected for analysis. The median age of the patient cohort was 62 (range 18–97) years, and 718 were males. *C. albicans* was the leading etiologic agent of candidemia (42 %), followed by *C. tropicalis* (20 %), *C. parapsilosis* (19 %) and *C. glabrata* (9 %). The 30-day crude mortality rate was 62.4 %.

In 647 episodes (46.5 %) the patient was in an ICU at the time candidemia was diagnosed. Comparison between these patients and those who were not in an ICU is shown in Table 1 where it can be seen that ICU patients were older (median of 66 vs. 58 years, $p < 0.001$) and more likely to present comorbidities such as renal failure and neurologic, cardiac or lung disease. Likewise, ICU patients were more likely to have been exposed to surgery, dialysis, mechanical ventilation, central venous catheterization and antibiotics. However, non-ICU patients with candidemia were more likely to have cancer (especially hematologic malignancies), organ transplantation and auto-immune diseases. Non-ICU patients were also more likely to have neutropenia and to have received anticancer chemotherapy and immunosuppressive drugs. The 30-day crude mortality rate was 70.3 % in ICU patients and 52.6 % in non-ICU patients ($p < 0.001$). In terms of species distribution, the only significant difference was a lower proportion of *C. parapsilosis* among ICU patients (17.2 vs. 21.7 %, $p = 0.03$). Of note, both the proportion of *C. glabrata* candidemia and prior exposure to azoles were similar among ICU and non-ICU patients.

The proportion of patients who developed candidemia while in the ICU increased from 44 % in period 1 to 50.9 % in period 2 ($p = 0.01$). Table 2 shows the comparisons of episodes in the two periods. As expected, the proportion of patients in private hospitals was higher in period 2, as was the proportion of patients with liver or neurologic diseases. Prior exposure to fluconazole (22.3 vs. 11.6 %, $p < 0.001$) and candidemia due to *C. glabrata* (13.1 vs. 7.8 %, $p = 0.03$) were also more frequent in period 2. Of note, the increase in the proportion of *C. glabrata* over the entire study period was mostly driven by a change in the proportion of public institutions [5.1 (period 1) vs. 10.5 % (period 2), $p = 0.07$] compared to private centers [11.1 (period 1) vs. 15.1 % (period 2), $p = 0.29$].

Antifungal treatment was given to 72.7 % of patients in period 1 and 77.3 % in period 2 ($p = 0.19$). During the study period the antifungal drugs prescribed for the primary treatment of candidemia changed, with a decrease in the use of deoxycholate amphotericin B (27.8 vs. 13.4 %, $p < 0.001$) and an increase in the use of echinocandins (5.9 vs. 18.0 %, $p < 0.001$). The use of lipid formulations of amphotericin B also increased from period 1 to period 2 (3.1 vs. 6.2 %, $p = 0.11$), but the difference was not statistically significant. Of interest, the 30-day crude mortality rate decreased from 76.4 % in period 1 to 60.8 % in period 2 ($p < 0.001$).

The main characteristics of candidemic patients according to admission to ICUs of public or private hospitals are shown in Table 3. Patients in public hospitals were significantly younger, and a higher proportion had autoimmune and lung diseases; in private hospitals, a higher number of patients had neutropenia and received cancer chemotherapy. In terms of species distribution, *C. albicans* was more frequently isolated in public institutions (48.6 vs. 39.6 %, $p = 0.02$), whereas *C. glabrata* (12.9 vs. 6.9 %, $p = 0.01$) and *C. krusei* (3.7 vs. 1.2 %, $p = 0.05$) were more prone to be isolated in private medical centers. In terms of antifungal therapy, echinocandins (2.9 vs. 18.5 %, $p < 0.001$) and lipid formulations of amphotericin B (1.3 vs. 7.4 %, $p = 0.001$) were more likely to be used for the treatment of candidemia in private institutions, whereas deoxycholate amphotericin B was more frequently used in the public institutions (31.8 vs. 12.3 %, $p < 0.001$). The 30-day crude mortality rate was 75.3 % in the public hospitals and 65.3 % in private institutions ($p = 0.006$).

As shown in Table 4, the following variables were associated with higher 30-day mortality by univariate analysis: older age, period 1, public hospital, higher acute physiologic and chronic health evaluation (APACHE) II score, cancer, lung disease, renal failure, dialysis, mechanical ventilation, receipt of corticosteroids, no treatment for candidemia and treatment with deoxycholate amphotericin B. Infection due to *C. parapsilosis* and treatment with an echinocandin were associated with lower mortality.

By multivariate analysis (Table 5), older age [odds ratio (OR) 1.03, 95 % confidence interval (CI) 1.01–1.05], period 1 (OR 2.49, 95 % CI 1.22–5.08), corticosteroid treatment (OR 4.00, 95 % CI 1.98–8.13) and higher APACHE II score (OR 1.05, 95 % CI 1.01–1.09) were associated with an increased risk of death. By contrast, treatment with an echinocandin (OR 0.20, 95 % CI 0.07–0.58) was associated with a higher probability of survival. Prognostic factors were also evaluated in the 745 patients who were not in an ICU (Electronic Supplementary Material Table A). Among

Table 1 Characteristics of patients admitted to an intensive care unit (ICU) versus those of patients not in an ICU at the time of candidemia diagnosis

Variable	In the ICU ($N = 647$)	Outside the ICU ($N = 745$)	p
Gender (*N*, male:female)	328:319	390:355	0.54
Age (years)	66 (18–97)	58 (18–97)	<0.001
Time (days) from admission to candidemia diagnosis	20 (0–188)	20 (0–159)	0.83
Cancer	174 (26.9)	283 (38.0)	<0.001
Hematologic	29 (4.5)	95 (12.8)	<0.001
Solid tumor	145 (22.4)	188 (25.2)	0.22
Diabetes	154 (24.4)	170 (22.8)	0.48
Renal failure	262 (40.5)	217 (29.1)	<0.001
Chronic renal failure	81 (12.5)	113 (15.2)	0.15
Dialysis	183 (28.3)	118 (15.8)	<0.001
Liver disease	74 (11.4)	91 (12.2)	0.65
Auto-immune disease	28 (4.3)	52 (7.0)	0.03
Neurologic disease	160 (24.7)	141 (18.9)	0.009
Transplant	3 (0.5)	27 (3.6)	<0.001
Cardiac disease	227 (35.1)	163 (21.9)	<0.001
Lung disease	185 (28.6)	120 (16.1)	<0.001
Surgery	336 (51.9)	328 (44.0)	0.003
Abdominal surgery	194 (30.0)	189 (25.4)	0.05
Mechanical ventilation	480 (74.2)	120 (16.1)	<0.001
Total parenteral nutrition	140 (21.6)	157 (21.1)	0.80
Central venous catheter	605 (93.5)	591 (79.3)	<0.001
Neutropenia	16 (2.5)	51 (6.8)	<0.001
Prior drug/treatment exposure			
Antibiotics	622 (96.1)	653 (87.7)	<0.001
Corticosteroids	338 (52.2)	223 (29.9)	<0.001
Other immunosuppressive drugs	38 (5.9)	67 (9.0)	0.03
Chemotherapy	22 (3.4)	76 (10.2)	<0.001
Fluconazole prior to candidemia	102 (15.8)	108 (14.5)	0.51
Candida spp.			
C. albicans	285 (44.0)	300 (40.3)	0.15
C. parapsilosis	111 (17.2)	162 (21.7)	0.03
C. tropicalis	141 (21.8)	140 (18.8)	0.16
C. glabrata	64 (9.9)	68 (9.1)	0.63
C. krusei	16 (2.5)	21 (2.8)	0.69
C. guilliermondii	12 (1.9)	22 (3.0)	0.19
Treatment received	482 (74.5)	577 (77.4)	0.20
Fluconazole	295/482 (61.2)	395/577 (68.5)	0.01
Deoxycholate AMB	106/482 (22.0)	106/577 (18.4)	0.14
Lipid AMB	21/482 (4.4)	8/577 (1.4)	0.003
Echinocandins	52/482 (10.8)	33/577 (5.7)	0.002
30-day crude mortality	450/640 (70.3)[a]	389/740 (52.6)[b]	<0.001

AMB, Amphotericin B

Data are presented as a number with the percentage given in parenthesis, or as the median with the range given in parenthesis, unless specified otherwise

[a] Status on day 30 was not known in 7 patients

[b] Status on day 30 was not known in 5 patients

these patients, the variables associated with 30-day mortality were period 1(OR 2.67, 95 % CI 1.33–5.33, $p = 0.005$), mechanical ventilation (OR 3.87, 95 % CI 1.46–10.31, $p = 0.007$) and antibiotic treatment (OR 5.87, 95 % CI 1.71–18.18, $p = 0.004$).

Discussion

In this study we observed that while the 30-day crude mortality rate of patients with candidemia admitted to an ICU was very high, it decreased from 76.4 % in period 1 (2003–2007) to 60.8 % in period 2 (2008–2012). We also observed that among the predictors of outcome identified by multivariate analysis, the use of an echinocandin as primary therapy for candidemia was associated with a better outcome and that echinocandins were increasingly being used as primary therapy for candidemia in period 2.

Critically ill patients still represent a large proportion of patients who develop candidemia in tertiary care hospitals. In the present study, the proportion of candidemic patients in an ICU was 46.5 % over the entire study period and increased in period 2. As expected, compared to non-ICU patients, patients already admitted to an ICU when candidemia was diagnosed were more likely to have

Table 2 Characteristics of ICU patients with candidemia in the two study periods, 2003–2007 (period 1) and 2008–2012 (period 2)

Variable	Period 1 ($N = 396$)	Period 2 ($N = 251$)	p
Gender (*N*, male:female)	206:190	122:129	0.40
Age (years)	67 (18–97)	63 (19–97)	0.67
Time (days) from admission to candidemia diagnosis	21 (0–142)	16 (0–188)	0.01
Private hospital	340 (37.8)	242 (49.3)	<0.001
APACHE II score, median (range)[a]	27 (0–46)	22 (3–42)	0.08
Cancer	102 (25.8)	72 (28.7)	0.41
Hematologic	14 (3.5)	15 (6.0)	0.14
Solid tumor	88 (22.2)	57 (22.7)	0.88
Diabetes	96 (24.2)	62 (24.7)	0.89
Renal failure	162 (40.9)	100 (39.8)	0.79
Chronic renal failure	57 (14.4)	24 (9.6)	0.07
Dialysis	112 (28.3)	71 (28.3)	1.00
Liver disease	32 (8.1)	42 (16.7)	0.001
Auto-immune disease	18 (4.5)	10 (4.0)	0.73
Neurologic disease	83 (21.0)	77 (30.7)	0.005
Transplant	2 (0.5)	1 (0.4)	1.00
Cardiac disease	142 (35.9)	85 (33.9)	0.60
Lung disease	106 (26.8)	79 (31.5)	0.20
Surgery	205 (51.8)	131 (52.2)	0.92
Abdominal surgery	129 (32.6)	66 (25.9)	0.07
Mechanical ventilation	296 (74.7)	184 (73.3)	0.68
Total parenteral nutrition	83 (21.0)	57 (22.7)	0.60
Central venous catheter	364 (91.9)	241 (96.0)	0.04
Neutropenia	9 (2.3)	7 (2.8)	0.68
Prior drug/treatment exposure			
Antibiotics	377 (95.2)	245 (97.6)	0.12
Corticosteroids	202 (51.0)	136 (54.2)	0.43
Other immunosuppressive drugs	23 (5.8)	15 (6.0)	0.93
Chemotherapy	7 (1.8)	15 (6.0)	0.004
Fluconazole prior to candidemia	46 (11.6)	56 (22.3)	<0.001
Candida spp.			
C. albicans	177 (44.7)	108 (43.0)	0.68
C. parapsilosis	72 (18.2)	39 (15.5)	0.38
C. tropicalis	90 (22.7)	51 (20.3)	0.47
C. glabrata	31 (7.8)	33 (13.1)	0.03
C. krusei	5 (1.3)	11 (4.4)	0.01
C. guilliermondii	9 (2.3)	3 (1.2)	0.38
Treatment received	288 (72.7)	194 (77.3)	0.19
Fluconazole	174/288 (60.4)	121/194 (62.4)	0.67
Deoxycholate AMB[b]	80/288 (27.8)	26/194 (13.4)	<0.001
Lipid AMB[b]	9/288 (3.1)	12/194 (6.2)	0.11
Echinocandin	17/288 (5.9)	35/194 (18.0)	<0.001
30-day crude mortality	298/390 (76.4)[c]	152/250 (60.8)[d]	<0.001

Data are presented as a number with the percentage given in parenthesis, or as the median with the range given in parenthesis, unless specified otherwise

[a] APACHE, Acute physiologic and chronic health evaluation (Data available for 261 patients only)

[b] AMB, amphotericin B

[c] Status on day 30 was not known in 6 patients

[d] Status on day 30 was not known in 1 patient

received antibiotics and invasive medical procedures, while cancer and transplantation were more frequent in non-ICU patients.

An interesting finding of our study relates to changes in the epidemiology and clinical management of candidemia over the 9-year period covered by this study. In parallel with the observed increase in the proportion of candidemic patients who had been exposed to fluconazole prior to being diagnosed with candidemia, we found a substantial rise in the proportion of candidemia due to *C. glabrata*. The association between previous exposure to fluconazole and candidemia due to *C. glabrata* has been extensively reported [16–19]. While epidemiologic studies of candidemia in Latin America still show a relatively low proportion of candidemia caused by species that exhibit a lower susceptibility to fluconazole [14], the emergence of *C. glabrata* has been documented in other studies from the region [20–22].

A dramatic finding in our study was the unacceptably high 30-day crude mortality of candidemic ICU patients, both in public and private hospitals. Indeed, two large studies published in the USA reported a decrease in the

Table 3 Characteristics of patients with candidemia according to admission to ICUs of public and private hospitals

Variable	Public ($N = 321$)	Private ($N = 326$)	p
Gender (*N*, male:female)	169:152	159:167	0.32
Age (years)	60 (18–97)	64 (18–97)	<0.001
Time (days) from admission to candidemia	20 (0–188)	19 (0–159)	0.62
Cancer	79 (24.6)	95 (29.1)	0.19
Hematologic	10 (3.1)	19 (5.8)	0.09
Solid tumor	69 (21.5)	76 (23.3)	0.58
Diabetes	69 (21.5)	89 (27.3)	0.09
Renal failure	126 (39.3)	136 (41.7)	0.52
Chronic renal failure	45 (14.0)	36 (11.0)	0.25
Dialysis	88 (27.4)	95 (29.1)	0.63
Liver disease	34 (10.6)	40 (12.3)	0.50
Auto-immune disease	20 (6.2)	8 (2.5)	0.02
Neurologic disease	75 (23.4)	85 (25.1)	0.42
Transplant	1 (0.3)	2 (0.6)	1.00
Cardiac disease	113 (35.2)	114 (35.0)	0.95
Lung disease	106 (33.0)	79 (24.2)	0.01
Surgery	164 (51.1)	172 (52.8)	0.67
Abdominal surgery	96 (29.9)	98 (30.1)	0.97
Mechanical ventilation	247 (76.9)	233 (71.5)	0.11
Total parenteral nutrition	68 (21.2)	72 (22.1)	0.78
Central venous catheter	297 (92.5)	308 (94.5)	0.31
Neutropenia	3 (0.9)	13 (4.0)	0.01
Prior drug/treatment exposure			
Antibiotics	310 (96.6)	312 (95.7)	0.57
Corticosteroids	173 (53.9)	165 (50.6)	0.40
Immunosuppressive drugs	18 (5.6)	20 (6.1)	0.77
Chemotherapy	4 (1.2)	18 (5.5)	0.003
Fluconazole prior to candidemia	43 (13.4)	59 (18.1)	0.10
Candida spp.			
C. albicans	156 (48.6)	129 (39.6)	0.02
C. parapsilosis	61 (19.0)	50 (15.3)	0.22
C. tropicalis	64 (19.9)	77 (23.6)	0.26
C. glabrata	22 (6.9)	42 (12.9)	0.01
C. krusei	4 (1.2)	12 (3.7)	0.05
C. guilliermondii	7 (2.2)	5 (1.5)	0.54
Treatment received	239 (74.5)	243 (74.5)	0.98
Fluconazole	147/239 (61.5)	148/243 (60.9)	0.89
Deoxycholate AMB	76/239 (31.8)	30/243 (12.3)	<0.001
Lipid AMB	3/239 (1.3)	18/243 (7.4)	0.001
Echinocandin	7/239 (2.9)	45/243 (18.5)	<0.001
30-day crude mortality	241/320 (75.3)[a]	209/320 (65.3)[b]	0.006

Data are presented as a number with the percentage given in parenthesis, or as the median with the range given in parenthesis, unless specified otherwise

[a] Status on day 30 was not known in 1 patient

[b] Status on day 30 was not known in 6 patients

mortality rate of patients with candidemia during the last 10 years [5, 18]. The crude mortality rate in the EPIC study evaluating candidemia in ICUs was 42 % [23], and two European studies reported 30-day mortality of 47 % [24, 25]. The high mortality rate observed in our series may be multifactorial and include poor general clinical conditions of sick patients (especially from public hospitals), delays in making a diagnosis and the choice of treatment.

Interestingly, we observed a significant decrease in the crude mortality rate of patients with candidemia in the second period of the analysis. When we compared the clinical characteristics of patients from both periods, we found that age distribution and underlying conditions were similar, with the exception of neurologic and liver diseases, which were more common in period 2. In addition, the APACHE II score was slightly lower in period 2, although the difference was not statistically significant. We do not believe that these differences explain the significant reduction in the death rate in period 2—rather, important differences in the clinical management of candidemia did occur in period 2. Patients from the latter period were more likely to have been treated with echinocandins and less likely to have received deoxycholate amphotericin B. Various studies, including a randomized clinical trial [26] and a patient-level pooled analysis of randomized clinical trials [27], have shown that the outcome of candidemia is better when an

Table 4 Factors associated with 30-day mortality among 640 ICU patients[a] with candidemia by univariate analysis

Variable	Alive ($N = 190$)	Dead ($N = 450$)	p value
Gender (*N*, male:female)	94:96	233:217	0.59
Age (years)	60 (19–97)	68 (18–97)	<0.001
Time (days) from admission to candidemia	17 (0–151)	20.5 (0–188)	0.10
Period 2 (2008–2012)	98 (51.6)	152 (33.8)	<0.001
Private hospital	111 (58.4)	79 (41.6)	0.006
APACHE II score[b]	19 (3–37)	27 (0–46)	<0.001
Cancer	31 (16.3)	140 (31.1)	<0.001
Hematologic	7 (3.7)	21 (4.7)	0.58
Solid tumor	24 (12.6)	119 (26.4)	<0.001
Cardiac disease	62 (32.6)	161 (35.8)	0.44
Lung disease	42 (22.1)	141 (31.3)	0.02
Diabetes	49 (25.8)	107 (23.8)	0.59
Renal failure	61 (32.1)	199 (44.2)	0.004
Chronic renal failure	20 (10.5)	60 (13.3)	0.33
Dialysis	32 (16.8)	149 (33.1)	<0.001
Liver disease	13 (8.9)	56 (12.4)	0.20
Auto-immune disease	4 (2.1)	24 (5.3)	0.07
Neurologic disease	53 (27.9)	104 (23.1)	0.20
Transplant	0	3 (0.7)	0.56
Surgery	108 (56.8)	226 (50.2)	0.13
Abdominal surgery	54 (28.4)	139 (30.9)	0.53
Mechanical ventilation	117 (61.6)	378 (79.6)	<0.001
Total parenteral nutrition	42 (22.1)	97 (21.6)	0.88
Central venous catheter	176 (92.6)	422 (93.8)	0.59
Neutropenia	2 (1.1)	14 (3.1)	0.17
Prior drug/treatment exposure			
Antibiotics	181 (95.3)	436 (96.9)	0.31
Corticosteroids	74 (38.9)	259 (57.6)	<0.001
Other immunosuppressive drugs	9 (4.7)	29 (6.4)	0.40
Chemotherapy	6 (3.2)	16 (3.6)	0.80
Fluconazole prior to candidemia	36 (18.9)	65 (14.4)	0.15
Candida spp.			
C. albicans	73 (38.4)	210 (46.7)	0.055
C. parapsilosis	43 (22.6)	67 (14.9)	0.02
C. tropicalis	39 (20.5)	99 (22.0)	0.68
C. glabrata	23 (12.1)	40 (8.9)	0.21
C. krusei	5 (2.6)	11 (2.4)	1.00
C. guilliermondii	2 (1.1)	10 (2.2)	0.52
Treatment received	176 (92.6)	301 (66.9)	<0.001
Fluconazole	106/176 (60.2)	185/301 (61.5)	0.79
Deoxycholate AMB	27/176 (15.3)	78/301 (25.9)	0.007
Lipid AMB	8/176 (4.5)	13/301 (4.3)	0.91
Echinocandin	31/176 (17.6)	21/301 (7.0)	<0.001
Time (days) from candidemia to treatment	2 (0–11)	2 (0–18)	0.12

Data are presented as a number with the percentage given in parenthesis, or as the median with the range given in parenthesis, unless specified otherwise

[a] Status on day 30 was not known in 7 patients

[b] Data available for 258 patients only

echinocandin is used as primary therapy. Therefore, it is reasonable to assume that the observed decrease in 30-day crude mortality in period 2 may have been, at least in part, due to the increase in the use of echinocandins as primary therapy, especially since treatment with an echinocandin was an independent predictor of better outcome by the multivariate analysis.

As already reported in other studies, older age, treatment with corticosteroids and higher APACHE II score were associated with an increased risk of death [2, 25, 28–31]. In addition, period 1 was also associated with a higher risk of death. It is possible that differences in factors related to patient care not captured in the present study contributed to the better survival observed in period 2.

Our study has a number of limitations related to its retrospective nature. For example, we did not have data to calculate incidence rates of candidemia in and outside the ICU. Likewise, data on trends in susceptibility of *Candida* bloodstream isolates could not be provided because of changing standards in reading the test over time. Nevertheless, according to the standards in each period, fluconazole resistance occurred in <10 % of isolates and was almost exclusively limited to *C. glabrata* and *C. krusei* (data not shown). Another limitation of our study is that

Table 5 Factors associated with 30-day mortality[a] among 640 ICU patients with candidemia by multivariate analysis

Variable	Odds ratio	95 % Confidence interval	*p* value
Receipt of corticosteroids	4.00	1.98–8.13	<0.001
Period 1	2.49	1.22–5.08	0.01
APACHE II score[b]	1.05	1.01–1.09	0.03
Age	1.03	1.01–1.05	0.003
Treatment with an echinocandin	0.20	0.07–0.58	0.003

[a] The factors associated with 30-day mortality were: age [odds ratio (OR) 1.02, 95 % confidence interval (CI) 1.01–1.03, $p < 0.001$), period 1 (OR 2.07, 95 % CI 1.36–1.16, $p = 0.001$), public hospital (OR 1.68, 95 % CI 1.09–2.58, $p = 0.02$), solid tumor (OR 2.45, 95 % CI 1.39–4.31, $p = 0.002$), receipt of dialysis (2.07, 95 % CI 1.28–3.33, $p = 0.003$), mechanical ventilation (OR 1.60, 95 % CI 1.01–2.55, $p = 0.04$), corticosteroids (OR 2.31, 95 % CI 1.52–3.52, $p < 0.001$), while treatment with an echinocandin was protective (OR 0.45, 95 % CI 0.22–0.89, $p = 0.02$)

[b] Since the APACHE II score was available in only approximately 40 % of patients, we ran the multivariate analysis without this variable

the APACHE II score was not available in a significant proportion of cases, limiting the number of patients analyzed in the multivariate analysis. Likewise, since the time of central venous catheter removal is critical to an analysis of its impact on the outcome [32], we were not able to do such an analysis because the date of catheter removal was not available for the majority of patients.

In conclusion, we found a clear change in the epidemiology and clinical management of candidemia in ICU patients during the 9-year period of this study. The incorporation of echinocandins as primary therapy for candidemia in critically ill patients seems to be associated with better outcomes.

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Conflicts of interest None.

Ethical standard Our study was approved by the respective ethics committees of the participating hospitals and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The ethics committees granted waiver for informed consent due to the observational nature of the study.

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