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ORIGINAL ARTICLE

Initial antifungal strategy does not correlate with mortality in patients with candidemia

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Abstract The incidence of *Candida* bloodstream infections (BSIs) has increased over time, especially in medical wards. The objective of this study was to evaluate the impact of different antifungal treatment strategies on 30-day mortality in patients with *Candida* BSI not admitted to intensive care units (ICUs) at disease onset. This prospective, monocentric, cohort study was conducted at an 1100-bed university hospital in Rome, Italy, where an infectious disease consultation team was implemented. All cases of *Candida* BSIs observed in adult patients from November 2012 to April 2014 were included. Patients were grouped according to the initial antifungal strategy: fluconazole, echinocandin, or liposomal amphotericin B. Cox regression analysis was used to identify risk factors significantly associated with 15-day and 30-day mortality. During the study period, 130 patients with candidemia were observed (58 % with *C. albicans*, 7 % with *C. glabrata*, and 23 % with *C. parapsilosis*). The first antifungal drug was fluconazole for 40 % of patients, echinocandin for 57.0 %, and liposomal amphotericin B for 4 %. During follow-up, 33 % of patients died. The cumulative mortality 30 days after the candidemia episode was 30.8 % and was similar among groups. In the Cox regression analysis, clinical presentation was the only independent factor associated with 15-day mortality, and Acute Physiology and Chronic Health Evaluation (APACHE) II score and clinical presentation were the independent factors associated with 30-day mortality. No differences in 15-day and 30-day mortality were observed between patients with and without *C. albicans* candidemia. In patients with candidemia admitted to medical or surgical wards, clinical severity but not the initial antifungal strategy were significantly correlated with mortality.

Introduction

The incidence of *Candida* bloodstream infections (BSIs) has increased over time, not only in intensive care units (ICUs), but also in medical wards. As recently reported in a study on 955 episodes of candidemia, half of the cases were found in internal medicine wards, 25 % in surgical wards, 20 % in ICUs, and 6 % in hemato-oncology wards [1].

Appropriate and timely antifungal therapy is correlated with better outcomes [2–5]. Mortality rates due to candidemia are very high, especially in patients admitted to ICUs, ranging from 40 % to 60 % [5, 6], even though data on attributable mortality are controversial [7, 8].

The first guidelines for first-line treatment of patients with invasive candidiasis were published in 2010 by the Infectious Diseases Society of America (IDSA) [9]. Echinocandin therapy was recommended only for unstable patients, patients with fluconazole-resistant *Candida*, or in patients who had previously received azole therapy. However, new guidelines from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in 2012 favor the use of echinocandin in all patients with invasive candidiasis [10]. Within the text, the ESCMID recommendations were considered especially for those admitted to ICUs. The new recommendations towards wider use of echinocandin instead of fluconazole were based on only a few publications and no new

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randomized clinical trials. An Italian panel published considerations that were very close to the position taken in the ESCMID guidelines [11].

The objective of this study was to evaluate the impact of different antifungal treatment strategies on 15-day and 30-day mortality in patients with *Candida* BSI who were not admitted to an ICU at the onset of their disease.

Materials and methods

This was a prospective, monocentric, cohort study. An inpatient infectious diseases consultation team (IDCT) was implemented in November 2012 in a 1100-bed university hospital in Rome, Italy (Policlinico A. Gemelli, Catholic University of Rome), with the goal of obtaining an early diagnosis of infection and optimizing antibiotic treatment [12]. The team comprised four infectious disease specialists who were entirely dedicated to this activity. Using the hospital's computerized information system, any physician in the medical and surgical units could request an infectious disease consultation. The consultation is performed at the bedside by the IDCT within 24 h. The team met daily to discuss controversial or complex clinical cases. The microbiological results were regularly discussed with microbiologists and management issues with clinical pharmacists and the risk management team. Data for every consultation were prospectively and routinely collected by the team using a standardized database.

We report here all cases of *Candida* BSIs observed in adult patients from November 2012 to April 2014. Patients with candidemia already being treated in ICUs and hematology clinics were excluded. A case of *Candida* BSI was defined as when a *Candida* species was isolated from at least one blood culture. Proven catheter-related candidemia was defined as when blood cultures were drawn simultaneously from a central venous catheter (CVC) and a peripheral vein, and the differential time to positivity was greater than or equal to 2 h.

Severity of illness was measured using the Acute Physiology and Chronic Health Evaluation (APACHE) II score on the day of candidemia [13]. According to the APACHE II score, people were stratified as low severity (0–15) and high severity (>15). The severity of sepsis was defined according to the International Sepsis Definitions Conference [14]. The time to removal of the CVC was also calculated.

Patients were grouped according to the initial antifungal strategy: fluconazole, echinocandin, or liposomal amphotericin B.

The outcome variables were 15-day and 30-day mortality. Demographic characteristics, risk factors for *Candida* infection, type of *Candida* isolated, and outcome during the follow-up period were also recorded.

Microbiological technique

Candida species were isolated from blood using the BACTEC 860 system (Becton Dickinson, Inc., Sparks, MD). The species were identified using the API ID 32C system (bioMérieux, Marcy l'Etoile, France) or the VITEK 2 system (bioMérieux). In the case of inconclusive results with both systems, isolates were definitively identified using supplemental tests, such as the presence/absence of well-formed pseudohyphae on Cornmeal Tween-80 agar and growth at 42–45 °C. The last test was also required to differentiate isolates of *C. albicans* from those of *C. dubliniensis*. Antifungal susceptibility testing to amphotericin B, caspofungin, fluconazole, itraconazole, and voriconazole was performed using the Sensititre YeastOne colorimetric plate (TREK Diagnostic Systems, Cleveland, OH).

Statistical analysis

Descriptive data are presented. The Chi-squared or Fisher's exact test were used to compare the distribution of categorical variables, and Student's *t*-test or the Mann–Whitney *U*-test were used to compare quantitative variables. A two-sided $p < 0.05$ was considered to be statistically significant. We only considered the first episode in the analysis. The Kaplan–Meier method was performed to show the correlation between antifungal strategy and 15-day and 30-day mortality. A Cox regression analysis was performed for each variable and mortality outcome. Variables that were clinically relevant and statistically significant ($p < 0.10$) in the univariate analysis were included in a final multivariate Cox regression model. Data analysis was performed using the SPSS software, version 17 (SPSS).

Results

The demographic and clinical characteristics of 130 patients with candidemia observed by April 30, 2014 are shown in Table 1. At the time of diagnosis of candidemia, 46.2 % patients were admitted to the medical ward, 48.5 % to the surgical ward, and 5.4 % to the cardiovascular ICU or stroke unit. The patients' mean APACHE II score was 15.1 [standard deviation (SD) 6.8]. Of note, 94 (72.3 %) patients with candidemia had a CVC. In the month prior to the candidemia diagnosis, 40 % of patients had received antibiotic therapy and 46.9 % had been hospitalized within 90 days prior to the candidemia diagnosis. None of the patients had hematological diseases and none were neutropenic.

Among the 130 episodes of candidemia, 58.4 % were due to *C. albicans*, 6.9 % to *C. glabrata*, and 23.1 % to *C. parapsilosis*. We simultaneously detected two *Candida* species in 2.3 % of cases, and *Candida* and a bacterial pathogen in 30 % of cases (a methicillin-resistant coagulase-negative *Staphylococcus* species

Table 1 Baseline characteristics of 130 patients with candidemia

Variables	All patients (*n*=130)
Males	70 (54.7)
Age, years, mean (SD)	65.6 (19.2)
At least two comorbidities	25 (19.5)
Risk factors	
Previous antibiotic therapy (30 days)	51 (39.8)
CVC	92 (71.9)
Malignancy	26 (20.3)
Dialysis	4 (3.1)
Previous surgery (30 days)	6 (4.7)
Previous hospitalization (90 days)	60 (46.9)
Previous steroids	2 (1.6)
Clinical characteristics	
APACHE II score, mean (SD)	15.1 (6.8)
Sepsis severity	
- SIRS	79 (62.2)
- Severe sepsis	32 (25.2)
- Septic shock	16 (12.6)
Admitted to ICU	16 (12.6)
Time to removal of CVC, mean days (SD), *n*=92	4.4 (5.4)
Microbiologic characteristics	
Non-*Candida albicans*	56 (43.8)
Polymicrobial	39 (30.5)

APACHE Acute Physiology and Chronic Health Evaluation; *CVC* central venous catheter; *ICU* intensive care unit; *SD* standard deviation; *SIRS* systemic inflammatory response syndrome

in 33 % of these cases, methicillin-resistant *S. aureus* in 13 %, and Enterobacteriaceae in 46 %) (Table 2).

All *C. albicans* isolates showed fluconazole susceptibility. Out of nine *C. glabrata* strains of the study population, five were susceptible to fluconazole [three with minimum inhibitory concentration (MIC)=8 μg/mL], one was resistant to fluconazole but susceptible to voriconazole, and three were resistant to both fluconazole and voriconazole.

The clinical presentation of the candidemia was systemic inflammatory response syndrome (SIRS) in 56.7 % cases,

Table 2 *Candida* species distribution, *n* (%)

C. albicans	76 (58.4)
C. glabrata	9 (6.9)
C. parapsilosis	30 (23.1)
C. krusei	2 (1.5)
C. tropicalis	7 (5.4)
Candida others (*guilliermondii, mucilaginosa, rodotorula*)	3 (2.3)
Polycandidal sepsis	3 (2.3)

severe sepsis in 25.2 % cases, and septic shock in 16 cases (12.6 %). Of the 130 patients with candidemia, 16 (12.5 %) were eventually admitted to the ICU because of sepsis. Evidence of metastatic dissemination of *Candida* was found in three cases (one endophthalmitis and two endocarditis). No significant differences in clinical severity were observed among the groups.

The median time to catheter removal was 3 days (interquartile range, 1–5 days), ranging from 0 to 32 days. In 33 out of 92 patients (35.9 %), the CVC was removed within 24 h and in one case, the CVC was not removed. The first antifungal drug was fluconazole for 50 (39.6 %) patients, echinocandin for 73 (57.0 %), and liposomal amphotericin B for 5 cases (3.9 %). In two cases, the patient died before treatment was started. Patients who started with liposomal amphotericin B or who were not treated with antifungals were more frequently receiving previous antibiotic treatments or had malignancies. The mean APACHE II score among five patients starting from the onset of candidemia with liposomal amphotericin B was 20.8 (SD 9.9).

No differences in epidemiological and clinical parameters (APACHE II score, clinical severity, rate of admission to ICU) were found between patients starting with fluconazole and those starting with echinocandin (Table 3). The distribution of *Candida* species according to the therapeutic strategy groups is presented in Table 4.

Forty-three patients (33 %) died during follow-up. The cumulative mortality after the candidemia episode was 20 % at 15 days and 30.8 % at 30 days. The Kaplan–Meier survival curves at 15 days and 30 days are shown in Fig. 1. As expected, patients with APACHE II score<15 had better survival (mean 27.6 days; SD 6.98) than patients with APACHE II score >15 (mean 21.4 days; SD 11.1; *p*<0.0001). Patients in both the echinocandin and liposomal amphotericin B groups showed a greater likelihood of mortality (*p*<0.001 at 30 days).

The Cox regression analysis results are shown in Tables 5 and 6. The clinical presentation was the only independent factor associated with 15-day or 30-day mortality. The same results were obtained when the analysis was performed only for people who had CVC removal. No differences in 30-day mortality were observed between patients with *C. albicans* candidemia and non-*C. albicans* candidemia (23.4±10.5 days vs. 24.6±9.9 days; *p*=0.61), even when excluding *C. parapsilosis* cases (23.4±10.5 days vs. 25.6±9.0 days; *p*=0.22). The adjusted risk of 30-days survival for people taking echinocandins was not different to the reference group, even when *C. parapsilosis* cases were excluded [hazard ratio (HR) 1.05; 95 % confidence interval (CI) 0.13–8.67; *p*=0.96).

Discussion

Our data show that the clinical severity but not the initial antifungal strategy were significantly correlated with

Table 3 Data distribution among the three antifungal starting therapies

Variables	All patients (*n*=130)	Starting with fluconazole (*n*=50)	Starting with echinocandin (*n*=73)	Starting with AmfB (*n*=5)	*p*-Value	*p*-value (fluconazole vs. echinocandin group)
Males	70	25 (50.0)	41 (56.2)	4 (80)	0.24	0.26
Age, years, mean (SD)	65.6 (19.2)	63.9 (21.6)	66.8 (17.1)	63.6 (24.5)	0.75	0.56
At least two comorbidities	25	6 (12.0)	16 (21.9)	3 (60.0)	0.04	0.19
Risk factors						
Antibiotics (30 days)	51	18 (36.0)	28 (38.3)	5 (100)	0.03	0.53
CVC	92	35 (70)	55 (75.3)	2 (40.0)	0.28	0.56
Malignancy	26	13 (26.0)	10 (13.7)	3 (60.0)	0.03	0.13
Dialysis	4	0 (0)	4 (5.5)	0 (0)	0.36	0.23
Surgery (30 days)	6	2 (4.0)	3 (4.1)	1 (20.0)	0.41	0.96
Hospitalization (90 days)	60	24 (48.0)	33 (45.2)	3 (60.0)	0.53	0.41
Steroids	2	0 (0)	2 (2.7)	0 (0)	0.66	0.48
Clinical characteristics						
APACHE II score, mean (SD)	15.1 (6.2)	14.8 (6.3)	14.9 (6.9)	20.8 (9.9)	0.07	0.16
APACHE II score above 15 (%)		23 (46)	34 (46.6)	3 (60.0)	0.83	0.95
Sepsis severity						
- SIRS	79	33 (66.0)	45 (61.6)	1 (20)		
- Severe sepsis	32	12 (24.0)	17 (23.3)	3 (60)	0.33	0.81
- Septic shock	16	5 (10.0)	10 (13.7)	1 (20)		
Admitted to ICU	16	8 (16.0)	7 (9.6)	1 (20.0)	0.64	0.49
Time to removal of CVC, mean (SD), *n*=92	4.4 (5.4)	3.9 (4.6)	4.3 (4.6)	–	0.67	0.67
Microbiological characteristics						
Non-*C. albicans*	56 (43.1)	40 (80.0)	31 (42.5)	5 (100)	0.04	0.48
C. parapsilosis	30 (23.1)	14 (28.0)	14 (19.2)	2 (40)	0.005	0.39
Polymicrobial	39 (30.0)	15 (30.0)	23 (31.5)	1 (20)	0.76	0.63
15-days surviving patients (%)	104 (80)	46 (92)	55 (75.3)	3 (60)	0.03	0.018
30-days surviving patients (%)	90 (69.2)	42 (84)	45 (61.6)	3 (60)	0.02	0.009

AmfB amphotericin B, *APACHE* Acute Physiology and Chronic Health Evaluation; *CVC* central venous catheter; *ICU* intensive care unit; *SD* standard deviation; *SIRS* systemic inflammatory response syndrome

mortality in patients with candidemia admitted to the medical or surgical wards.

Few guidelines have been published on the treatment of candidemia. The 2009 IDSA guidelines recommend fluconazole or an echinocandin as an initial therapy for most adult patients (evidence A-I). The Expert Panel favored an echinocandin for patients with moderately severe to severe illness or for those who were recently exposed to azoles (evidence A-III). Fluconazole is recommended for patients who are less critically ill and

Table 4 *Candida* species distribution among the three antifungal starting therapies

	Starting with fluconazole (*n*=50)	Starting with echinocandin (*n*=73)	Starting with AmfB (*n*=5)	No therapy (*n*=2)
C. albicans (%)	32 (64)	42 (57.5)	0 (0)	2 (100)
C. glabrata (%)	1 (2)	8 (10.9)	0 (0)	0 (0)
C. parapsilosis (%)	14 (28)	14 (19.2)	2 (40)	0 (0)
C. tropicalis (%)	3 (6)	3 (4.1)	1 (20)	0 (0)
C. krusei (%)	0 (0)	2 (2.7)	0 (0)	0 (0)
Other (%)	0 (0)	2 (2.7)	1 (20)	0 (0)
Polycandidal (%)	1 (2)	2 (2.7)	0 (0)	0 (0)

AmfB amphotericin B
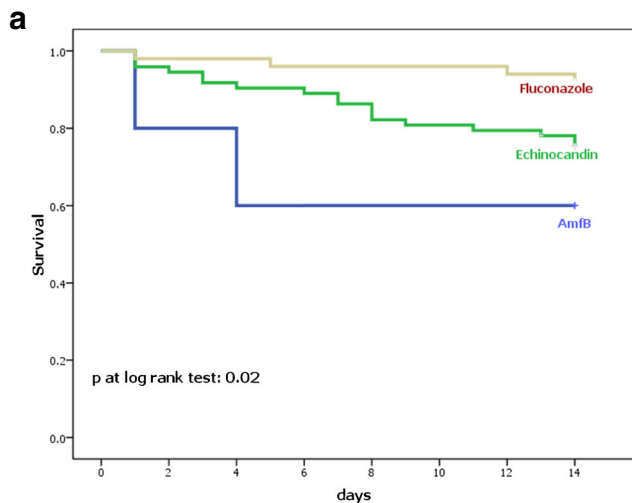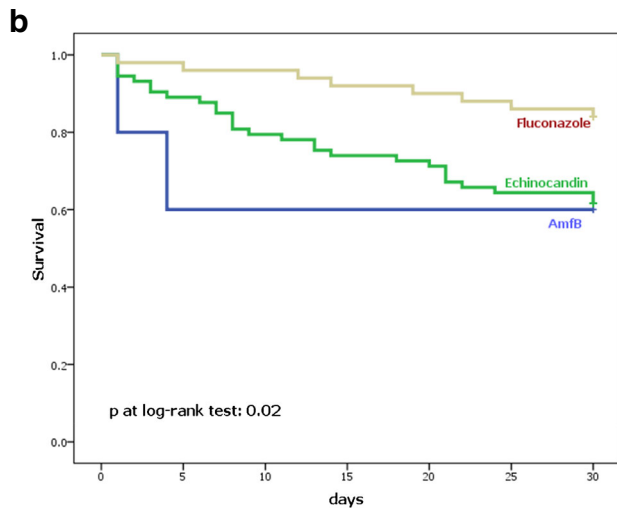
Fig. 1 a 15-day survival estimated according to the antifungal starting therapies. b 30-day survival estimated according to the antifungal starting therapies

who have had no recent exposure to azoles (evidence A-III) [9].

In the 2012 ESCMID guidelines for non-neutropenic adults, the treatment of candidemia with echinocandin is strongly recommended. The recommendation for liposomal amphotericin B or voriconazole is less stringent, and fluconazole is recommended at marginal strength only, except for *C. parapsilosis*. They also underline that treatment can probably be simplified by stepping down to oral fluconazole after 10 days of intravenous treatment if the patient is stable, tolerates the oral route, and the species is susceptible [10]. It should be noted that, even though not explicitly written in the recommendations, the guidelines refer to patients admitted to the ICU. Treatments for specific *Candida* species (e.g., *C. glabrata*) were also reported.

Surprisingly, no new randomized clinical trials have been published between 2009 and 2012 comparing echinocandin and fluconazole in the treatment of candidemia in non-neutropenic adult patients.

We observed a 30-day mortality rate of 31 %, which is close to the overall rate of 39 % reported by Bassetti and colleagues [1] and the rate of 38 % reported by Wisplinghoff and colleagues on nosocomial BSIs due to *Candida* in 52 hospitals in the United States [15]. In a recent Italian survey, a crude mortality rate of 27 % was reported in 2009 [16]. A debate is ongoing regarding the real magnitude of mortality attributable to candidemia, ranging from 14.5 % to 49 % [7, 8, 17]. Our results support the hypothesis that comorbidities and clinical severity at baseline may strongly influence the mortality rate in patients with candidemia.

In our experience, no clinical or epidemiological factors correlated with adopting the approach suggested by the IDSA (i.e., fluconazole for all patients except those with moderately severe to severe infection or previously treated with fluconazole) or the ESCMID (echinocandin for all patients), and no differences were found in terms of the mortality rate between those starting with fluconazole or echinocandin. It is important to note, however, that no difference in mortality was found in the single randomized clinical trial that compared an echinocandin (anidulafungin) to fluconazole [18]. No differences in mortality between patients on an echinocandin-based treatment and a fluconazole-based treatment were found, even in a substudy of the randomized clinical trial comparing fluconazole and anidulafungin that included only severely ill patients [19]. Even in a recently published study on septic shock due to candidemia, no differences in mortality were detected between people receiving echinocandin or fluconazole [5]. Two previous observational studies [20, 21] and a substudy of the randomized clinical trial considering only patients infected with *C. albicans* reported some advantages of echinocandin over fluconazole in terms of survival [22]. Unexpectedly, people receiving echinocandins or liposomal amphotericin B in our study had a slightly worse survival than the other groups.

We did not observe any differences in mortality between patients with *C. albicans* and without *C. albicans* (even excluding *C. parapsilosis*).

The number of non-ICU patients with candidemia is high [1]. In the present study, few people with candidemia had been admitted into an ICU. Based on these data, the

Table 5 Variables correlated to 15-day survival. Cox regression analysis

	Unadjusted HR 95 % CI	p-Value	Adjusted HR 95 % CI	p-Value
APACHE II score above 15	1.07 (0.80–1.72)	0.35	2.25 (0.85–5.93)	0.10
At least two comorbidities	1.56 (1.01–2.39)	0.05	1.22 (0.46–3.24)	0.69
Clinical presentation of *Candida* bloodstream infection				
SIRS	Ref	–	Ref	–
Severe sepsis	1.20 (0.70–1.90)	0.17	3.57 (1.11–11.44)	0.03
Septic shock	6.03 (0.07–512.9)	0.09	14.88 (4.62–47.94)	0.001
Initial antifungal strategy				
Fluconazole	Ref	–	Ref	–
Echinocandin	0.70 (0.28–1.76)	0.45	0.69 (0.14–3.44)	0.65
AmfB	0.90 (0.36–2.23)	0.83	0.19 (0.3–1.33)	0.09

AmfB amphotericin B; *APACHE* Acute Physiology and Chronic Health Evaluation; *CI* confidence interval; *HR* hazard ratio; *Ref* reference value; *SIRS* systemic inflammatory response syndrome

conclusions of the present study cannot be generalizable to the ICU patients, to which the ESCMID guidelines were targeted. According to our study, 35.4 % of candidemia were CVC-related. As in previously published studies [6, 23] and in our experience, the time to CVC removal was not associated with survival. This result seems at odds with two recent studies demonstrating that failure of the source control was associated with higher mortality [5, 24]. However, it is possible that the removal itself and not the time to removal is the most important variable related to mortality in CVC-related candidemia.

Since large randomized clinical trials on the impact of different antifungal therapies on mortality are difficult to conduct, our results should be interpreted cautiously. We believe that observational studies representing real-life situations could provide interesting results. Our study has some limitations. Although the study population was recruited from a single center over a relatively short time period (1.5 years), the small sample size may be

insufficient to draw definitive conclusions. Because of the real-world setting of our study, we did not perform routine daily blood cultures after diagnosis, but, rather, only after an initial clinical response. Therefore, we can compare our early and late mortality results with those of other published studies, but not the data on microbiological and global response.

If our data is confirmed in future studies, fluconazole could remain a valid first-line treatment option for many patients with candidemia for several reasons: no difference in mortality was observed in this or many other published studies; wider use of echinocandin could be related to the spread of echinocandin resistance, losing an important antifungal option in patients with severe sepsis [25, 26]; and, lastly, fluconazole is less costly. From these perspectives, further studies evaluating the tolerability, impact of drug interactions, and costs of the different therapeutic strategies for patients with candidemia not admitted to an ICU are warranted.

Table 6 Variables correlated to 30-day survival. Cox regression analysis

	Unadjusted HR 95 % CI	p-Value	Adjusted HR 95 % CI	p-Value
APACHE II score above 15	1.43 (1.01–2.03)	0.04	2.28 (1.07–4.85)	0.03
At least two comorbidities	1.56 (1.01–2.39)	0.05	1.19 (0.53–2.65)	0.68
Clinical presentation of *Candida* bloodstream infection				
SIRS	Ref	–	Ref	–
Severe sepsis	1.34 (0.89–2.03)	0.16	2.57 (1.07–6.17)	0.03
Septic shock	2.81 (2.10–3.76)	<0.001	14.98 (6.24–36.0)	<0.001
Initial antifungal strategy				
Fluconazole	Ref	–	Ref	–
Echinocandin	0.70 (0.28–1.76)	0.45	0.98 (0.21–4.69)	0.98
AmfB	0.90 (0.36–2.23)	0.83	0.81 (0.30–2.19)	0.68

AmfB amphotericin B; *APACHE* Acute Physiology and Chronic Health Evaluation; *CI* confidence interval; *HR* hazard ratio; *Ref* reference value; *SIRS* systemic inflammatory response syndrome

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