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ORIGINAL ARTICLE

Risk factors for candidemia with non-*albicans* *Candida* spp. in intensive care unit patients with end-stage renal disease on chronic hemodialysis

Kivanc Serefhanoglu [a,*], Funda Timurkaynak [a], Fusun Can [b], Unal Cagir [a], Hande Arslan [a], F. Nurhan Ozdemir [c]

[a] *Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Baskent University, TR 06490, Ankara, Turkey*
[b] *Department of Microbiology and Clinical Microbiology, Faculty of Medicine, Baskent University, TR 06490, Ankara, Turkey*
[c] *Department of Internal Medicine, Division of Nephrology, Faculty of Medicine, Baskent University, TR 06490, Ankara, Turkey*

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non-*albicans* candidemia;
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Background/Purpose: The objective of this study was to describe factors associated with bloodstream infections (BSIs) with non-*albicans Candida* species (NAC), compared with *Candida albicans* BSIs, and antifungal susceptibility patterns in adult intensive care unit (ICU) patients with chronic renal failure undergoing hemodialysis. To the best of our knowledge, this is the first study to report the potential factors for NAC candidemia in ICU patients with end-stage renal disease on chronic hemodialysis.
Methods: This prospective, observational, multicenter study was conducted in the two centers of Baskent University between January 2007 and July 2010. All adult patients excluding patients with neutropenia, malignancy, glucocorticoid treatment or AIDS, were included.
Results: Sixty cases (58.8%) of candidemia were due to *C. albicans* and 42 (41.2%) to NAC. Multivariate regression analysis revealed that the presence of a central venous catheter was the only risk factor independently associated with BSI due to NAC ($p = 0.046$, odds ratio: 5.90, 95% confidence interval: 1.032–33.717). Mortality was more frequent in those with NAC than *C. albicans* BSIs (64.3% vs. 55%), but the difference was not significant ($p = 0.067$). Except for two *Candida glabrata* strains, which were dose–dependently

* Corresponding author. Baskent Universitesi Istanbul Saglik, Uygulama ve Arastirma Hastanesi, Altunizade M, Kisikli C. Oymaci S. No. 7, 34662 Uskudar, Istanbul, TR Turkey.
E-mail address: kivanc1972@gmail.com (K. Serefhanoglu).

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fluconazole susceptible, all *Candida* species were susceptible to fluconazole, caspofungin, voriconazole and amphotericin B.
Conclusion: Central venous catheterization was the only factor significantly associated with BSI due to NAC in ICU patients with end-stage renal disease.

Introduction

Chronic renal failure is a risk factor that is independently associated with the development of nosocomial candidemia.[1,2] Candidemia is a serious problem in intensive care units (ICUs), and an estimated 33—55% of all episodes occur in ICUs.[3] *Candida* spp. are the third most common cause of blood stream infections (BSIs) in ICUs, accounting for 10% of such infections.[4] Candidemia is associated with significant mortality and prolonged hospital stay in ICU patients.[5]

C. albicans accounts for the majority of cases with candidemia, but an increase in the proportion of the bloodstream isolates due to non-*albicans Candida* spp. (NAC) has been reported.[1] NAC has even surpassed *C. albicans* as a cause of candidemia in some European and Latin American centers.[6] Although *C. albicans* is generally susceptible to fluconazole, several NACs have reduced susceptibility to fluconazole and more likely require greater doses of fluconazole or an another more effective agent (e.g., amphotericin B) for clinical cure. Fluconazole is an inexpensive and well-tolerated agent for the empirical treatment of *C. albicans* candidemia. Therefore, data that help differentiate *C. albicans* from NAC infections are of value.[4,7] However, factors associated with NAC infections have differed in several surveys, and the reasons for this changing epidemiology remain unclear.[1,5] It may be partly due to variations in several factors including the study population and standard of the healthcare facilities available between institutions, localities and countries.[8] In addition to this changing epidemiology from several surveys, information regarding the differences between *C. albicans* and NAC BSIs in adult non-neutropenic ICU patients remains uncommon.[9] Therefore, there is an ever-increasing need to determine the data regarding the factors associated with NAC BSIs in adult non-neutropenic ICU patients, particularly in selected populations, and to the best of our knowledge none in a single cohort of patients with end-stage renal disease on chronic hemodialysis.

This is the first report to identify potential factors associated with NAC BSIs that occurred in adult non-neutropenic ICU patients with end-stage renal disease on chronic hemodialysis at two tertiary care centers of a Turkish university hospital. The second aim of this study was to determine the susceptibility of the study isolates to four antifungal agents.

Patients and methods

Surveillance

This prospective, observational, active surveillance of candidemia was conducted at the two tertiary care centers of Baskent University (Istanbul and Ankara) from January 2007 to July 2010. All patients with end-stage renal disease on chronic hemodialysis who were admitted to the adult medical and surgical ICUs were evaluated for possible inclusion in the study. Patients with *Candida* BSI were eligible for inclusion if they had a length of stay $>$ 48 hours after ICU admission. Patients who developed a clinically and microbiologically documented candidemia were identified through a microbiological laboratory survey. Episodes of candidemia were defined as at least one positive blood culture yielding *Candida* spp. in a patient with fever or other clinical signs of infection. The cases were classified according to the responsible *Candida* spp. in the *C. albicans* and NAC candidemia groups. All patients with *Candida* BSI were evaluated for inclusion in the study. After inclusion, the patients were followed up for 30 days to assess the outcome.

The potential factors have been evaluated by analyzing the clinical history of the patients in the 4 weeks before candidemia was diagnosed. A standardized case report form was used to collect medical records to gather data including: age; sex; underlying conditions (liver disease, diabetes, pulmonary disease and cardiac disease); reason for ICU admission (medical or surgical); total parenteral nutrition (TPN) ($>$ 2 days at time of diagnosis); surgical procedures within 30 days; previous antibacterial or antifungal therapies ($>$ 2 days within previous 30 days); Acute Physiology and Chronic Health Evaluation II (APACHE II) score; presence or absence of a central venous catheter (CVC) ($>$ 2 days at the time of diagnosis); time from hospitalization to onset of candidemia (patient days); and outcome. The outcome was defined as survival or death within 30 days after the candidemia episode. Hospital length of stay was calculated as the difference between the date of admission (total of ICU and ward) and the date of collection of a positive blood culture. When a patient had more than one episode of candidemia, the first episode was used in the potential factor analysis. All patients with candidemia were initially treated with fluconazole. The treatment was initiated empirically when candidemia was clinically suspected. The therapy was modified to caspofungin, or amphotericin B, when necessary, on the basis of the *Candida* species or the clinical response. The initial antifungal treatment was considered inadequate when $>$ 72 hours elapsed between the time a culture was obtained and initiation of the treatment to which the infecting organism was shown to be susceptible. This was an observational study, therefore, all decisions regarding patient management, including the need to obtain blood cultures when fever was present or sepsis was clinically suspected, and the initiation of an antifungal agent and/or switching to another antifungal agent were left to the discretion of the attending physicians.

All the existing catheters were removed within 24 hours if the blood culture system showed a positive sign for *Candida* growth, and/or if there were pronounced signs of local infection at the insertion site and/or clinical suspicion of catheter-induced sepsis. Pediatric or immunosuppressed patients including those with neutropenia (neutrophil count $\leq 1000/mm^3$), glucocorticoid and/or other immunosuppressive treatment, and malignancy or AIDS were excluded from the study. Patients with candidemia diagnosed before ICU admission were also excluded.

Microbiological methods

The isolates of *Candida* spp. recovered from blood cultures using the BACTEC 9050 system (Becton Dickinson, Sparks, MD, USA) from each hospital were sent to the Mycology Laboratory of Baskent University, Ankara, for identification to the species level, and antifungal susceptibility testing. Isolates were stored on YPD glycerol (1% yeast extract, 2% peptone, 2% dextrose, and 3% glycerol) at −70°C until they were tested. The isolates were identified to the species level by API *Candida* (BioMerieux, Marcy L-Etoile, France) in accordance with the manufacturer's guidelines. Before testing, each isolate was subcultured on a Sabouraud dextrose agar plate to check the purity and optimal growth. Antifungal susceptibility testing was performed using a broth microdilution assay method described by the Clinical Laboratory Standards Institute (CLSI).[10] *Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC 6258 were used as the quality control strains. The following antifungal drugs, supplied by the manufacturers as pure standard compounds, were tested: amphotericin B (Sigma), fluconazole and voriconazole (Pfizer, New York, NY, USA), and caspofungin (Janssen Pharmaceutica, Titusville, NJ, USA). Interpretive susceptibility criteria for fluconazole and voriconazole were those recommended by the CLSI. For fluconazole, isolates showing minimum inhibitory concentrations (MICs) $\leq$ 8.0 μg/mL, 16−32 μg/mL and $\geq$ 64 μg/mL were regarded as susceptible, dose-dependent susceptible (SDD) and resistant, respectively. For voriconazole, $\leq$ 1.0 μg/mL, 2.0 μg/mL and $\geq$ 4 μg/mL were regarded as susceptible, SDD and resistant, respectively. Due to the lack of defined breakpoints for amphotericin B and caspofungin, MICs of $\leq$ 2.0 μg/mL and $\leq$ 1.0 μg/mL were regarded as susceptible for caspofungin and amphotericin B, respectively.[11]

Statistical analysis

The χ^2 test was used to compare categorical variables and the *t* test to evaluate continuous variables. *P* values < 0.05 were considered significant. Multivariate, backwards stepwise, logistic regression analyses were performed to identify independent variables associated with candidemia due to NAC. Potential risk factors were included in these models if they were associated with the dependent variables in the univariate analyses at a statistical level of $p < 0.5$. Mortality was evaluated using the Kaplan−Meier method and the log rank test. This study was approved by Baskent University Institutional Review Board and Ethics Committee and supported by Baskent University Research Fund.

Results

Three hundred and forty-six patients with candidemia were identified during the study period. Of 191 (Istanbul Center) and 612 (Ankara Center) patients with chronic renal failure admitted in the study period, 114 had candidemia. Twelve patients were excluded from the study because of lack of sufficient data ($n = 5$), presence of neutropenia ($n = 1$), glucocorticoid and/or other immunosuppressive treatment ($n = 2$), a single positive blood culture for *Candida* without signs of infection ($n = 2$), and presence of malignancy ($n = 2$). Thus, a total of 102 cases of candidemia were analyzed in Istanbul ($n = 24$) and Ankara ($n = 78$) centers. Demographic and clinical information about the patients with candidemia is summarized in Table 1. All the variables were similar in the two hospitals. In all patients, a single *Candida* spp. was identified. Sixty cases (58.8%) of candidemia were due to *C. albicans* and 42 (41.2%) to NAC. Distribution of NAC is shown in Table 2.

Table 3 compares the demographic and clinical characteristics and outcomes of the patients in relation to the causative species, *C. albicans* and NAC. Previous antibiotic therapy, total parenteral nutrition, the presence of chronic renal failure, assisted ventilation, and CVC were noted frequently in both groups. The results of the univariate and multivariate analyses regarding comparison of the distribution of different variables between the two groups showed that the only factor independently associated with candidemia due to NAC (in the multivariate logistic regression analysis) was CVC placement ($p = 0.046$, odds ratio: 5.90, 95% confidence interval: 1.032−33.717). A total of 60 patients died within 30 days of the diagnosis of candidemia, for an overall crude mortality rate of 58.8%. The mortality was more frequent in patients with NAC than those with *C. albicans* (64.3% vs. 55%, respectively.), but the difference was not significant ($p = 0.067$).

The *in vitro* susceptibility results of the 102 *Candida* isolates to four antifungal agents are shown in Table 4. Except for two *C. glabrata* strains that were dose-dependently fluconazole susceptible, all *Candida* species were susceptible to fluconazole, caspofungin, voriconazole and amphotericin B.

Discussion

Several published studies assessing factors associated with candidemia due to NAC have generally focused on cancer patients,[4] mixed patient populations,[12] or noncritically ill patients.[5] However, few data are available regarding the differences in the factors associated with and outcome for non-neutropenic ICU-acquired NAC BSIs.[1,4,5] To the best of our knowledge, this is the first study to report potential factors associated with BSI due to NAC that occurred in ICUs in a distinct patient population: patients with end-stage

Table 1 Demographic and clinical characteristics of candidemia cases in the Istanbul and Ankara centers, *n* (%).

Characteristics	Patients (total, $n = 102$)	Patients (Istanbul) ($n = 24$)	Patients (Ankara) ($n = 78$)	*P*
Male sex	45 (44.1)	11 (45.8)	34 (43.6)	0,847
Age mean ± SD (range)	57.5 ± 19.0 (18–90)	54.1 ± 17.38 (27–85)	58.8 ± 17.90 (18–88)	0.721
Hospital length of stay, mean ± SD (range)[a]	34.98 ± 17.46 (10–95)	36.29 ± 22.19 (12–95)	34.54 ± 16.49 (10–86)	0.891
30 days mortality	60 (58.8)	14 (58.3)	46 (59)	0.272
APACHE II score, mean ± SD (range)	24.8 ± 5.02 (14–40)	24.9 ± 6.60 (14–40)	24.4 ± 4.22 (15–34)	0.320
Type of patient, medical/surgical	74/28 (72.5/27.5)	18/6 (75/25)	56/22 (71.8/28.2)	0.956
Species				
Candida albicans/NAC	60/42 (58.8/41.2)	14/10 (58.3/41.7)	46/32 (59/41)	0.956
Inadequate initial antifungal treatment[b]	7 (6.9)	1 (4.2)	6 (7.7)	0.762
Primary site of infection				0.827
CVC	44 (43.1)	11 (45.8)	33 (42.3)	
Unknown	58 (56.9)	13 (54.2)	45 (57.7)	
Underlying diseases and conditions				
Diabetes mellitus	50 (49)	12 (50)	38 (48.7)	0.913
Chronic obstructive lung Disease	3 (2.9)	1 (4.2)	2 (2.6)	0.684
Liver disease	2 (2)	0	2 (2.6)	0.428
Chronic heart failure	20 (19.6)	4 (16.7)	16 (20.5)	0.678
Therapeutic factors				
Surgery within prior 4 wk	37 (36.3)	9 (37.5)	28 (35.9)	0.886
CVC in place at time of diagnosis	88 (86.3)	21 (87.5)	67 (85.9)	0.842
CVC days left in place prior to development of candidemia, mean (range)	25.40 ± 15.09 (9–82)	26.85 ± 14.75 (10–78)	24.22 ± 13.61 (9–82)	0.628
Type of CVC				0.372
Temporary double-lumen catheter	78 (88.6)	20 (95.2)	58 (86.6)	
Hemodialysis catheter	10 (11.4)	1 (4.8)	9 (13.4)	
Total parenteral nutrition	83 (81.4)	19 (79.2)	64 (82.1)	0.751
Antibiotic therapy within prior 4 wk	101 (99)	23 (95.8)	78 (100)	0.08
Carbapenem[c]	60 (58.8)	14 (58.3)	46 (59)	0.956
Broad-spectrum Cephalosporin[d]	47 (46.1)	10 (41.7)	37 (47.4)	0.620
Piperacillin–tazobactam	39 (38.2)	9 (37.5)	30 (38.5)	0.932
Quinolone[e]	21 (20.6)	4 (16.7)	17 (21.8)	0.587
Aminoglycoside[f]	13 (12.7)	3 (12.5)	10 (12.8)	0.967
Glycopeptide[g]	72 (70.6)	16 (66.7)	56 (71.8)	0.630
Antifungal therapy within prior 4 wk	14 (13.7)	4 (16.7)	10 (12.8)	0.632
Fluconazole	13 (12.7)	4 (16.7)	9 (11.5)	
Other	1 (1)	0	1 (1.3)	
Assisted ventilation	53 (52)	13 (54.2)	40 (51.3)	0.636
Vascular access for hemodialysis				0.822
CVC	83 (81.4)	20 (83.3)	63 (80.8)	
Fistula	15 (14.7)	3 (12.5)	12 (15.4)	
Graft	4 (3.9)	1 (4.2)	3 (3.8)	

APACHE = acute physiology and chronic health evaluation; CVC = central venous catheter; NAC = non-*albicans Candida*; SD = standard deviation.

[a] Number of days hospitalization before onset of candidemia.

[b] initial antifungal treatment was considered inadequate when > 72 hours elapsed between the time a culture was obtained and initiation of treatment to which the infecting organism was susceptible.

[c] imipenem, meropenem.

[d] third- and fourth-generation cephalosporins including ceftriaxone, cefoperazone–sulbactam, ceftazidime and cefepime.

[e] ofloxacin, moxifloxacin, levofloxacin or ciprofloxacin.

[f] amikacin, gentamicin or netilmicin.

[g] vancomycin or teicoplanin.

Table 2 Distribution of NAC isolated from blood, *n* (%).

Species	Istanbul ($n = 10$)	Ankara ($n = 32$)	Total ($n = 42$)
Candida tropicalis	3 (30)	12 (37.5)	15 (35.7)
Candida glabrata	4 (40)	7 (21.9)	11 (26.2)
Candida parapsilosis	1 (10)	7 (21.9)	8 (19)
Others[a]	2 (20)	6 (18.8)	8 (19)

NAC = non-*albicans Candida*.
[a] *Candida famata* (3), *Candida humonicola* (2), *Candida keyfr* (2), *Candida guillermondi* (1).

renal disease on chronic hemodialysis. In the present study, we conducted a prospective multicenter survey of candidemia, and excluded pediatric patients and patients with malignancy, human immunodeficiency virus infection, or neutropenia.

In the present study, *C. albicans* was found in 58.8% of cases (Table 1). The predominance of *C. albicans* is consistent with other reported ICU series.[8,13–15] Despite the fact that *C. albicans* remains the most common species causing invasive candidiasis worldwide, a decreasing trend in the isolation of *C. albicans* over time has been noted in ICUs in several countries including the USA.[16] Even in a study reported by Bassetti et al,[6] only 40% of candidemia episodes in the ICU patients were caused by *C. albicans*. It is noteworthy that, although hematology–oncology patients, in whom a high frequency of NAC–associated BSI has been reported,[5,12] were not included in our study (an exclusion criterion), we found a relatively high proportion of NAC (41.2%). One possible explanation for this could be the patient cohort in our study. In a recent study, chronic renal disease was found to be an independent risk factor associated with candidemia caused by NAC.[17] The increased use of invasive medical procedures, particularly CVCs (86.3%), which is well known to enhance the risk of NAC (i.e., *C. parapsilosis*) infections,[5] could have played a role in promoting the increase in NAC BSIs in our patients.

In our study, the results of the univariate and multivariate analyses regarding comparison of the distribution of different variables between the two groups showed that the only factor independently associated with candidemia due to NAC (in the multivariate logistic regression analysis) was CVC placement ($p = 0.046$, odds ratio: 5.90, 95% confidence interval: 1.032–33.717) (Table 3). This finding is consistent with previously published independent factors associated with ICU-acquired candidemia caused by NAC.[3–5] However, unlike other studies, we did not find previous use of an antifungal agent (e.g., fluconazole),[3,4,6,12] increasing age,[12] or antibiotic exposure[12] to be independent factors associated with candidemia caused by NAC. Pre-existing candiduria, which was not investigated in the present study, is another factor previously identified as being independently associated with candidemia caused by NAC.[3–5] An important potential factor difference between the present study and those discussed above was the patient cohorts: the patients in the present study did not have malignancy, human immunodeficiency virus infection, or neutropenia, but they did have chronic renal failure.

It has been reported that *Candida* BSIs affect the survival of ICU patients. Mortality in patients with ICU-acquired candidemia has been reported to be 50–80%.[18] In our study, the overall 30-day mortality rate in all patients with candidemia was 58.8% (Table 1). Although the mortality was more frequent in patients with NAC than with *C. albicans* BSI, the difference was not statistically significant (64.3% vs. 55%, $p = 0.067$) (Table 3). Although the presence of the increased mortality was reported in patients with NAC candidemia,[5,12,19,20] the relationship has not been reported in other studies.[4,9,18,21]

Our results showed that fluconazole, caspofungin, voriconazole and amphotericin B were very active against the *Candida* bloodstream isolates tested (Table 4). Except for two *C. glabrata* strains, which were fluconazole SDD, all *Candida* species tested were susceptible to fluconazole, caspofungin, voriconazole and amphotericin B. The absence of fluconazole resistance among *Candida* strains in our study may, in part, be explained by exclusion of the immunosuppressed patients, who receive frequent fluconazole prophylaxis and/or treatment in their clinical course that is associated with azole resistance.[22–24] In addition, in those patients, the use of fluconazole has been implicated in the increased isolation rate of *C. glabrata* and *C. krusei* species, which are generally less sensitive or resistant to azoles.[24]

The absence of fluconazole resistance among all *Candida* strains tested has important implications for the management of *Candida* infections, especially given that fluconazole is an efficacious, inexpensive and safe drug, and is one of the most commonly used antifungal agents for the treatment of candidemia.[25] Our data pertaining to fluconazole susceptibility for common *Candida* species (i.e. *C. albicans*, *C. parapsilosis* and *Candidia tropicalis*) were similar to that seen in other major surveillance studies of *Candida* BSI isolates, in which resistance to fluconazole was reported to be $\leq$ 3%.[15,21] In contrast to our findings, elevated rates of fluconazole resistance among *C. glabrata* isolates have been reported in the USA (7–22.8%) and Europe (4–40%).[16,23] Our data pertaining to the excellent activity of caspofungin, voriconazole and amphotericin B against *Candida* species tested were in agreement with other reports.[16,22,26,27]

Our data are consistent with the current belief that antifungal susceptibility testing should not be routinely performed for such common *Candida* species such as *C. albicans*, *C. parapsilosis* and *C. tropicalis*, but may be indicated for patients who fail to respond to initial therapy or who develop breakthrough candidemia while receiving fluconazole prophylaxis.[28]

In conclusion, among end-stage renal disease patients with *Candida* BSIs in ICUs, although *C. albicans* remained the leading *Candida* species, NAC was indentified in 41.2% of the cases. Presence of CVCs was found to be the only independent factor associated with BSIs due to NAC. The severity of *Candida* BSIs was confirmed by an overall 30-day mortality rate of 58.8%. The mortality was higher in patients with BSIs due to NAC, however, the difference was not significant. Our results also demonstrated that fluconazole, voriconazole, caspofungin and amphotericin B were active against almost all the *Candida* bloodstream isolates tested.

Table 3 Risk factors for blood stream infection with non-*albicans Candida* in intensive care units patients with chronic renal failure, *n* (%).

Univariate analyses	*Candida albicans* ($n = 60$)	non-*albicans Candida* ($n = 42$)	Unadjusted OR (95% CI)	*P*
Male sex	25 (41.7)	20 (47.6)	1.27 (0.57–2.81)	0.551
Age (y), mean ± SD (range)	58.1 ± 19.79 (24–90)	56.8 ± 18.03 (18–88)	1.07 (0.49–2.35)	0.868
Hospital length of stay[a], mean ± SD (range)	35.9 ± 18.93 (10–95)	33.6 ± 15.22 (11–73)	0.96 (0.96–1.01)	0.381
Inadequate initial antifungal treatment[b]	4 (6.7)	3 (7.1)	0.88 (0.28–2.76)	0.925
Primary site of infection			0.69 (0.28–3.19)	0.275
CVC	25 (41.7)	19 (45.2)		
Unknown	35 (58.3)	23 (54.8)		
30 d mortality	33 (55)	27 (64.3)		0.067
APACHE II score, mean ± SD (range)	24.2 ± 4.18 (16–34)	25.7 ± 5.97 (14–40)	1.52 (0.69–3.37)	0.298
Type of patient, medical	35 (58.3)	24 (57.1)	1.14 (0.44–2.97)	0.783
Underlying diseases and conditions				
Diabetes mellitus	30 (50)	20 (47.6)	0.86 (0.35–2.11)	0.745
Chronic obstructive lung disease	2 (3.3)	1 (2.4)	0.58 (0.05–7.04)	0.666
Liver disease	1 (1.7)	1 (2.4)	2.09 (0.07–60.92)	0.667
Chronic heart failure	10 (16.7)	10 (23.8)	1.33 (0.43–4.09)	0.615
Therapeutic factors				
Surgery within prior 4 wk	21 (35)	16 (38.1)	0.87 (0.39–1.98)	0.749
CVC in place at time of diagnosis	48 (80)	40 (95.2)	5.30 (1.01–27.91)	**0.028**
CVC days left in place prior to development of candidemia, mean ± SD (range)	25.97 ± 15.91 (9–82)	24.60 ± 13.98 (10–73)	1.00 (0.97–1.03)	0.939
Type of CVC			0.82 (0.18–2.08)	0.73
Temporary double-lumencatheter	41 (85.4)	37 (88.1)		
Hemodialysis catheter	7 (14.6)	3 (11.9)		
Total parenteral nutrition	49 (81.7)	34 (81)	0.94 (0.31–2.81)	0.913
Assisted ventilation	30 (50)	23 (54.8)	1.00 (0.41–2.45)	0.998
Antifungal therapy within prior 4 wk	9 (15)	5 (11.9)	0.73 (0.21–2.60)	0.632
Fluconazole	8 (13.3)	5 (11.9)		
Other	1 (1.7)	0		
Antibiotic therapy within prior 4 wk	59 (98.3)	42 (100)	0.584 (0.496–0.689)	0.400
Broad-spectrum cephalosporin[c]	27 (45)	20 (47.6)	0.90 (0.41–1.98)	0.794
Carbapenem[d]	36 (60)	24 (57.1)	1.12 (0.51–2.50)	0.773
Piperacillin–tazobactam	22 (36.7)	17 (40.5)	0.85 (0.38–1.91)	0.697
Quinolone[e]	11 (18.3)	10 (23.8)	0.72 (0.27–1.89)	0.501
Aminoglycoside[f]	8 (13.3)	5 (11.9)	1.14 (0.34–3.76)	0.831
Glycopeptide[g]	43 (71.7)	29 (69)	1.13 (0.48–2.68)	0.775
Vascular access for hemodialysis			1.24 (0.57–2.43)	0.917
CVC	48 (80)	35 (83.3)		
Fistula	10 (18.3)	5 (11.9)		
Graft	2 (1.7)	2 (4.8)		
Multivariate regression analyses				
CVC placement			5.90 (1.032–33.717)	0.046

APACHE = acute physiology and chronic health evaluation; CI = confidence interval; CVC = central venous catheter; OR = odds ratio; SD = standard deviation.

[a] Number of days of hospitalization before onset of candidemia.

[b] initial antifungal treatment was considered inadequate when > 72 hours elapsed between diagnosis of candidemia and initiation of treatment to which the infecting organism was susceptible.

[c] third- and fourth-generation cephalosporins including ceftriaxone, cefoperazone–sulbactam, ceftazidime and cefepime.

[d] imipenem or meropenem.

[e] ofloxacin, moxifloxacin, levofloxacin or ciprofloxacin.

[f] amikacin, gentamicin or netilmicin.

[g] vancomycin or teicoplanin.

Table 4 *In vitro* susceptibility of *Candida* bloodstream isolates to four antifungal agents.

Species (no. tested)	Antifungal agent	MIC (μg/mL) range	No of isolates R[a] (%)	No of isolates SDD (%)
Candida albicans (60)	Amphotericin B	0.03–1	0 (0)	–
	Caspofungin	0.015–0.03	0 (0)	–
	Voriconazole	< 0.015–0.06	0 (0)	0 (0)
	Fluconazole	0.01–2	0 (0)	0 (0)
Candida tropicalis (15)	Amphotericin B	0.125–1	0 (0)	–
	Caspofungin	0.06–0.5	0 (0)	–
	Voriconazole	0.03–0.5	0 (0)	0 (0)
	Fluconazole	0.250–4	0 (0)	0 (0)
Candida glabrata (11)	Amphotericin B	0.06–1	0 (0)	–
	Caspofungin	< 0.015–0.25	0 (0)	–
	Voriconazole	0.125–1	0 (0)	0 (0)
	Fluconazole	1–16	0 (0)	2 (18.2)
Candida parapsilosis (8)	Amphotericin B	0.125–1	0 (0)	–
	Caspofungin	< 0.015–0.25		–
	Voriconazole	0.03–0.25	0 (0)	0 (0)
	Fluconazole	0.250–2	0 (0)	0 (0)
Other species (8)[b]	Amphotericin B	0.125–2	0 (0)	–
	Caspofungin	< 0.015–0.25		–
	Voriconazole	< 0.015–0.25	0 (0)	0 (0)
	Fluconazole	0.125–2	0 (0)	0 (0)
All organisms (102)	Amphotericin B	0.03–2	0 (0)	–
	Caspofungin	< 0.015–0.5	0 (0)	–
	Voriconazole	< 0.015–1	0 (0)	0 (0)
	Fluconazole	0.01–16	0 (0)	2 (1.96)

R = resistant; S = sensitive; SDD = susceptible, dose-dependent susceptible.

[a] Susceptibility breakpoints (μg/mL): fluconazole ≤ 8 (S),16–32 (SDD), ≥ 64 (R); amphotericin B ≤ 1.0 (S), > 1 (R); voriconazole ≤ 1.0 (S), 2.0 (SDD), ≥ 4 (R); caspofungin ≤ 2.0 (S), > 2 (R).

[b] *Candida famata* (3), *Candida humonicola* (2), *Candida keyfr* (2) and *Candida guillermondi* (1).

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