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ORIGINAL ARTICLE

Risk factors of mortality and comparative *in-vitro* efficacy of anidulafungin, caspofungin, and micafungin for candidemia

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Micafungin

Background: Although echinocandins have high *in vitro* antifungal efficacy according to prior reports, comparative studies on the clinical cure rates of anidulafungin, caspofungin, and micafungin in systemic candida infections have not yet been reported.
Methods: Interpretation of clinical and microbiological responses to anidulafungin, caspofungin, and micafungin in 109 cases of candidemia was done according to the published criteria. The clinical cure rates between patients treated with echinocandins and patients treated with fluconazole were also compared. The minimal inhibitory concentrations (MICs) of anidulafungin, caspofungin, micafungin, and fluconazole for these 109 blood isolates of candida were determined with the Clinical and Laboratory Standards Institute M27-A reference microdilution method. Logistic regression with forward selection was used to determine the important factors of prognosis with variables such as age, underlying diseases, acute physiology and chronic health evaluation (APACHE) III score, persistent candidemia, and antimicrobial therapy.
Results: Among the 109 cases of candidemia, 70 were treated with echinocandins, azoles, or amphotericin B for $\geq$7 days. The clinical cure rate of cases treated with antifungal agents adequately ($\geq$7 days) and inadequately ($<$7 days) were 44/70 (62.9%) and 4/39 (10.2%),

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respectively, with significant difference ($p < 0.0001$). Clinical cure rates of anidulafungin, caspofungin, micafungin, and fluconazole were 18/30 (60.0%), 8/9 (88.9%), 5/7 (71.4%), and 9/18 (50%), respectively. The difference in APACHE III score between treatment success and failure cases was significant. The MIC_{50}/MIC_{90} of anidulafungin, caspofungin, and micafungin for all *Candida* spp. were 0.03/1 μg/mL, 0.06/0.5 μg/mL, and 0.008/1 μg/mL, respectively.
Conclusion: Adequate antifungal therapy and APACHE III score are both independent factors affecting the clinical outcome. The clinical cure rate of the echinocandins group was higher than that of the fluconazole group without significant difference. Although caspofungin had the best clinical cure rate in this study, there was no significant difference between the clinical cure rates among these three echinocandins. All *Candida* spp. were susceptible *in vitro* to these three echinocandins.

Introduction

Significant factors affecting the clinical outcome of candidemia and the associated mortality among critical patients in medical intensive care units have been reported.[1,2] Prior studies indicate that echinocandins such as anidulafungin, caspofungin, and micafungin manifest *in vitro* fungicidal activity against candida.[3—10] Furthermore, the clinical cure rate of caspofungin has been compared with that of micafungin and liposomal amphotericin B in invasive candida infections.[11,12] Anidulafungin has also been compared with fluconazole in the treatment of candidemia.[9] Nonetheless, to our knowledge, comparative studies on the clinical cure rates of anidulafungin, caspofungin, and micafungin in systemic candida infections has not yet been reported.[10—17] Therefore, this study sought to compare the clinical efficacy of these three echinocandins, as well as their *in vitro* efficacy in patients of candidemia. The clinical cure rates between patients treated with echincandins and patients treated with fluconazole were compared. Associated risk factors for treatment failure and mortality in candidemia were also investigated.

Methods

Patient enrollment

Keelung Chang Gung Memorial Hospital is a 1088-bed, tertiary-care, teaching hospital in Taiwan. This research was started in March 1, 2010 after being approved in February 2010. All candidemia patients in Keelung Chang Gung Memorial Hospital were enrolled between March 1, 2010 and December 31, 2011 for retrospective clinical analysis. Inclusion criteria were: (1) at least one blood culture positive for *Candida* spp.; (2) pre-existing risk factors for invasive *Candida* infection mentioned in literature[2]; and (3) clinical manifestation of sepsis. The patients' *Candida* isolates were stored for *in vitro* susceptibility study.

Treatment regimens

All candidemia patients were treated with fluconazole or echinocandins with approval from an infectious disease specialist according to the Clinical Practice Guidelines for the Management of Candidiasis by the Infectious Diseases Society of America in 2009.[18] In patients with serum creatinine levels below 3 mg/dL, 200 mg of fluconazole was administered intravenously twice daily after a loading dose of 300 mg for 1—4 weeks (at least 1 week after blood culture-negative), depending on the patients' clinical response.[19] In patients with serum creatinine levels above 3 mg/dL, a 200 mg dose of fluconazole was administered intravenously once daily.[19] The loading dose of anidulafungin was 200 mg followed by a maintenance dose of 100 mg intravenously once daily for 1—4 weeks. The loading dose of caspofungin was 70 mg followed by a maintenance dose of 50 mg intravenously once daily for 1—4 weeks.[9,10,20] In the case of micafungin, there was no loading dose and a maintenance dose of 100 mg intravenously was given once daily for 1—4 weeks.[21] Coexisting bacterial infections were treated with appropriate antibiotics according to the antimicrobial susceptibility.[19] Surgery was performed if necessary to eradicate the infections upon obtaining informed patient consent.[19] Dosage of echinocandins including anidulafungin, caspofungin, and micafungin remained unchanged for patients with abnormal renal function.

Evaluation criteria

Follow-up evaluations were performed daily by the attending physician in charge after the start of treatment. Standard clinical laboratory evaluations (blood chemistry, urinalysis, complete blood count, blood bacterial and fungal culture, and chest roentgenogram) were performed prior to, during, and after treatment as medically indicated. Interpretation of the clinical and microbiological responses was done according to the following criteria.[19] Clinical cure was indicated by the resolution of clinical signs and symptoms of infection due to the original *Candida* species, without signs of infection relapse caused by the original *Candida* species within 3 months after the discontinuation of the antifungal agent and the absence of the original *Candida* species in repeated post-therapy cultures.[19] Any coexisting bacterial infection was treated with appropriate antibiotics as recommended by infectious diseases specialists. Clinical treatment failure was indicated by an absence of clinical response to antifungal therapy after a minimum of 1 week of therapy, with persistence of

positive culture or development of unacceptable drug toxicity.[19] Superinfection or reinfection due to *Candida* species different from the original *Candida* species were excluded prior to evaluation.[19] Surgical intervention essential to the eradication of infection was performed prior to evaluation. Mortality due to candidemia was defined as death of patients due to sepsis within 30 days of the last detection of *Candida*-positive blood culture without clinical response to antifungal therapy or with persistence of positive culture after a minimum of 1 week of therapy.[19] Death of candidemia patients >30 days after the last detection of candidemia after completing an adequate course of antifungal therapy and with repeated negative blood culture was defined as mortality due to other causes.[19] Early antifungal therapy was defined as an antifungal therapy being started within 48 hours of positive blood culture. Inadequate treatment was defined as treatment with fluconazole and/or echinocandins for <7 days whereas adequate treatment was defined as treatment with fluconazole and/or echinocandins for ≥7 days. Persistent candidemia was diagnosed when repeated blood culture still presented positive for the same *Candida* spp. >24 hours after the first positive blood culture even under antifungal therapy or after a completed course of antifungal therapy. The relationship of the acute physiology and chronic health evaluation (APACHE) III score to clinical cure rate and mortality due to candidemia were also evaluated on the blood culture-positive day.[22]

In vitro susceptibility test

MICs were determined and interpreted for the 109 *Candida* isolates causing 109 candidemia episodes according to the procedure of the current reference method for broth dilution antifungal susceptibility testing of yeasts (M27-A3 and M27-S3) by the Clinical and Laboratory Standards Institute (CLSI).[23,24] Briefly, *Candida* isolates at a final concentration of 5.0×10^5 cells/L to 2.5×10^6 cells/L were incubated in air at 35°C for 24 hours with two-fold dilutions of antifungal agents of 0.03–16 μg/mL for amphotericin B; 0.125–64 μg/mL for fluconazole; 0.008–16 ug/mL for itraconazole, posaconazole, and voriconazole; and 0.008–8 ug/mL for anidulafungin, caspofungin, and micafungin. The MIC of amphotericin B was defined as the lowest drug concentration to prevent any discernible growth.[23,24] MICs of azoles and echinocandins were defined as the lowest drug concentration to produce a prominent decrease in turbidity (score of 2), which translated to an approximately 50% reduction in growth relative to the drug-free growth control.[24] RPMI-1640 buffered to pH 7.0 with 0.165 M morpholinepropanesulfonic acid was applied.[24] The control strains *Candida albicans* ATCC 90028 and *Candida krusei* ATCC 6258 were used in all tests.[23,24]

Statistical analysis

Descriptive statistics such as means, standard deviation, frequency, and percentage were conducted. Chi-square test, Fisher's exact test, unpaired *t* test, and analysis of variance were used to compare data among groups when appropriate. Logistic regression with forward selection was

Table 1 Outcome of 109 cases of candidemia

	Group A (70)[a]	Group B (17)[b]	Group C (22)[c]	*p*	APACHE III score, mean (range)			
					Group A (70)	*P*	Group B (17) Group C (22)	*p*
Treatment duration (d), mean (range)	18.6 ± 9.1 (7–51)	3.8 ± 1.4 (2–6)	0	<0.001[d]				
Candidemia treatment Cured	44 (62.9)	1 (5.9)	3 (13.6)	<0.001[e]	42.3 ± 20.7 (4–84)	0.0083[d]	28.5 ± 19.8 (0–46)	0.0003[d]
Failure	26 (37.1)	16 (94.1)	19 (86.4)		57.9 ± 27.2 (13–112)		74.8 ± 22.4 (37–128)	
Expired due to candidemia	20 (28.6)	14 (82.4)	18 (81.8)	<0.001[e]				
APACHE III score	48.1 ± 24.4 (4–112)	78.9 ± 22.2 (35–128)	63.2 ± 27.3 (0–114)	<0.001[f]				

[a] Group A: Treated with echinocandins or azoles or amphotericin B for ≥7 days.
[b] Group B: Receiving antifungal treatment for <7 days.
[c] Group C: Receiving no antifungal treatment.
[d] Independent *t* test.
[e] Fisher's exact test.
[f] Analysis of variance.
Data are presented as *n* (%), mean ± SD, or mean (range).

Table 2 Analysis of outcome of 109 evaluable cases of candidemia with multiple logistic regression

	Candidemia treatment			Multiple logistic regression	
	Cured	Failure	*p*	Adjusted odds ratio	*p*
Group			<0.001[a]		
Group A	44 (62.9)	26 (37.1)		Reference	
Group B, Group C	4 (10.3)	35 (89.7)		11.0 (3.4–36.0)	<0.001
APACHE III			<0.001[a]		0.0099
<40	25 (69.4)	11 (30.6)		Reference	
40–60	13 (50.0)	13 (50.0)		1.6 (0.5–5.1)	0.4531
>60	10 (21.3)	37 (78.7)		5.2 (1.7–15.4)	0.0032

[a] Chi-square test.
Data are presented as *n* (%).
APACHE = Acute Physiology and Chronic Health Evaluation.

used to determine the important factors for prognosis with variables such as age, underlying diseases, APACHE III score, persistent candidemia, and antimicrobial therapy. Odds ratios (ORs) with 95% confidence interval (CI) were determined to indicate the risk of failure. A p value < 0.05 was considered statistically significant.

Results

A total of 109 cases of candidemia were included in our analysis. Of these, 70 cases were treated with echinocandins, azoles, or amphotericin B for ≥7 days and the other 39 cases were treated inadequately. The clinical cure rates of cases treated adequately and inadequately due to late or postmortem diagnosis were 44/70 (62.9%) and 4/39 (10.2%) respectively, and with significant difference (Table 1). According to logistic regression, adequate antifungal therapy and the APACHE III score were both independent significant factors for the clinical outcome (Table 2). Because one case of candidemia was treated with amphotericin B only, there were 69 evaluable cases of candidemia adequately treated with echinocandins or azoles. Clinical cure rates of anidulafungin, caspofungin, micafungin, and fluconazole were 18/30 (60.0%), 8/9 (88.9%), 5/7 (71.4%), and 9/18 (50%), respectively (Table 3). Regarding the APACHE III score, there was no significant difference among these four treatment groups. However, the difference in APACHE III score between treatment cure and failure cases was significant, indicating that patients with high APACHE III score were too sick to complete the course of treatment (Table 3). When echinocandins were evaluated together and compared with fluconazole group, the clinical cure rate was higher in the echinocandins group (72.7% in echinocandins group; 50.0% in fluconazole group; Table 4) without significant difference (Table 4). Regarding the mortality rate due to candidemia, significant differences were found between cases with and without early antifungal therapy and between those with and without adequate antifungal therapy (Table 5). The outcome of another nine cases of candidemia was in the treatment failure group who ultimately survived and was not included in the study of risk factors for mortality (Table 5). However, there was no significant difference in the mortality rate due to candidemia between those cases with and without persistent candidemia (Table 5). The *in vitro* activities of azoles to *Candida* isolates of candidemia are shown in Table 6. *Candida glabrata* and *C. krusei* were totally resistant to fluconazole whereas the other azoles such as itraconazole, posaconazole, and voriconazole showed lower MIC implicated clinical efficient (Table 6). The MICs of anidulafungin, caspofungin, and micafungin in *C. parapsilosis* were higher than that in other *Candida* spp. (Table 6). The MIC_{50}/MIC_{90} of anidulafungin, caspofungin, and micafungin for all *Candida* spp. were 0.03/1 μg/mL, 0.06/0.5 μg/mL, and 0.008/1 μg/mL, respectively (Table 6).

Discussion

According to a prior report, the clinical correlation of the reference antifungal susceptibility test results was high in hematogenous and deep-seated *Candida* infections when co-existing bacterial infections were treated with appropriate antibiotics, superinfection or reinfection as defined in the exclusion criteria was excluded, inadequate antifungal therapy was avoided, and essential surgical intervention was performed.[19] Because the MICs of echinocandins to all *Candida* spp. were still within the susceptible range, factors other than susceptibility result should be present to explain those candidemia cases treated unsuccessfully with echinocandins. In the present study, a significant difference was seen between the APACHE III score of the treatment cure group and the treatment failure group (Tables 1–4). Therefore, APACHE III score on the culture-positive day affects the clinical outcome. The impact on the outcome was significant when the APACHE III score was above 60 (Table 2). Because the APACHE III score was lower in the candidemia cases treated successfully with echinocandins or azoles, we clarified the relationship between adequate antifungal therapy and APACHE III score with multiple logistic regression and thus found that adequate antifungal therapy and APACHE III score are the independent factors affecting the clinical outcome (Table 2). We also found a significant difference in the treatment failure rate between cases treated adequately (≥7 days) with antifungal agents and treated inadequately with antifungal agents (<7 days) or not

Table 3 Outcome of 69 evaluable cases of candidemia adequately treated with echinocandins or azoles[a]

		Casp ($n = 9$)	Anid ($n = 30$)	Mica ($n = 7$)	Flu ($n = 18$)	Candins or azoles combination ($n = 5$)	p	APACHE III score, mean (range)	p
Total treatment duration (d)		19.9 ± 6.6 (12–28)	19.4 ± 10.6 (7–51)	21.1 ± 9.3 (9–37)	14.8 ± 6.5 (7–30)	23.4 ± 9.5 (10–34)	0.2521[b]		
Candins treatment duration (d), mean (range)		13.8 ± 4.2 (7–22)	12.9 ± 7.4 (4–34)	14.86 ± 8.4 (2–28)	—	—	0.7919[b]		
Candidemia treatment	Cured	8 (88.9)	18 (60.0)	5 (71.4)	9 (50.0)	4 (80.0)	0.3358[c]	42.3 ± 20.7 (4–84)	0.0038[d]
	Failure	1 (11.1)	12 (40.0)	2 (28.6)	9 (50.0)	1 (20.0)		59.5 ± 26.6 (13–112)	
Expired due to candidemia		1 (11.1)	8 (26.7)	2 (28.6)	7 (38.9)	1 (20.0)	0.7044[c]		
APACHE III score		50.9 ± 23.5 (26–84)	47.3 ± 26.4 (4–112)	48.0 ± 25.1 (20–81)	50.6 ± 21.2 (23–90)	44.4 ± 30.4 (10–88)	0.9805[a]		
MIC μg/mL		Fluc:1.028 (0.25–4) Casp:0.29 (0.03–1)	Fluc:3.58 (0.25–16) Anid:0.258 (0.015–1)	Fluc:0.367 (0.12–1) Mica:0.047 (0.015–0.25)	3.451 (0.12–32)	Fluc:1.1 (0.5–2) Anid:0.072 (0.03–0.12) Casp:0.61 (0.06–0.25) Mica:0.02 (0.008–0.03) Vori:0.06 (0.015–0.12)			

[a] Five cases were unresponsive to 5–18 days of fluconazole initially, of which three cases had persistent candidemia; 19 cases were unresponsive to 1–20 days of fluconazole initially, of which five cases had persistent candidemia; two cases were unresponsive to 20–24 days of fluconazole initially, of which one case had persistent candidemia. Candins or azoles combination: Fluc + Anid + Casp (1); Fluc + Anid + Mica (1); Fluc + Casp + Vori (1); Anid + Mica (1); Cas + Mica (1). Of 109 cases of candidemia, only 69 cases adequately treated with echinocandins or fluconazole could be evaluated for response to these antifungal agents. One case of candidemia was treated with amphotericin B only.

[b] Analysis of variance.

[c] Fisher's exact test.

[d] Independent t test.

Data are presented as n (%), mean ± SD (range), or mean (range).

Anid = anidulafungin; APACHE = Acute Physiology and Chronic Health Evaluation; Casp = caspofungin; Fluc = fluconazole; Mica = micafungin; MIC = minimal inhibitory concentration; SD = standard deviation.

Table 4 Outcome of 40 evaluable cases of candidemia adequately treated with only echinocandins or fluconazole

	Candins (n = 22)[a]	Fluconazole (n = 18)	p	APACHE III score, mean (range)	p
Candidemia cured	16 (72.7)	9 (50.0)	0.1396[b]	42.5 ± 21.8 (12–84)	0.0460[d]
Candidemia treatment failure	6 (27.3)	9 (50.0)		57.9 ± 24.5 (13–90)	
Expired due to candidemia	4 (18.2)	7 (38.9)	0.1734[c]		
Treatment duration, d	15.5 ± 0.8 (7–34)	14.8 ± 6.5 (7–30)	0.7739[d]		
APACHE III score	46.3 ± 26.0 (12–88)	50.6 ± 21.2 (23–90)	0.5765[d]		

[a] Twenty-two candidemia cases treated with echinocandins only included caspofungin (n = 4), anidulafungin (n = 11), micafungin (n = 5), anidulafungin followed by micafungin (n = 1) and caspofungin followed by micafungin (n = 1).
[b] Chi-square test.
[c] Fisher's exact test.
[d] Independent t test.
Data are presented as n (%) or mean (range).
APACHE = Acute Physiology and Chronic Health Evaluation.

treated with antifungal agents (Table 1). In those cases not treated with antifungal agents (Group C), the result of blood culture was known *postmortem*. In those cases treated inadequately with antifungal agents for <7 days (Group B), the result of blood culture was known late in the course of candidemia. Therefore, early diagnosis of candidemia and early initiation of effective antifungal therapy are both very important in the treatment of candidemia in order to provide adequate antifungal therapy prior to when the patients become very critical. In Group B of the 17 candidemia cases that were inadequately treated (<7 days), one case survived, 14 cases expired due to candidemia, and the remaining two cases expired due to non-candidemia causes. In Group C of the 22 candidemia cases without any antifungal therapy, three cases survived, 18 cases expired due to candidemia and the remaining case expired due to noncandidemia cause. Survival for these four candidemia cases without adequate or any antifungal therapy might be resulted from the transient nature of candidemia and the better physiological immune status in them. The APACHE III score of these four survival patients was 28.5 ± 19.8, significantly lower than that of the failure cases in Groups B and C (Table 1).

In cases treated with fluconazole, the MICs of fluconazole had a wide range, some within the susceptible ranges (*C. albicans, Candida parapsilosis, Candida tropicalis,* Table 6) and the others outside the susceptible ranges (*C. glabrata, C. krusei,* Table 6). The mean was 3.45 μg/mL and the range was 0.12–32 μg/mL. However, in cases treated with echinocandions, the MICs of anidulafungin, caspofungin, and micafungin were very low, all within the susceptible ranges. Such difference of susceptibility to *Candida* spp. between echinocandins and fluconazole may explain the higher cure rate of echinocandins (72.7%) and the lower cure rate of fluconazole (50%) for candidemia (Table 4). Thus, fluconazole was inferior to echinocandins in the treatment of candidemia clinically. The *in vitro* activity of fluconazole was also inferior to echinocandins except for *C. parapsilosis*, in which the MICs of echinocandins and fluconazole were similar (Table 6). We had analyzed the relationship between MICs of fluconazole and the outcome of candidemia cases caused by *C. parapsilosis*. Among the 26 cases of candidemia due to *C. parapsilosis*, nine cases with APACHE III score 41.11 ± 25.33 (range, 4–81) were treated with fluconazole adequately of which six cases were cured and three cases expired within 30 days of the culture-positive date; nine cases with APACHE III score 41.22 ± 28.89 (range, 12–84) were treated adequately with echinocandins of which eight cases were cured and one case expired within 30 days of the culture-positive date. One case of candidemia due to *C. parapsilosis* with APACHE III score 19 was cured with amphotericin B but died of other causes 3 months later. The remaining seven cases of candidemia due to *C. parapsilosis* were not treated with any antifungal agent due to late or *postmortem* diagnosis of which four cases with APACHE III score 30.00 ± 20.70 (range, 0–46) survived and three cases with APACHE III score 56.67 ± 24.42 (range, 37–84) expired within 10 days of culture-positive date. These data indicated that although fluconazole is not inferior to echinocandins in MIC susceptibility test of *C. parapsilosis*, echinocandins is not inferior to fluconazole in treating candidemia due to *C. parapsilosis* clinically. In candidemia cases that are frequently critical and severe, echinocandins are preferred rather than fluconazole unless the MICs of fluconazole can be known immediately and are found within the susceptible range.

Although the number of candidemia cases was small in some groups of treatment with various antifungal agents, the difference in treatment outcome with different antifungal agents were revealed (Table 3). However, significant difference in the clinical cure rates among these three echinocandins still might not be achieved even if we include more candidemia cases by extending the study period. Alternatively, a comparative *in vitro* fungicidal activity study of these three echinocandins may disclose which echinocandin has the highest clinical cure rate. Although the MIC of micafungin was the lowest among the three echinocandins (Table 6), the clinical cure rate of caspofungin was higher than that of anidulafungin and micafungin in this study although this was not statistically significant (Table 3). According to Table 3, the APACHE III scores of candidemia cases using caspofungin, anidulafungin, micafungin, and fluconazole were not significant

Table 5 Evaluation of risk factors for mortality due to candidemia in 100 evaluable cases of candidemia[a]

		Cured of candidemia ($n = 48$)	Expired due to candidemia ($n = 52$)	p
Sex	M	25 (52.1)[b]	29 (55.8)[b]	0.7118[d]
	F	23 (47.9)[b]	23 (44.2)[b]	
Age, y, mean (range)		70.4 ± 12.2 (43–91)	70.8 ± 19.1 (10–103)	0.9021[e]
Underlying diseases				
Chronic obstructive pulmonary diseases	Y	5 (10.4)[b]	6 (11.5)[c]	0.8578[d]
	N	43 (89.6)[b]	46 (88.5)[c]	
Congestive heart failure	Y	3 (6.3)[b]	4 (7.7)[c]	0.7776[d]
	N	45 (93.8)[b]	48 (92.3)[c]	
End-stage renal diseases under regular hemodialysis	Y	7 (14.6)[b]	10 (19.2)[c]	0.5365[d]
	N	41 (85.4)[b]	42 (80.8)[c]	
Chronic renal failure without hemodialysis	Y	1 (2.1)[b]	2 (3.9)[c]	0.6057[d]
	N	47 (97.9)[b]	50 (96.2)[c]	
Chronic cerebral vascular diseases	Y	9 (18.8)[b]	5 (9.6)[b]	0.1884[d]
	N	39 (81.3)[b]	47 (90.3)[b]	
Liver cirrhosis	Y	2 (4.2)[b]	8 (15.4)[b]	0.0945[f]
	N	46 (95.8)[b]	44 (84.6)[b]	
Malignancy	Y	21 (43.8)[b]	16 (30.8)[b]	0.1792[d]
	N	27 (56.3)[b]	36 (69.2)[b]	
Rheumatic diseases	Y	7 (14.6)[b]	5 (9.6)[b]	0.4450[d]
	N	41 (85.4)[b]	47 (90.4)[b]	
Neutropenia	Y	4 (8.3)[b]	4 (7.7)[b]	0.9060[d]
	N	44 (91.7)[b]	48 (92.3)[b]	
Others	Y	37 (77.1)[b]	39 (75.0)[b]	0.8075[d]
	N	11 (22.9)[b]	13 (25.0)[b]	
APACHE III, mean (range)		41.1 ± 20.8 (0–84)	69.3 ± 23.9 (19–128)	<0.0001[e]
Persistent candidemia > 24 h ($n = 24$)	Y	13 (27.1)[b]	11 (21.2)[b]	0.4879[d]
	N	35 (72.9)[b]	41 (78.9)[b]	
Persistent candidemia > 72 h ($n = 20$)	Y	10 (20.8)[b]	10 (19.2)[b]	0.8414[d]
	N	38 (79.2)[b]	42 (80.8)[b]	
Persistent candidemia > 24 h with fluconazole		2 (40.0)[c]	3 (60.0)[c]	0.6299[f]
Persistent candidemia > 24 h with candins		11 (57.9)[c]	8 (42.1)[c]	
Persisitent candidemia, d, mean (range)		6.93 ± 6.3 (1–25)	8.4 ± 8.6 (1–33)	0.6160[e]
Early AT ($n = 40$)	Y	25 (52.1)[b]	15 (28.9)[b]	0.0178[d]
	N	23 (47.9)[b]	37 (71.2)[b]	
Adequate AT ($n = 64$)	Y	44 (91.7)[b]	20 (38.5)[b]	<0.0001[d]
	N	4 (8.3)[b]	32 (61.5)[b]	
Adequate AT with fluconazole ($n = 16$)		9 (56.3)[c]	7 (43.8)[c]	0.2092[f]
Adequate AT with candins ($n = 20$)		16 (80.0)[c]	4 (20.0)[c]	
Adequate AT with candins + azole ($n = 27$)		19 (70.4)[c]	8 (29.6)[c]	
Adequate AT with amphotericin B		0	1 (100.0)[c]	

[a] Outcome of another nine cases of candidemia was in the treatment failure group who ultimately survived.
[b] Column percentage.
[c] Row percentage.
[d] Chi-square test.
[e] Independent t test.
[f] Fisher's exact test.
Data are presented as n (%).
AT = antimicrobial therapy.

Table 6 Comparative in-vitro activities of amphotericin B, fluconazole, itraconazole, posaconazole, voriconazole, anidulfungin, caspofungin, and micafungin against 109 blood isolates of Candida spp. with microdilution

Organism	No. of isolates	MIC (μg/ml)															
		AMB(%)		FLC(%)		ITC(%)		POS(%)		VRC(%)		ANID(%)		CASP(%)		MICA(%)	
		50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90
All Candida spp.	109	0.5	0.5	0.25	16	0.06	0.5	0.015	1	0.008	0.25	0.03	1	0.06	0.5	0.008	1
C. albicans	48	0.5	0.5	0.5	1	0.06	0.12	0.03	0.06	0.008	0.015	0.06	0.06	0.12	0.12	0.008	0.015
C. glabrata	18	0.5	1	16	16	0.5	1	1	2	0.25	0.5	0.03	0.06	0.12	0.25	0.015	0.015
C. parapsilosis	26	0.5	0.5	1	1	0.12	0.12	0.06	0.06	0.015	0.03	1	1	0.5	1	1	2
C. tropicalis	15	0.5	0.5	0.5	2	0.12	0.5	0.06	0.5	0.06	0.12	0.12	0.12	0.06	0.25	0.03	0.03
C. krusei	2	0.5	1	32	64	0.25	0.5	0.25	0.5	0.25	0.5	0.03	0.06	0.5	0.5	0.12	0.12

different. Therefore, under the same APACHE III score level, caspofungin still had a better outcome though the difference of outcome among cases treated with these three drugs were not significant. Because there was no significant difference in the APACHE III score among the three groups of candidemia cases treated with anidulafungin, caspofungin, and micafungin respectively, there should be other factors such as fungicidal activity that were responsible for the difference in the cure rates among these three echinocandins.

Regarding risk factors of mortality due to candidemia, only APACHE III score, early antifungal therapy, and adequate antifungal therapy are significant statistically in the present study (Table 5) and are consistent with prior reports.[25–27] However, persistent candidemia is not a risk factor of mortality in candidemia treated with echocandins or fluconazole in this study, which differs from prior reports.[28] The outcome of another nine cases of candidemia in the treatment failure group who ultimately survived was not included in the study of risk factors for mortality. This finding indicates that the antifungal agents used in these nine cases of candidemia are not effective enough to cure the candidemia with a persistence of fever or sign of active infection, although they clinically improved and the repeated blood culture became negative. Subsequently, the immune status of the patients improved and candidemia became resolved completely.

We conclude that: (1) adequate antifungal therapy and APACHE III score are independent factors affecting the clinical outcome; (2) the clinical cure rate of the echinocandins group was higher than that of the fluconazole group without significant difference; (3) although caspofungin has the best clinical cure rate in this study, there is no significant difference between the clinical cure rate among these three echinocandins; and (4) all *Candida* spp. were susceptible *in vitro* to these three echinocandins. Further clinical and *in vitro* studies are needed to clarify the difference in the clinical cure rates among anidulafungin, caspofungin, and micafungin.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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