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Original Article

Risk factors for candidemia-related mortality at a medical center in central Taiwan

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Background and Purpose: Bloodstream infections due to *Candida* spp. are associated with significant mortality and morbidity. This study analysed the epidemiology and outcome of candidemia cases in a teaching hospital in central Taiwan.

Methods: We retrospectively studied the clinical characteristics and antifungal susceptibility of isolates and risk factors for mortality in 91 cases of candidemia treated from January 1, 2001 to June 30, 2003.

Results: The mean age of the patients was 67 years (range, 30-90 years). Three episodes (3%) were community acquired. Adequate antifungal therapy was given to 78 patients (78%). Cancer (38.5%) and diabetes mellitus (36.3%) were the 2 most common underlying diseases. The most frequent risk factors identified for candidemia were prior broad-spectrum antibiotic use (84.6%), central venous catheterization (83.5%) and *Candida* colonization (79.5%). The most frequent isolates were *Candida albicans* (64.8%) and *Candida tropicalis* (19.8%). All of the *C. albicans* and *C. tropicalis* isolates were sensitive to fluconazole (minimal inhibitory concentration ≤8 μg/mL). Susceptibility to amphotericin B and fluconazole was found in 96.7% (88/91) and 95.6% (87/91) of *Candida* spp., respectively. Risk factors for mortality due to candidemia in the univariate analysis included central venous catheterization, shock, and high Acute Physiology and Chronic Health Evaluation II (APACHE II) score. APACHE II score was the only independent prognostic factor in the multivariate analysis.

Conclusions: Candidemia has a high mortality rate and *C. albicans* remains the most common isolate. Fluconazole and amphotericin B maintained good in vitro antifungal activity against *Candida* spp. APACHE II score was the only independent factor for mortality in patients with candidemia.

Key words: Antifungal agents, *Candida*, fungemia, microbial sensitivity tests, risk factors

Introduction

Bloodstream infections due to *Candida* spp. have become an important cause of morbidity and mortality in hospitalized patients [1-3]. Over the past 2 decades, *Candida* spp. have become the fourth most common cause of nosocomial bloodstream infections in the United States [4]. In northern Taiwan, *Candida* spp. are the leading pathogens of nosocomial bloodstream infections [5]. In addition, concerns about the emerging resistance of *Candida* spp. to azoles and the variable susceptibility of the non-albicans *Candida* spp. to fluconazole are increasing because of the extensive use of fluconazole treatment and prophylaxis in immunocompromised patients [6,7].

The aim of this retrospective study was to analyze the incidence, demographic features, risk factors for mortality, antifungal susceptibilities, and outcome of bloodstream infections due to *Candida* spp. in Changhua Christian Hospital, a 1600-bed teaching hospital in central Taiwan.

Methods

Clinical characteristics of the patients

The medical records of all patients with positive blood cultures for *Candida* spp. isolated in the microbiologic laboratory of Changhua Christian Hospital between

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January 1, 2001 and July 30, 2003 were reviewed. Data collected from the medical records of adult patients (>16 years of age) whose blood cultures were positive for *Candida* spp. included demographic characteristics, underlying diseases (e.g., malignancy, diabetes mellitus, renal failure, liver cirrhosis), other associated conditions (e.g., preceding bacteremia, *Candida* colonization, neutropenia, broad-spectrum antibiotic use, central venous catheterization, shock, parenteral nutrition, abdominal surgery, and steroid use), Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, and outcome.

Definitions

Candidemia was documented by at least 1 positive culture from a peripheral blood specimen. Episodes of candidemia were categorized as community-aquired or nosocomial following the definitions of the Centers for Disease Control and Prevention in 1988 [8]. The classification of *Candida* colonization in non-sterile specimens (such as urine, stool, pus from surgical wound) and sterile specimens (such as central venous catheter [CVC] tip) required that the colonizing organism was the same member of *Candida* spp. as that isolated in subsequent blood culture(s), and that the cultures were performed within the 14 days preceding candidemia onset. Neutropenia was defined as a neutrophil count of <500 cells/mm^3. Central venous catheterization was defined as inserted or retained within 2 weeks of the onset of candidemia [9,10]. Shock was defined as a decrease in systolic blood pressure to less than 90 mm Hg or a decrease of at least 40 mm Hg below baseline blood pressure despite adequate fluid resuscitation. Corticosteroids treatment was defined as use of a dose equivalent to at least 20 mg/day prednisolone for more than 7 days within 4 weeks of the onset of candidemia [10,11]. Abdominal surgical procedure was included in the analysis of potential risk factors for mortality if it had been performed within 1 month of the onset of candidemia [9,10]. Severity of illness was assessed by the APACHE II score. Antifungal therapy was considered to be adequate if antifungal agents were active in vitro against the corresponding isolate, and given at an adequate dosage via an appropriate route for at least 3 days after obtaining blood cultures that yielded positive results. Patients who received less than 3 days of antifungal therapy or no antifungal therapy were defined as having received inadequate therapy.

Outcome was defined as survival until discharge or death. Patients were excluded from the analyses if they were transferred to another hospital in critical status and lost to follow-up. Mortality was considered to be related to candidemia if the patient was being treated for candidemia when death occurred, unless clinical and pathological data clearly suggested otherwise. Only patients with candidemia-related mortality were included in the analysis of factors influencing mortality.

Species identification and antifungal susceptibility testing

Blood isolates were identified by the Vitek II YBC system (BioMerieux Vitek, Hazelwood, MO, USA). Prior to testing, each isolate was subcultured at least twice on Sabouraud dextrose agar to ensure viability, purity, and optimal growth characteristics. All yeasts were maintained at -70°C.

The susceptibility of each isolate was tested to 4 antifungal agents, including amphotericin B (concentration range, 0.002 to 32 μg/mL), fluconazole (0.016 to 256 μg/mL), itraconazole (0.002 to 32 μg/mL), and ketoconazole (0.002 to 32 μg/mL) by the E-test method (AB Biodisk, Stockholm, Sweden) according to the manufacturer's instructions. The QC strain *Candida glabrata* ATCC 2001 was selected for testing. Briefly, E-test was performed by inoculation on Sabouraud dextrose agar. The inoculum was prepared from growth on Sabouraud dextrose agar subcultures incubated at 30°C for 48 h. Colonies were suspended in 0.85% saline and the turbidity of the resulting suspension was adjusted to a calibrated 0.5 McFarland standard. The E-test strips were applied after the excess moisture had been absorbed into the agar. The plates were incubated at 35°C, and the results were read after 24 h.

Interpretive breakpoints defined by the National Committee for Clinical Laboratory Standards (NCCLS) were used for fluconazole and itraconazole [12]. For fluconazole, minimal inhibitory concentration (MIC) ≤8 μg/mL and MIC ≥64 μg/mL were classified as susceptible and resistant, respectively. For itraconazole, MIC ≤0.125 μg/mL and MIC ≥1 μg/mL were classified as susceptible and resistant, respectively. Interpretive breakpoints for amphotericin B have not been established by the NCCLS. However, when isolates that appeared to be resistant to amphotericin B in animal models were tested by the E-test with Roswell Park Memorial Institute (RPMI) 1640 medium, MICs

≥30.38 μg/mL were obtained [13,14]. For ketoconazole, no specific breakpoints have been proposed, but aggregate data suggest that isolates for ketoconazole with an MIC >0.125 μg/mL by M27-A are less likely to respond [15].

Statistical analysis

Univariate analyses were performed to identify risk factors associated with candidemia-related death. For categorical measures, Pearson's chi-squared or Fisher's exact test was used as appropriate. For continuous measures, unpaired Student's *t* test was used. A value of $p<0.05$ was considered statistically significant. Multivariate analyses were performed to identify independent factors associated with candidemia-related death using stepwise logistic regression. Factors that were significant on the univariate analyses were entered into the multiple logistic regression model.

Results

From January 2001 to June 2003, there were 91 episodes of candidemia in 91 patients. The clinical characteristics of these 91 patients are summarized in Table 1. Three episodes (3%) were community-acquired and 88 (97%) were nosocomial in origin. The clinical characteristics of the 3 patients with community-acquired candidemia were as follows: 1 had diabetes mellitus and was chronically bedridden at home with a huge bedsore; 1 had chronic obstructive pulmonary disease and received long-term steroid therapy; the other had diabetes mellitus, renal failure and urosepsis. The incidence of nosocomial candidemia was 7.6 per 10,000 discharges. More cases of nosocomial candidemia were diagnosed in the surgical intensive care unit (37.5%) than in any other unit.

The most frequently identified risk factors for candidemia were treatment with broad-spectrum antibiotics (84.6%) and central venous catheterization (83.5%). The overall percentage of episodes with *Candida* spp. colonization was 79.5% (66/83), including 53.2% (33/62) in urine specimens, 9.6% (5/52) in sputum specimens, 28.2% (11/39) in pus specimens from wound or drainage tube, and 70.7% (29/41) in CVC tip specimens.

Species distribution of *Candida* bloodstream isolates and antifungal susceptibility

The frequency of bloodstream infection due to various species of *Candida* and in vitro susceptibilities to fluconazole, itraconazole, ketoconzole and amphotericin B as determined by E-test are shown in Table 2.

Outcome

Thirteen patients were excluded from the outcome evaluation for the following reasons: 10 patients died of causes unrelated to candidemia, including death due to underlying malignancy in 6 and due to secondary bacteremia in 4; and 3 patients were transferred to other hospitals in critical status. Univariate analyses of risk factors for mortality in the 78 patients with candidemia included in the analysis are shown in Table 3. The overall case fatality rate in this study was 60% (47/78). Significant risk factors for mortality included higher APACHE II score, central venous catheterization and shock. APACHE II score was the only independent factor associated with candidemia-related death in the multivariate analysis (Table 4).

Table 1. Clinical characteristics of 91 candidemia patients

Variable	Mean ± SD (range) or no. (%)
Age (years)	67 ± 12 (30-90)
Gender (male)	56%
Duration from admission to candidemia (days)	19 ± 17 (0-107)
Delay from candidemia onset to antifungal therapy (days)	2 ± 3 (–11-8)
Days of parenteral nutrition	23 ± 13
APACHE II score	20 ± 8 (3 ± 38)
Admitting ward	88 (100)
Surgery ward	13 (14.8)
Medical ward, non hemato-oncology	9 (10.2)
Medical ward, hemato-oncology	11 (12.5)
MICU	22 (25)
SICU	33 (37.5)
Underlying disease	
Malignancy	38.5
Diabetic mellitus	36.3
Renal failure	28.6
Liver cirrhosis	9.9
Risk factors for candidemia	
Broad-spectrum antibiotics	84.6
Central venous catheterization	83.5
Candida colonization	79.5 (66/83)[a]
Parenteral nutrition	40.7
Abdominal surgery	39.6
Corticosteroid use	30.8
Neutropenia	5.5

Abbreviations: SD = standard deviation; APACHE II = Acute Physiology and Chronic Health Evaluation II; MICU = medical intensive care unit; SICU = surgical intensive care unit

[a]Our investigation rate was 91% (83/91).

Discussion

During the 30-month period of this survey, the incidence of nosocomial candidemia was 7.6 per 10,000 discharges. *C. albicans* accounted for 64.8% of the total fungal isolates from blood in this study, which is a higher percentage than in reports from tertiary care hospitals in northern Taiwan (48%), southern Taiwan (43%), the USA (55%), Canada (60%), Latin America (45%), and Europe (58%) [16-18]. The reason for the lower percentage of non-albicans candidemia in this study is not clear. The increased incidence of *C. glabrata* and *C. krusei* has been attributed to the use of azole antifungal derivatives and the selection of species resistant to azoles [19]. In our institution, routine use of azole antifungals for prophylaxis is low. In this study, all of the *C. albicans* and *C. tropicalis* isolates were sensitive to fluconazole (MIC ≤8 μg/mL). Only 4 *Candida* isolates (4.4%; 4/91) were resistant to fluconazole, indicating that fluconazole remains the drug of choice for empirical therapy of candidemia in our hospital. But the rate of resistance was still higher than that reported by the Taiwan surveillance of antimicrobial resistance of yeasts study in 2002 (2.4%; 3/126) [20].

Table 2. In vitro susceptibilities of *Candida* species to 4 antifungal agents

Species (no.)	Antifungal agent	MIC (μg/mL)	Range	MIC (μg/mL)		R (%)
				50%	90%	
C. albicans (59)	Amphotericin B	0.023	0.094	0.064	0.094	0
	Fluconazole	0.125	1.000	0.380	0.750	0
	Itraconazole	0.012	0.125	0.032	0.064	0
	Ketoconazole	0.003	0.016	0.008	0.012	
C. tropicalis (18)	Amphotericin B	0.013	0.125	0.074	0.125	0
	Fluconazole	0.250	1.500	0.500	1.000	0
	Itraconazole	0.016	0.470	0.032	0.380	0
	Ketoconazole	0.006	0.047	0.016	0.032	
C. guilliermondii (6)	Amphotericin B	0.019	0.190	0.157	0.190	0
	Fluconazole	6.000	32.000	12.000	32.000	0
	Itraconazole	1.500	12.000	2.750	12.000	100
	Ketoconazole	0.125	0.380	0.190	0.380	
C. parapsilosis (2)	Amphotericin B	0.094	0.094			0
	Fluconazole	0.750	1.000			0
	Itraconazole	0.016	0.064			0
	Ketoconazole	0.016	0.032			
C. krusei (1)	Amphotericin B	0.250	0.250			0
	Fluconazole	48.000	48.000			100
	Itraconazole	0.500	0.500			0
	Ketoconazole	0.380	0.380			
C. famata (1)	Amphotericin B	32.000	32.000			100
	Fluconazole	256.000	256.000			100
	Itraconazole	32.000	32.000			100
	Ketoconazole	32.000	32.000			
C. membranefaciens (2)	Amphotericin B	32.000	32.000			100
	Fluconazole	256.000	256.000			100
	Itraconazole	32.000	32.000			100
	Ketoconazole	32.000	32.000			
C. sake (1)	Amphotericin B	0.016	0.016			0
	Fluconazole	0.190	0.190			0
	Itraconazole	0.012	0.012			0
	Ketoconazole	0.003	0.003			
C. glabrata (1)	Amphotericin B	0.250	0.250			0
	Fluconazole	4.000	4.000			0
	Itraconazole	0.190	0.190			0
	Ketoconazole	0.094	0.094			

Abbreviations: MIC = minimal inhibitory concentration; R = resistance rate

Table 3. Univariate analyses of risk factors of candidemia-associated mortality in 78 candidemia patients

Variable	Survived (n = 31) Mean ± SD or no. (%)	Died (n = 47) Mean ± SD or no. (%)	*p*
Age (years)	64 ± 13	68 ± 12	0.089
Gender [male (%)]	18 (58)	23 (49)	0.429
Duration from admission to candidemia onset (days)	15 ± 12	20 ± 16	0.119
Delay from candidemia onset to antifungal therapy (days)	1.6 ± 3.5	1.4 ± 3.4	0.857
Days of parenteral nutrition	24 ± 11	20 ± 13	0.394
APACHE II score	15 ± 7	23 ± 7	<0.001
Malignancy	10 (32)	20 (43)	0.360
Diabetes mellitus	11 (36)	17 (36)	0.951
Renal failure	8 (26)	14 (30)	0.702
Liver cirrhosis	1 (3)	7 (15)	0.136
Broad-spectrum antibiotics	25 (81)	39 (83)	0.793
Central venous catheterization	22 (71)	42 (89)	0.038
Concomitant bacteremia	15 (48)	32 (68)	0.082
Shock	6 (19)	28 (60)	<0.001
Parenteral nutrition	13 (42)	19 (40)	0.894
Abdominal surgery	10 (32)	21 (45)	0.273
Steroid use	12 (39)	15 (32)	0.537
Removal of central venous catheter (%)	17 (77)	25 (60)	0.156
Neutropenia	0 (0)	4 (9)	0.250
Adequate antifungal therapy[a]	25 (81)	34 (72)	0.403
Candida spp.			
C. albicans	15 (48)	33 (70)	0.053
Non-albicans	16 (52)	14 (30)	

Abbreviations: SD = standard deviation; APACHE II = Acute Physiology and Chronic Health Evaluation II

[a]Antifungal therapy was considered to be adequate if antifungal agents were active in vitro against the corresponding isolate when the agent was given at an adequate dosage via an appropriate route for at least 3 days after a positive blood culture result.

Although drug susceptibility was assessed by E-test in this study, the agreement has been shown to be good between the E-test and NCCLS methods for fluconazole and amphotericin B [21]. Another study from Taiwan showed the E-test had equivalent performance to the broth macrodilution method, suggesting that E-test can be used as an alternative technique for determining MICs in antifungal susceptibility testing [22].

Candidemia has been associated with a number of underlying diseases. Cancer (38.5%) was the most common underlying disease in this study, followed by diabetes mellitus (36.3%) and renal failure (28.6%). The most common risk factors for candidemia were prior

Table 4. Multivariate analysis of predictors of candidemia-related mortality

Variable	Total	Dead	Odds ratio	95% CI	*p*
APACHE II score (mean ± SD)	78	22.6 ± 6.6	1.2	1.0-1.3	0.009
Median (range)		22 (11-38)			
Delay from candidemia onset to antifungal therapy (days) [mean ± SD]	78	1.4 ± 3.4	0.9	0.8-1.1	0.509
Median (range)		2 (–11-6)			
Central venous catheter [n (%)]					
No	14	5 (35.7)	1.0		
Yes but removed	22	17 (77.3)	3.4	0.4-32.3	0.285
Yes but retained	42	25 (59.5)	2.1	0.3-15.8	0.476
Adequate antifungal therapy [n (%)]					
Yes	59	34 (57.6)	1.0		
No	19	13 (68.4)	6.0	0.3-108.7	0.225

Abbreviations: CI = confidence interval; SD = standard deviation; APACHE II = Acute Physiology and Chronic Health Evaluation II

antibiotic use (84.6%), central venous catheterization (83.5%) and *Candida* colonization (79.5%). Only 3% of the candidemias were not nosocomial, but all 3 of the patients had identifiable risk factors.

Previous studies showed the importance of *Candida* colonization as a risk factor for invasive infection because the pathogenesis of *Candida* infection follows progressively from colonization to local amplification and to invasion [23-27]. In this study, *Candida* colonization preceded candidemia in 79.5% of episodes (66/83), with the highest colonization rates in urine (40%) and CVC (35%).

The overall mortality in this series was 60%. This is within the range of previously reported mortality rates for candidemia, from 40% to 76% [10,16,28,29]. In the present study, univariate analysis revealed that risk factors for mortality in patients with candidemia included central venous catheterization, high APACHE II score, and shock; however, APACHE II score was the only independent factor predictor of outcome in the multivariate analysis (p=0.009). In contrast with previous studies, retention of CVC, neutropenia or inadequate antifungal treatment was not associated with a higher mortality rate [10,28,29].

In conclusion, candidemia has a high mortality rate and *C. albicans* remains the most common isolate. Fluconazole and amphotericin B maintained good in vitro antifungal activity against *Candida* spp.

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