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Original Article

Adult candidemia at a medical center in northern Taiwan: a retrospective study

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Background and Purpose: Candidemia has been associated with a very high mortality. This study evaluated the predictors of candidemia-related mortality at a teaching hospital in northern Taiwan.

Methods: We conducted a retrospective analysis of adult patients with candidemia between September 2003 and May 2005. A stepwise logistic regression analysis was performed to determine the predictors of candidemia-associated mortality. All *Candida* isolates were identified to species by use of the ATB ID 32C kit and their susceptibilities to antifungal agents were tested by ATB Fungus 2 system.

Results: 179 episodes in 174 adult patients with candidemia were identified retrospectively. The predictors of mortality included duration of prior antibiotics ≥28 days, Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥23 and retention of central venous catheters (CVCs). There was no statistically significant association between the time to the start of antifungal therapy and mortality from nosocomial candidemia. In addition, there was no significant association between the time to CVC removal and mortality after stratification by APACHE II score.

Conclusions: Despite effective antifungal therapy after the onset of candidemia in more than half of the patients studied, mortality remained very high, especially in the groups with longer duration of prior antibiotic treatment, higher APACHE II score and CVC retention. Timing of CVC removal after onset of candidemia was not correlated with mortality.

Key words: Antifungal agents; Candidiasis; Fungemia; Mortality; Risk factors

Introduction

Candida spp. account for approximately 15% of total hospital-acquired infections and more than 72% of nosocomial fungal infections, and have become the fourth most common cause of nosocomial bloodstream infection in the United States [1]. The infection rate increased 219% to 487% between 1980 and 1989 [2,3] and this trend has continued into the last decade [1]. In Taiwan, candidemia was the most common nosocomial bloodstream infection in a reported study by Chen et al [4].

In several reports, bloodstream infection due to *Candida* spp. led to a greater mortality than expected from the underlying disease alone [5-7]. A recent review of candidemia identified crude mortality rates of 44% to 46% in Switzerland, 44% to 45% in Spain, and 30% to 52% in Canada [8]. In Taiwan, the reported mortality rates of candidemia were about 43% to 60% [9-11]. High crude mortality in patients with candidemia is thus a global trend. We retrospectively reviewed our experience of candidemia from 2003 to 2005 to determine the predictors of candidemia-associated mortality and to identify possible strategies to lower this mortality.

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Methods

Study population

We enrolled adult patients with candidemia between September 2003 and May 2005 at the Taipei Veterans General Hospital, Taipei, Taiwan, a 2900-bed tertiary referral medical center with special units for bone marrow and solid organ transplantation, burn care, and intensive care. The medical records of patients were reviewed and data including demographic characteristics, medical history, invasive procedures, medications, laboratory data and outcome were collected for analysis.

Definition of terms

Candidemia was defined as the presence of positive blood culture of *Candida* spp. with concomitant signs and symptoms of infection. Candidemia was considered to be nosocomial if it occurred more than 48 h after admission. Death was considered to be attributable to candidemia if any of the following was noted during the same hospital stay: death within 7 days after a positive blood culture for *Candida* spp. without other cause for death; death in the presence of other clinical evidence of persistent candidiasis (for example, persistent fever, hypotension, or positive cultures for *Candida* spp. at clinically involved sites, such as peritoneal fluid, renal abscess or endophthalmitis); autopsy evidence of disseminated candidiasis; or cause of death as candidemia on the death certificate [11,12]. The patient was considered a survivor of candidemia if ether of the following was noted during the same hospital stay: survival at discharge or improvement of candidemia-associated symptoms without recurrence within 30 days.

According to the Sepsis-related Organ Failure Score criteria [13], the diagnosis of respiratory failure is based on the ratio of arterial oxygen tension (PaO_2) to fractional inspired oxygen (FiO_2) less than 200 mm Hg. The severity of initial presentation of candidemia was assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II score 72 h after the occurrence of candidemia. Corticosteroid treatment was defined as the use of a dose equivalent to at least 20 mg prednisolone per day for more than 7 days within 4 weeks of the onset of candidemia [14,15]. The presence of invasive procedures was defined as invasive instruments existing at the time of onset of candidemia. Acid suppressant therapy was defined as the use of proton pump inhibitors or histamine H2 blockers for more than 7 days within 4 weeks of the onset of candidemia.

Species identification and antifungal susceptibility testing

Blood samples were tested daily for microbial growth by use of the BACTEC® NR-660 system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA). Organisms were initially identified by germ tube analysis and colony morphology on brain heart infusion agar. If necessary, they were determined by standard biochemical testing with ATB ID 32C kit (bioMérieux Inc., Hazelwood, MO, USA) and Yeast Biochemical Card (bioMérieux Vitek, Inc., Hazelwood, MO, USA).

Susceptibility testing of isolates was performed using 4 antifungal agents (flucytosine, itraconazole, fluconazole and amphotericin B) with the ATB Fungus 2 system (bioMérieux SA, Marcy-l'Etoile, France) according to the manufacturer's instructions. Susceptibilities of *Candida* spp. to flucytosine, itraconazole, fluconazole and amphotericin B read by ATB instrument were identical to the minimal inhibitory concentration (MIC) values of ≤4, ≤0.125, ≤8 and ≤2 mg/L, respectively [16,17].

Statistical analysis

Univariate analyses were used to identify the risk factors associated with candidemia-related death. Pearson's chi-squared or Fisher's exact 2-tailed test was used to examine nominal data and unpaired Student's *t* test used for continuous data. A value of $p<0.05$ was considered statistically significant. The independent predictors of candidemia-associated mortality were identified by stepwise logistic regression of multivariate analysis for the significant risk factors on the univariate analyses. Statistical Package for the Social Sciences (SPSS) for Windows (Version 11.5; SPSS, Chicago, IL, USA) software was used for statistical analysis.

Results

A total of 179 episodes were identified retrospectively in 174 adult patients with candidemia; their demographic data and clinical characteristics are summarized in Table 1. Sixty seven percent of patients were male and the mean age was 67 years (range, 21-91 years). The overall mean (± standard deviation) duration of hospitalization was 64 ± 50 days and 89.4% of infections were nosocomial. The mean duration of

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Table 1. Clinical characteristics of 179 adult episodes of candidemia

Variable	No. (%)
Age (years; mean ± SD)	67 ± 15
Male gender	120 (67.0)
Nosocomial candidemia	160 (89.4)
Duration from admission to symptoms of nosocomial candidemia (days; mean ± SD)	38 ± 37
Duration of hospitalization (days; mean ± SD)	64 ± 50
Duration of admission in ICU before candidemia (days; mean ± SD)	8 ± 19
Underlying disease	
Chronic respiratory failure	39 (21.8)
Solid tumor	89 (49.7)
Diabetes mellitus	43 (24.0)
Duration of antibiotics used before candidemia (days; mean ± SD)	25 ± 31
Steroid therapy	45 (25.1)
Acid suppressant therapy	96 (53.6)
Total parenteral nutrition	59 (33.0)
Symptoms and signs	
Fever	172 (96.1)
Tachypnea	117 (65.4)
Tachycardia	176 (98.3)
Shock	68 (38.0)
Acute renal failure	52 (29.1)
Acute respiratory failure	34 (19.0)
Conscious change	59 (33.0)
Leukocytosis	90 (50.3)
Thrombocytopenia	99 (55.3)
APACHE II score (mean ± SD)	22 ± 7
Invasive procedure	
Central venous catheterization	164 (91.6)
Foley catheter	107 (59.8)
Endotracheal tube	61 (34.1)

Abbreviations: SD = standard deviation; ICU = intensive care unit; APACHE = Acute Physiology and Chronic Health Evaluation

antibiotic use before onset of candidemia was 25 ± 31 days. Tachycardia, fever and central venous catheterization were noted in almost all episodes. The mean APACHE II score was 22 ± 7 points.

Candida albicans was the leading species (63.7%), followed by *Candida tropicalis*, *Candida glabrata* and *Candida parapsilosis*. The in vitro susceptibilities of *Candida* spp. to antifungal agents are listed in Table 2. Almost all isolates were susceptible to the four antifungal agents. In 26 episodes of nosocomial and community-acquired candidemia, treatment was shifted from fluconazole to amphotericin B due to the persistence of septic status and in 10 of these episodes patients survived candidemia. In 9 episodes, antifungal therapy was being used at the time of onset of candidemia and the mortality in this group was 88.9%. In 6 of these 9 episodes, fluconazole was continued due to the isolates being susceptible to fluconazole; all of these patients died from candidemia. In 2 of the 9 episodes, fluconazole was shifted to amphotericin B, and 1 patient survived.

The overall mortality attributable to candidemia was 56.4% (101/179). Three of the 78 non-fatal episodes did not meet the criteria of the survivor due to death within 30 days and were excluded. Risk factors of mortality in the univariate analysis are listed in Table 3. In multivariate logistic regression analysis, statistically significant risk factors were identified as duration of prior antibiotic usage ≥28 days, APACHE II score ≥23 and retention of central venous catheter (CVC) [Table 4].

In order to assess the relationship between mortality and time to removal of CVCs in patients with nosocomial candidemia, the interval between removal of CVC and the culture of the first blood sample positive for yeast was calculated for 108 episodes in which the CVCs were removed after the onset of candidemia. There was no statistically significant difference or trend after analysis by Pearson's chi-squared test, despite stratification by APACHE II score (Table 5).

Antifungal agents were used for nosocomial candidemia in 144 episodes. Nine episodes were considered as breakthrough or persistent infection because of use of antifungal therapy at the time of onset of candidemia. In order to assess the relationship between mortality and time to the start of antifungal therapy in patients with nosocomial candidemia, we calculated the interval between the date of initiation of antifungal therapy and the culture date of the first blood sample positive for yeast for the other 135 episodes (Table 6). There was no statistically significant difference or trend after analysis. In addition, there was no statistically significant difference in mortality between cases initially treated with fluconazole and amphotericin B (52.8% vs 56.3%; p=0.998). Of the 119 nosocomial candidemia cases initially treated with fluconazole, 24 were shifted to amphotericin B because of persistent septic status of who 10 survived.

Discussion

The ratio of *C. albicans* in all episodes with candidemia was similar to that reported by other institutions in Taiwan [4,9] and was higher than reported in the period 1996 to 1999 [18]. Non-*albicans Candida*

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Table 2. In vitro susceptibility data of *Candida* spp.

Species	Flucytosine No. susceptible (%) MIC ≤4 mg/L	Fluconazole No. susceptible (%) MIC ≤8 mg/L	Itraconazole No. susceptible (%) MIC ≤0.125 mg/L	Amphotericin B No. susceptible (%) MIC ≤2 mg/L
Candida albicans (n = 114)	114 (100.0)	114 (100.0)	114 (100.0)	114 (100.0)
Candida parapsilosis (n = 19)	19 (100.0)	19 (100.0)	19 (100.0)	19 (100.0)
Candida sake (n = 2)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)
Candida glabrata (n = 21)	21 (100.0)	20 (95.2)	20 (95.2)	21 (100.0)
Candida tropicalis (n = 22)	22 (100.0)	22 (100.0)	22 (100.0)	22 (100.0)
Candida pelliculosa (n = 1)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)

Abbreviation: MIC = minimal inhibitory concentration

spp. were not as common as in studies in the United States [1] and Europe [19]. Data on susceptibility to antifungal agents were similar to previous results [18], presumably because of a low rate of use of azole antifungal agents for prophylaxis [20]. At another medical institution in Taiwan, stable susceptibility of *Candida* blood isolates to fluconazole was found, despite increasing consumption of this antifungal agent [21], but this phenomenon was not noted in several other countries [19,22-24]. Susceptibility to fluconazole was determined according to the National Committee for Clinical Laboratory Standards criteria [25] and local data in Taiwan [26]. The dosage of fluconazole prescribed in our institution was 400 mg/day, equivalent to a dose/MIC value of >50 [27]. The mortality attributable to candidemia in our study was very high, despite treatment with fluconazole. Fluconazole MIC values ≥1 μg/mL as determined by flow cytometry in

Table 3. Univariate analysis of risk factors of candidemia-associated mortality in 176 episodes

Variable	Survival (n = 75) No. (%)	Death attributable to candidemia (n = 101) No. (%)	*p*
Age (≥65 years old)	50 (66.7)	68 (67.3)	1.000
Male gender	45 (60.0)	72 (71.3)	0.159
Duration of ICU admission before candidemia (days; mean ± SD)	8 ± 18.3	9 ± 19.3	0.732
Underlying disease			
Chronic respiratory failure	17 (22.7)	22 (21.8)	1.000
Solid tumor	32 (42.7)	54 (53.5)	0.206
Diabetes mellitus	23 (30.7)	20 (19.8)	0.138
Steroid therapy	18 (24.0)	26 (25.7)	0.930
Acid suppressant therapy	39 (52.0)	56 (55.4)	0.764
Total parenteral nutrition	22 (29.3)	36 (35.6)	0.472
Duration of antibiotic treatment before candidemia ≥28 days	12 (16.0)	35 (34.7)	0.009[a]
Symptoms and signs			
Acute respiratory failure	6 (8.0)	27 (26.7)	0.003[a]
Shock	21 (28.0)	45 (44.6)	0.037[a]
Acute renal failure	13 (17.3)	38 (37.6)	0.006[a]
Consciousness change	19 (25.3)	39 (38.6)	0.091
Leukocytosis	33 (44.0)	55 (54.5)	0.223
Thrombocytopenia	30 (40.0)	67 (66.3)	0.001[a]
APACHE II score ≥23	21 (28.0)	55 (54.5)	0.001[a]
Candida albicans	44 (58.7)	69 (68.3)	0.245
Invasive procedure			
Foley catheter	44 (58.7)	61 (60.4)	0.939
Endotracheal tube	24 (32.0)	36 (35.6)	0.731
Therapy			
Lack of antifungal therapy	3 (4.0)	17 (16.8)	0.016[a]
Retention of central venous catheter	7/69 (10.1)	40/92 (43.5)	<0.001[a]

Abbreviations: ICU = intensive care unit; SD = standard deviation; APACHE = Acute Physiology and Chronic Health Evaluation
[a]$p<0.05$.

Table 4. Multivariate logistic regression analysis of risk factors associated with mortality in episodes of candidemia

Variable	OR (95% CI)	*p*
Thrombocytopenia	2.102 (0.981-4.505)	0.056
APACHE II score ≥23	3.167 (1.305-7.685)	0.011[a]
Shock	1.699 (0.749-3.855)	0.204
Acute renal failure	1.539 (0.620-3.821)	0.353
Acute respiratory failure	1.405 (0.426-4.634)	0.576
Duration of antibiotic treatment before candidemia ≥28 days	3.527 (1.458-8.528)	0.005[a]
Retention of central venous catheter	6.861 (2.491-18.896)	<0.001[a]
Lack of antifungal therapy	3.259 (0.528-20.123)	0.203

Abbreviations: OR = odds ratio; CI = confidence interval; APACHE = Acute Physiology and Chronic Health Evaluation
[a]$p<0.05$.

1 study [28], and ≥2 μg/mL as determined by E-test in another study [10], were reported to be associated with higher mortality when patients were treated with fluconazole. There was no significant difference in mortality between initial treatment with fluconazole and amphotericin B in our study, but some cases without response to fluconazole survived after shifting to amphotericin B. Stable susceptibility to amphotericin B in *Candida* spp. was noted in spite of increasing use of this agent [29]. It might be appropriate to lower the cut-off value of susceptibility to fluconazole in the ATB Fungus test. Amphotericin B should be the first choice for treatment of severe candidemia.

The gastrointestinal tract as a primary origin of *Candida* infection was first proposed in 1969 [30], and the relationship is supported by multiple studies [31-33]. However, the very high rate of presence of CVCs in patients with candidemia noted in our study and other studies [9-11,34-38] is consistent with a role of these devices in the development of candidemia. Biofilm production has been implicated as a potential virulence factor for *C. parapsilosis* and associated with the stronger capacity to colonize indwelling CVCs [39]. In addition, the large size of *Candida* hyphae and pseudohyphae may preclude their phagocytosis by macrophages, and invasion of the vascular structure facilitates dissemination of *Candida* [40]. CVCs are considered the prominent final site of *Candida* infection and can lead to thrombophlebitis with seeding of organisms into the clot [41]. Removal of CVCs was associated with lower mortality in our study and 2 other studies [42,43]. We considered the presence of CVCs not only as a marker for severity of illness, but also a predisposing factor for the persistence of candidemia, and thus CVC removal could reasonably be expected to decrease mortality from candidemia.

APACHE II score was the most common independent predictor of candidemia-associated mortality reported in other institutions of Taiwan [9,11]. Multiple parameters calculated for APACHE II score were very useful in the prediction of candidemia-associated mortality. Broad-spectrum antibiotic therapy was associated with the occurrence of candidemia in many reports [9,14,44]. Longer duration of antibiotic use before candidemia may reflect a more difficult clinical condition of persistent infectious focus or compromised immune status. Although there was no evidence that coinfection with *Candida* spp. or more compromised immune status would increase mortality, longer duration of antibiotic therapy before the onset of candidemia was associated with a higher mortality rate in our study.

Table 5. Relationship between candidemia-associated mortality and time to removal of central venous catheter (CVC) in the patients with nosocomial candidemia

Risk factors	Mortality No. of deaths/total episodes (%)				*p* for trend
	Days to removal of CVC				
	≤3 (n = 67)	4-6 (n = 25)	≥7 (n = 16)	*p*	
APACHE II score <23	15/41 (36.6)	4/13 (30.8)	3/11 (27.3)	0.817	0.531
APACHE II score ≥23	17/26 (65.4)	6/12 (50.0)	3/5 (60.0)	0.666	0.563
Total	32/67 (47.8)	10/25 (40.0)	6/16 (37.5)	0.667	0.384

Abbreviation: APACHE = Acute Physiology and Chronic Health Evaluation

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Table 6. Relationship between candidemia-associated mortality and time to initiation of antifungal therapy in patients with nosocomial candidemia

Antifungal agent	Mortality No. of deaths/total episodes (%)					*p* for trend
	Days to initiation of antifungal therapy					
	0 (n = 6)	1 (n = 19)	2 (n = 29)	≥3 (n = 81)	*p*	
Fluconazole	2/5 (40.0)	8/16 (50.0)	12/27 (44.4)	38/71 (53.5)	0.831	0.487
Amphotericin B	0/1 (0.0)	1/3 (33.3)	1/2 (50.0)	6/9 (66.7)	0.517	0.151
Voriconazole	-	-	-	1/1 (100.0)	-	(-)
Total	2/6 (33.3)	9/19 (47.4)	13/29 (44.8)	44/81 (54.3)	0.615	0.233

In the study by Morrell et al, patients receiving antifungal therapy more than 12 h after a blood sample was obtained for culture (n = 148, 94.3%) had 2.09-fold (p=0.018) higher mortality than those with culture within 12 h (n = 9, 5.7%), after controlling for APACHE II score [45]. Garey et al reported that earlier fluconazole therapy was associated with lower mortality in 172 patients with candidemia (p=0.0009, chi-squared test for trend) [46]. Similar analysis was conducted for our data. A relatively lower mortality rate was noted in the group receiving earlier antifungal therapy, but statistical significance was not reached. Rare episodes in the group receiving earlier antifungal therapy precluded the demonstration of a trend in this regard, and made it difficult to stratify according to the severity of initial presentation. Antifungal agents were usually used after report of culture in our hospital, and lack of empirical antifungal therapy before positive report of blood culture may be due in part to the medical insurance payment system in place in Taiwan, and also to lack of awareness of clinicians of the urgency of this clinical situation.

Earlier removal of CVCs was associated with better survival rate in 2 studies [47,48]. In Karlowicz et al's study [47], all patients were infants. In Raad et al's study [48], removal within 3 days after onset of candidemia improved response to antifungal therapy in the patients with catheter-related candidemia. We did not demonstrate similar findings, despite patients being stratified by APACHE II score. However, CVCs were replaced soon after being removed in most of our patients with candidemia, especially those receiving total parenteral nutrition. Recolonization before eradication of intravenous pathogens may be a problem in this regard.

In conclusion, mortality was very high in patients with candidemia, especially in the groups with higher APACHE II score, longer duration of prior antibiotic use, and retention of CVCs. Although the isolates showed susceptibility to fluconazole, apparent failure of this agent was noted in our study and amphotericin B proved effective in some patients that were unresponsive to fluconazole. Removal of CVCs was mandatory for treating candidemia, but timing was undecided. Prompt empirical antifungal therapy is still advised for treatment of suspected candidemia.

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