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ORIGINAL ARTICLE

Candida albicans versus non-*albicans* bloodstream infections: The comparison of risk factors and outcome

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KEYWORDS
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Background: Candidemia caused by non-*albicans Candida* spp. is of special concern because of its high drug resistance and increase in prevalence. In clinical practice, early identification of non-*albicans* candidemia is crucial. We investigated the outcome in patients with candidemia caused by *Candida albicans* and *Candida* non-*albicans*.
Methods: We retrospectively evaluated candidemic patients from October 2007 to July 2009. Underlying diseases, predisposing factors, laboratory data, and outcome were analyzed.
Results: One hundred and eight patients of candidemia were enrolled. *Candida albicans* and non-*albicans* spp. were responsible for 56.5% (61 of 108) and 43.5% (47 of 108) of candidemia cases, respectively. Among patients with non-*albicans* candidemia, significantly more patients had neutropenia ($p = 0.001$) and less patients had candiduria ($p = 0.001$) and intensive care unit stay ($p = 0.002$) in comparison with those with *C albicans* candidemia. All-cause Day 7 mortality was high in both *C albicans* and non-*albicans* spp. candidemia [44.3% (27 of 61) *vs.* 29.8% (14 of 47)]. Multivariate analysis revealed that poor renal function (odds ratio, 1.035; 95% confidence interval, 1.001–1.071; $p = 0.04$) and shock (odds ratio, 19.4; 95% confidence interval, 2.53–149.5; $p = 0.004$) are independent risk factors for fatal candidemia.

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Conclusions: The outcome of candidemia was poor. The identified risk factors may help us to differentiate fatal candidemia in early infection.

Introduction

Candidemia is a serious health care—related infection and is associated with a poor prognosis. The incidence of candidemia is increasing significantly in recent years. It is the fourth common cause of bloodstream infections (BSIs) in U.S. hospitals and the leading cause of nosocomial BSIs in some hospitals in Taiwan.[1—4] The major risk factors for candidemia include intravascular catheters, parenteral hyperalimentation, and broad-spectrum antibiotics. In terms of *Candida* spp., a recent shift from *Candida albicans* to non-*albicans* has been reported.[5,6] Non-*albicans* candidemia (NAC) has been shown to be responsible for 36—63% of all candidemia cases.[7—9] Furthermore, certain *Candida* spp., such as *Candida glabrata*, have a tendency toward decreased susceptibility to fluconazole, and others, such as *Candida krusei*, are resistant to fluconazole.[10,11] Several reports have suggested that delayed initiation of antifungal therapy for candidemia is associated with increased mortality.[12,13] NAC patients tend to be less susceptible to fluconazole than *C albicans* candidemia patients.[14—16] Thus, early and appropriate usage of antifungal therapy is important for NAC. In the present study, we compared the risk factors and prognosis of patients with *C albicans* candidemia and NAC.

Methods

Patient enrollment and data collection

We retrospectively evaluated the medical and microbiological data of all cases of candidemia in Tri-Service General Hospital from October 2007 to July 2009. Demographic data, comorbidities, microbiological data, and patients' outcomes were evaluated. The inclusion criteria comprised age greater than 16 years and at least one positive blood culture yielding *Candida*. Patients with candidemia caused by more than one species were excluded. For patients with multiple candidemic episodes, only the first episode was included.

Mycological studies

Blood cultures of present cases were performed using BacT/ALERT Microbial Detection System (bioMèrieux SA, Marcy-l'Etoile, France). The isolates of the present cases initially grew on Sabouraud dextrose agar and then identified in our laboratory by morphological (CHROMagar and corn meal agar; Beckton, Dickinson and Company, Paris, France) and biochemical methods (Vitek 2 YST, bioMèrieux, USA). Susceptibility to antifungal agents was tested by the ATB Fungus 3 system (bioMèrieux SA) according to the manufacturer's instructions. Two reference strains, *Candida parasilosis* ATCC 22019 and *C krusei* ATCC 6258, were used as control strains for susceptibility testing. The reference breakpoints of minimal inhibition concentrations (MICs) were defined by Clinical and Laboratory Standards Institute in 2008. MICs less than or equal to 4, less than or equal to 8, less than or equal to 0.125, and less than or equal to 1 were considered susceptible to flucytosine, fluconazole, itraconazole, and voriconazole, respectively. Interpretive breakpoints for amphotericin B have not been established by the Clinical and Laboratory Standards Institute. Clinical and Laboratory Standards Institute developed and published an approved reference method for broth microdilution testing of yeast.[17—19] The acceptable percent essential agreement for MICs was set at greater than or equal to 90% for each antifungal agent against all organisms tested.

Study variables

Clinical data, including age at the time of diagnosis, gender, and underlying diseases, of 108 patients with candidemia were recorded on standardized forms. Diseases, including alcoholism, liver cirrhosis, heart failure, renal failure, solid organ malignancy, hematologic malignancy, diabetes, and neutropenia, were recorded. Predisposing factors that occurred within 30 days before the onset of candidemia were also collected. These included central venous catheter usage; presence of a prosthesis, implant, or indwelling of urinary catheter; receipt of mechanical ventilation; total parental nutrition or peripheral parental nutrition usage; receipt of corticosteroids; blood product transfusions; hemodialysis; gastrointestinal procedures and operations; concomitant infections; bacteremia; total number of antibiotics; candiduria; exposure to antifungal agents; and intensive care unit (ICU) stay. Laboratory data within 7 days before obtaining the first positive blood culture were analyzed.

Definitions

Candidemia was defined as at least one positive blood culture for *Candida* spp. in patients with symptoms or signs of infection. Neutropenia was defined as an absolute neutrophil count less than 500 cells/μL or less than 1,000 cells/μL, with a predicted nadir of less than 500 cells/μL. Presence of prosthesis/implant was defined as Port-A or peripherally inserted central catheter implantation. Receipt of corticosteroids was defined as the usage 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. Candiduria was defined as the presence of more than 100,000 CFU/mL of *Candida* spp. in the urine

sample obtained within 1 month of the candidemia. Gastrointestinal procedures and operations included endoscopic retrograde cholangiopancreatography; use of biliary tubes and percutaneous endoscopic gastrostomy tubes; and other abdominal surgical procedures. All-cause Day 7 mortality was defined as death that occurred within 1 week of the onset of candidemia. All-cause in-hospital mortality was defined as all death that occurred during hospitalization after the onset of candidemia. The severity of the initial presentation of candidemia was assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) III score after the occurrence of candidemia.

Statistical analysis

All statistical analyses were performed by using the SPSS for windows (Version 15.0; SPSS, Chicago, IL, USA). Univariate analysis using Pearson χ^2 test (for categorical measures) and unpaired Student's *t* test (for continuous measures) were performed to demonstrate the correlation of the possible risk factors of all-cause Day 7 mortality. A *p* value less than 0.05 was considered statistically significant. Multivariate analyses were performed to identify the independent factors associated with all-cause Day 7 mortality by using stepwise logistic regression.

Results

One hundred and eight patients of candidemia were enrolled in our study. *Candida albicans* and non-*albicans* spp. were responsible for 56.5% (61 of 108) and 43.5% (47 of 108) of candidemia cases, respectively. The distribution of *C* non-*albicans* spp. was as follows: *C glabrata*, 17.6% (19 of 108); *Candida tropicalis*, 13.0% (14 of 108); *C parasilosis*, 11.1% (12 of 108); *C krusei*, 1% (1 of 108); and *Candida haemonulonii*, 1% (1 of 108) (Table 1).

Among patients with NAC, significantly more patients had neutropenia ($p = 0.001$), and less patients had candiduria ($p = 0.001$) and ICU stay ($p = 0.002$) (Table 2). The patients with receipt of mechanical ventilation ($p = 0.109$) and indwelling of urinary catheter ($p = 0.097$) tend to have more *C albicans* BSIs when compared with non-*albicans* BSIs. However, these trends did not reach statistical significance.

Susceptibility to itraconazole between patients with *C albicans* BSIs and *C* non-*albicans* BSIs was statistically different [95.1% (58 of 61) *vs.* 61.7% (29 of 47), $p < 0.001$] (Table 3). The *in vitro* susceptibilities of *Candida* spp. to antifungal agents are listed in Table 4.

Among patients with candidemia, all-cause Day 7 mortality rate was 38.0% (41 of 108). Day 7 mortality rates of *C albicans* and NAC were demonstrated as 44.3% (27 of 61) and 29.8% (14 of 47) (Table 3). The respective all-cause Day 7 mortality rates among NAC were as follows: *C glabrata*, 31.6% (6 of 19); *C tropicalis*, 42.9% (6 of 14); *C parasilosis*, 8.3% (1 of 12); *C krusei*, 100% (1 of 1); and *Candida haemulonii*, 0% (0 of 1) (Table 1). Excluding patients with candidemia of *C krusei* and *C haemulonii* because of the small number of cases, patients with *C albicans* candidemia had the highest rate (44.2%) of all-cause Day 7 mortality, whereas those with *C parasilosis* candidemia had the lowest mortality rate. The crude all-cause in-hospital mortality rate was 55.6% (60 of 108). Patients with candidemia with poor outcome have been demonstrated. Using univariate analysis, receipt of corticosteroids ($p = 0.018$); blood product transfusion ($p = 0.003$); hemodialysis ($p = 0.012$); thrombocytopenia ($p = 0.001$); poor renal function (judged by blood urea nitrogen and creatinine, $p < 0.001$ respectively); and shock ($p < 0.001$) were found to be significantly associated with all-cause Day 7 mortality (Table 5). By multivariate analysis, only poor renal function (odds ratio, 1.035; 95% confidence interval, 1.001−1.071; $p = 0.04$) and shock (odds ratio, 19.4; 95% CI, 2.53−149.5; $p = 0.004$) were found to be independently associated with all-cause Day 7 mortality (Table 6).

Discussion

During the 22-month period of this survey, *C albicans* accounted for 56.5% of all candidemia cases in this study, which is higher than the reports of another tertiary care hospital in northern Taiwan (48%), lower than those of central Taiwan (64.8%), but close to those of the United States (55%) and Europe (58%).[20–22] Even though *C albicans* remains the most common species causing candidemia, the

Table 1 Distribution of *Candida* species and mortality rate of patients with candidemia

Species	Candidemia ($n = 108$)	All-cause Day 7 mortality ($n = 41$)		All-cause in-hospital mortality ($n = 60$)	
	n (%)	*n* (%)	Percentage of mortality in species of candidemia (%)	*n* (%)	Percentage of mortality in species of candidemia (%)
Candida albicans	61 (56.5)	27 (65.9)	44.3	36 (60.0)	59.0
non-*albicans Candida* species	47 (43.5)	14 (34.1)	29.8	24 (40.0)	51.1
Candida glabrata	19 (17.6)	6 (14.6)	31.6	12 (20.0)	63.2
Candida tropicalis	14 (13.0)	6 (14.6)	42.9	9 (15.0)	64.3
Candida parasilosis	12 (11.1)	1 (2.4)	8.3	2 (3.3)	16.6
Candida krusei	1 (1.0)	1 (2.4)	100	1 (1.7)	100
Candida haemulonii	1 (1.0)	0 (0)	0	0 (0)	0

Table 2 Demographic data of *Candida albicans* and non-*albicans* candidemia

Variables	*C albicans* ($n = 61$)	*C* non-*albicans* ($n = 47$)	*p*
	n (%)	*n* (%)	
Age, mean years ± SD (range)	70 ± 17 (23–95)	66 ± 15 (23–94)	0.102
Male sex	42 (68.9)	32 (68.1)	0.487
Underlying condition			
Alcoholism	1 (1.6)	2 (4.3)	0.387
Liver cirrhosis	6 (9.8)	3 (6.4)	0.417
Heart failure	8 (13.1)	4 (8.5)	0.361
Renal failure	12 (19.6)	13 (27.7)	0.268
Solid organ malignancy	24 (39.3)	23 (49.9)	0.217
Hematologic malignancy	1 (1.6)	2 (4.3)	0.387
Diabetes	20 (32.8)	15 (32.0)	0.513
Neutropenia	2 (3.3)	13 (27.7)	0.001*
Predisposing factors			
Central venous catheter use	35 (57.4)	22 (46.8)	0.185
Presence of prosthesis/implant	33 (54.1)	21 (44.7)	0.241
Indwelling of urinary catheter	45 (73.8)	28 (59.6)	0.097
Receipt of mechanical ventilation	37 (60.7)	22 (46.8)	0.109
TPN or PPN usage	38 (62.3)	24 (51.1)	0.163
Receipt of corticosteroids	9 (14.8)	3 (6.4)	0.160
Blood product transfusion	45 (73.8)	36 (76.6)	0.483
Hemodialysis	21 (34.4)	13 (27.7)	0.283
GI procedure and operation	15 (24.6)	8 (17.0)	0.260
Concomitant infections	57 (93.4)	44 (93.6)	0.649
Bacteremia	20 (32.8)	14 (29.8)	0.443
Total number of antibiotics, mean ± SD	3.76 ± 2.57	3.64 ± 2.85	0.624
Candiduria	38 (62.3)	13 (27.7)	0.001*
Exposure to antifungal therapy	6 (9.8)	8 (17.0)	0.180
ICU stay	43 (70.5)	19 (40.4)	0.002*

GI = gastrointestinal; ICU = intensive care unit; PPN = peripheral parental nutrition; SD = standard deviation; TPN = total parental nutrition.
* *p* value was statistically significant.

Table 3 Laboratory data, susceptibility of antifungal agents, and prognosis of candidemia (*C albicans* and non-*albicans*)

Variables	*C albicans* ($n = 61$)	*C* non-*albicans* ($n = 47$)	*p*
Laboratory data, mean ± SD			
White cell count ($\times 10^9$/L)	12,524 ± 7669	12,971 ± 9672	0.792
Hemoglobin (g/L)	9.5 ± 1.6	9.9 ± 1.5	0.173
Platelets ($\times 10^9$/L)	150,466 ± 112,767	146,000 ± 120,564	0.534
Blood urea nitrogen	56.3 ± 41.1	45.9 ± 43.3	0.224
Creatinine (μmol/L)	2.13 ± 1.51	1.63 ± 1.49	0.100
Alanine aminotransferase (U/L)	55.4 ± 118.1	51.8 ± 61.9	0.887
C-reactive protein (μmol/L)	15.3 ± 10.01	13.9 ± 10.74	0.553
Sodium	135.1 ± 9.2	133.6 ± 16.8	0.549
Potassium	3.66 ± 0.77	3.64 ± 0.88	0.907
No. of patients susceptible to antifungal agents, *n* (%)			
Flucytosine	61 (100)	47 (100)	1.000
Fluconazole	59 (96.7)	43 (91.5)	0.236
Itraconazole	58 (95.1)	29 (61.7)	<0.001*
Voriconazole	59 (96.7)	45 (95.7)	0.569
APACHE III score, mean ± SD	71 ± 42.7	57.2 ± 14.3	0.392
Outcome, *n* (%)			
Shock	35 (57.4)	24 (51.1)	0.322
All-cause Day 7 mortality	27 (44.3)	14 (29.8)	0.079
All-cause in-hospital mortality	36 (59.0)	24 (51.1)	0.270

APACHE = Acute Physiology and Chronic Health Evaluation; SD = standard deviation.
* *p* value was statistically significant.

Table 4 *In vitro* susceptibility data of *Candida* spp.

Species	Flucytosine, MIC $\leq$ 4 mg/L	Fluconazole, MIC $\leq$ 8 mg/L	Itraconazole, MIC $\leq$ 0.125 mg/L	Voriconazole, MIC $\leq$ 1 mg/L
	No. susceptible (%)	No. susceptible (%)	No. susceptible (%)	No. susceptible (%)
Candida albicans ($n = 61$)	61 (100)	59 (96.7)	58 (95.1)	59 (96.7)
Candida glabrata ($n = 19$)	19 (100)	19 (100)	8 (42.1)	19 (100)
Candida tropicalis ($n = 14$)	14 (100)	11 (78.6)	9 (64.3)	12 (85.7)
Candida parasilosis ($n = 12$)	12 (100)	11 (91.7)	11 (91.7)	12 (100)
Candida krusei ($n = 1$)	0 (0)	0 (0)	0 (0)	1 (100)
Candida haemulonii ($n = 1$)	1 (100)	1 (100)	1 (100)	1 (100)

MIC = minimal inhibition concentrations.

proportion of NAC is increasing.[8,14] The proportion of NAC in our study is 17.6% for *C glabrata*, 13.0% for *C tropicalis*, 11.1% for *C parasilosis*. Our results are in accordance with the conclusions of previously published studies in two populations: diabetic and ICU patients.[9,23] Patients with NAC are more likely to require greater dosage of fluconazole to cure clinically.[24,25] Thus, there is a need to identify patients at risk of NAC to initiate empirical amphotericin B therapy or high-dose fluconazole.

In our study, we found that an increased risk of NAC was associated with neutropenia ($p = 0.001$). Other published studies found that NAC has been associated with factors, such as neutropenia, hematologic malignancies, allogenic stem cell transplantation, illness severity, and prior fluconazole prophylaxis.[5,26–28]

Among patients with *albicans* candidemia, significantly more patients had candiduria ($p = 0.001$) and ICU stay ($p = 0.002$). This phenomenon can be explained by the spectrum in the extent of adherence to tissues, which correlates with the pathogenicity in humans and animals.[29] *Candida albicans* exhibits the greatest capacity to adhere to gingival epithelial cells, followed by *C tropicalis* and *C glabrata*.

Furthermore, there is no significant difference in the antifungal susceptibilities between NAC and *C albicans*, except to itraconazole. This may be the result of the relatively small number of cases of *C krusei* in our study and the antifungal susceptibilities among our patients with *C glabrata* candidemia. Our patients with *C glabrata* candidemia have 100% susceptibility rate to fluconazole.

Table 5 Univariate analysis of factors associated with all-cause Day 7 mortality or nonmortality in patients with candidemia

Analysis	All-cause Day 7 mortality ($n = 41$)	Nonmortality ($n = 67$)	p
Underlying condition, *n* (%)			
Alcoholism	3 (7.3)	0 (0)	0.051
Renal failure	13 (31.7)	11 (16.4)	0.051
Hematologic malignancy	3 (7.3)	0 (0)	0.051
Predisposing factors, *n* (%)			
Central venous catheter use	31 (75.6)	31 (46.3)	0.088
Receipt of corticosteroids	9 (21.9)	3 (4.5)	0.018*
Blood product transfusion	37 (90.2)	43 (64.2)	0.003*
Hemodialysis	18 (43.9)	15 (22.4)	0.012*
ICU stay	28 (68.3)	34 (50.7)	0.071
Laboratory data, mean $\pm$ SD			
Platelets ($\times 10^9$/L)	108,000 $\pm$ 92,990	186,507 $\pm$ 118,931	0.001*
Blood urea nitrogen (mg/dL)	71.0 $\pm$ 43.4	38.9 $\pm$ 36.4	<0.001*
Creatinine (mg/dL)	2.55 $\pm$ 1.61	1.49 $\pm$ 1.30	<0.001*
Patients susceptible to antifungal agents, susceptibility rate (%)			
Flucytosine	41 (100)	67 (100)	1.000
Fluconazole	40 (97.6)	62 (92.5)	0.459
Itraconazole	33 (80.5)	55 (82.1)	0.909
Voriconazole	40 (97.6)	64 (95.5)	0.514
APACHE III score, mean $\pm$ SD	88.3 $\pm$ 43.1	55.3 $\pm$ 26.9	0.111
Outcome			
Shock	38 (92.7)	21 (31.3)	<0.001*

APACHE = Acute Physiology and Chronic Health Evaluation.
* p value was statistically significant.

Table 6 Multivariate analysis of factors associated with all-cause Day 7 mortality or nonmortality in patients with candidemia

Variables	OR	95% CI		*P*
		Lower	Upper	
Predisposing factors				
Receipt of corticosteroids	8.551	0.741	98.631	0.09
Blood product transfusions	2.921	0.342	24.977	0.33
Hemodialysis	0.302	0.036	2.556	0.27
Laboratory data				
Platelets ($\times 10^9$/L)	1.004	0.995	1.012	0.39
Blood urea nitrogen	1.035	1.001	1.071	0.04*
Creatinine (μmol/L)	1.126	0.479	2.648	0.79
Outcome				
Shock	19.465	2.535	149.462	0.004*

CI = confidence interval; OR = odds ratio.
* *p* value was statistically significant.

However, fluconazole susceptibility and the choice of antifungal regimen were not correlated with mortality. Some studies also reported that patients with candidemia were often seriously ill, and the outcome appeared to be associated with the underlying conditions rather than with fluconazole susceptibility or antifungal agents.[30–32]

All-cause Day 7 mortality was high in both patients with *C albicans* and *C* non-*albicans* spp. BSIs in our study (44.3% and 29.8%, respectively). Our findings suggest that patients with *C parasilosis* candidemia have the lowest mortality rate (8.3%); this finding is consistent with the result of prior studies.[5,33,34] *Candida* infections are not solely related to the pathogenicity of the *Candida* spp., but also to a failure of host-defense mechanisms and to complications associated with the patients underlying disease.[35] The more severely ill patients are at a higher risk of *Candida* infection and have a worse prognosis. This is particularly evident in ICU patients who require indwelling central venous catheter and receipt of mechanical ventilation. Furthermore, *C albicans* is known to be more virulent than NAC.[26,36] These factors may explain the higher all-cause Day 7 mortality rate among patients with *C albicans* BSIs.

APACHE II score was the most common independent predictor of candidemia-related mortality in other institutions of Taiwan.[22,37] In our study, higher APACHE III score at the onset of candidemia trended toward an increased risk of all-cause Day 7 mortality ($p = 0.111$), compared with nonmortality, but the difference did not reach statistical significance. The overall all-cause in-hospital mortality rate in this study was found to be 55.6%, which is compatible with previous reports of candidemia, in which a rate of 40–76% was noted.[13,30,38] Univariate analysis revealed the receipt of corticosteroids, blood product transfusion, and hemodialysis to be the risk factors for all-cause Day 7 mortality among candidemic patients. Administration of glucocorticosteroids reduces chemotaxis, phagocytosis, and phagosomal function. This may contribute to all-cause Day 7 mortality of candidemic patients. However, poor renal function and shock were the only two independent factors for all-cause Day 7 mortality in the multivariate analysis. In clinical practice, these factors could be considered as warning signs of candidemia.

In conclusion, this article defines a number of factors with an increased risk of candidemia because of NAC compared with *C albicans* candidemia. Our findings suggest that neutropenia was associated with an increased risk and that candiduria and ICU stay were associated with decreased risk of BSI because of NAC. Candidemia is associated with a poor outcome and a high mortality rate. The independent risk factors identified in this study, such as poor renal function and shock, may help us, in clinical practice, to differentiate fatal candidemia from nonfatal candidemia.

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