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ORIGINAL ARTICLE

Associated clinical characteristics of patients with candidemia among different *Candida* species

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Total parenteral nutrition

Background: The rising incidence of non-*albicans Candida* (NAC) infection has been associated with a potentially adverse outcome for patients with candidemia. However, categorizing various species causing candidemia into a single NAC group might lead to inappropriate conclusions due to heterogeneity in species. Thus we examined the associated factors among patients with candidemia caused by different species.
Methods: This retrospective study was conducted at a tertiary medical center in Taiwan from 2006 to 2009. Mortality rate, demographic and clinical characteristics, albumin levels, and severity scores of acute illness of patients at the onset of candidemia were analyzed.
Results: A total of 447 episodes among 418 patients were included for analysis. The overall 30-day crude mortality was 48.2%, with no significant difference between *C. albicans* and NAC candidemia, but apparently *C. parapsilosis* candidemia was associated with a lower mortality rate. Time to positivity for yeast was significantly different between species. Compared with infection involving *C. albicans*, more frequent use of total parenteral nutrition,

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lower Sequential Organ Failure Assessment score and higher albumin levels were observed for *C. parapsilosis* candidemia.
Conclusion: Identifying associated factors for each species may be a more effective approach than single NAC grouping. Time to positivity may be a hint for treatment guidance in candidemia. More frequent use of total parenteral nutrition and less virulent nature were noted for *C. parapsilosis* candidemia.

Introduction

Invasive fungal infections in hospitalized patients are associated with significant morbidity and mortality rates.[1] *Candida* species are the most common cause of invasive fungal infections, accounting for approximately 15% of all hospital-acquired infections and >72% of nosocomial fungal infections.[1,2] The mortality rate associated with invasive candidiasis has been reported to be as high as 40% to 50%.[3,4] Furthermore, candidemia is the fourth most common cause of nosocomial bloodstream infections in the United States and is prevalent in much of the developed world.[1,5]

The rising incidence of *Candida* infections, including non-*albicans* candidemia, has been well described through several epidemiological studies since the 1980s.[6–8] The increasing incidence of *Candida* infections has been associated with an increased use of broad-spectrum antibacterial agents, central venous catheters, and implantable prosthetic devices, as well as increased receipt of parenteral nutrition, renal replacement therapy, and immunosuppressive agents.[9–11]

Candida albicans remains the primary cause of invasive candidiasis according to the ARTEMIS DISK global antifungal surveillance study.[12] However, the emergence of non-*albicans Candida* (NAC) infections has become a major problem due to increased exposure to antifungals for prophylactic use in patients receiving bone marrow transplantation and for pre-emptive treatment of critical patients.[13] Risk factors for non-*albicans* candidemia, which have been studied extensively in different clinical settings, include recent antifungal exposure, gastrointestinal surgery, increased patient age, and intravenous drug use relative to *C. albicans* candidemia.[14–17] Potential fluconazole resistance and delayed treatment associated with *C. glabrata* and *C. krusei* infections may be related to an increased incidence of an adverse outcome. However, half of the NAC species, including *C. tropicalis* and *C. parapsilosis*, continued to show susceptibility to fluconazole. As such, categorizing different *Candida* species into a single NAC group may lead to ineffective treatment.

The aim of this study was to analyze associated factors and clinical characteristics of patients with candidemia caused by different *Candida* species and elucidate the differences among NAC species compared with *C. albicans* candidemia. In addition to underlying diseases, invasive procedures, and mortality, the significance of two scoring systems for determining acute illness severity as well as time to positivity (TTP) of blood cultures for yeast were also explored.

Materials and methods

Patient identification and data collection

This retrospective study examined patients with positive blood culture for yeast, as determined using microbiological laboratory findings, at a 2900-bed tertiary medical center from January 1, 2006, to December 31, 2009. Blood cultures were collected using standard sterile procedures via peripheral vessels. Culture results were considered true candidemia when the positive blood culture was sampled via the peripheral vessels for at least one set and the patient was associated with concomitant symptoms and signs of systemic inflammatory response syndrome.[18] Infection control staff identified each episode as true candidemia by reviewing patient medical records. Patient characteristics and information regarding comorbidities, length of hospital stay, number and types of invasive procedures, TTP for yeast, final reports of species identification, and 30-day crude mortality were collected for analysis. The acute physiological and chronic health evaluation II (APACHE II)[19] and sequential organ failure assessment (SOFA) scores[20] were used to determine the severity of acute illness.

Patients were excluded from participating in the study if they were younger than 16 years, were identified as having two or more *Candida* species at the same time, or had another episode diagnosed within 30 days. Patients with two episodes of candidemia diagnosed 30 days apart were considered as having acquired another infectious episode unless a failed primary focus eradication was identified.

Microbiological identification and antimicrobial susceptibility

Pathogens were initially isolated from blood cultures using the BacT/ALERT 3D system (bioMérieux, Marcy l'Étoile, France) during the study period. Species identification and antifungal agent susceptibility was determined using standard biochemical testing with an ATB ID 32C kit (bioMérieux, Hazelwood, MO, USA) and using the Vitek 2 system with the ID-YST Card (bioMérieux). Susceptibility results were interpreted based on species-specific criteria updated in 2010 by the Clinical Laboratory and Standards Institute.[21]

Definition

Underlying comorbidities were identified based on previous medical records with clear documentation. Catheter-related

infections were identified using semiquantitative tip culture of indwelling catheters with growth of ≥15 colonies identical to the species identified from the peripheral blood culture. Chronic renal insufficiency was identified based on serum creatinine levels >1.5 mg/dL or an estimated serum creatinine clearance <30 mL/min/1.73 m^2 for >6 months, and end stage renal disease was defined as serum creatinine levels >6.0 mg/dL or estimated serum creatinine clearance <10 mL/min/1.73 m^2 for >6 months. Antacid use included only usage of proton-pump inhibitors or H_2 channel blockers for ≥3 days. Immunosuppressive therapy was defined at immunosuppressant or corticosteroid use at a dosage equivalent to prednisolone ≥20 mg per day for at least 3 days. Patients with neutropenia included those with absolute neutrophil counts of $<1.0 \times 10^9$ cells/L with candidemia. Patients with thrombocytopenia included those with platelet counts of $<100{,}000 \times 10^9$ cells/L with candidemia. Peripheral parenteral nutrition only included those patients receiving administration of a lipid-containing formulation. Colonization was defined as positive growth of yeast from at least one surveillance site.[22]

Statistical analysis

The Chi-square test or Fisher's exact test was used for categorical comparisons of data. Differences between continuous variables among the different *Candida* species were analyzed by analysis of variance (ANOVA) with *posthoc* tests. A p value <0.05 was considered statistically significant. Variables with a p value <0.1 according to univariate analysis were included in a logistic regression model to identify the most important risk factors. All analyses were performed using the SPSS for Windows, version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

A total of 485 episodes of candidemia were recorded during the study period. Thirty-eight episodes were excluded due to double species infection or incomplete clinical data collection. A total of 447 episodes occurring in 418 patients were included for analysis. The demographic and clinical characteristics of these patients are shown in Table 1. Overall 30-day crude mortality was 48.2%. The 30-day mortality among patients with *C. albicans* and NAC candidemia was 51.9% and 42.9% respectively ($p = 0.058$).

Candida albicans was the most common pathogen identified in this study (57.7%), followed by *C. tropicalis* (15.0%), *C. parapsilosis* (13.0%), and *C. glabrata* (8.3%). The final identification of yeast in case of candidemia is shown in Table 2. A total of 420 episodes with final identification of one of the four aforementioned common species were included for further analysis. Demographic characteristics, clinical conditions, and comparison by univariate analysis among the different *Candida* species are summarized in Table 3. Although the mortality rates had no significant difference between *C. albicans* and NAC candidemia, apparently *C. parapsilosis* candidemia was associated with a lower mortality rate.

Table 1 Demographics and clinical characteristics of patients with candidemia

Variable	Overall $n = 447$
Age (years)	68 ± 16
Male sex	300 (67.1)
Onset at ICUs	157 (35.1)
14-d mortality	161 (36.0)
30-d mortality	215 (48.1)
Precandidemia LOS (d)	40 ± 76
LOS (d)	77 ± 110
TTP for yeast (h)	61.9 ± 21.8
APACHE II score	24.6 ± 8.8
SOFA score	6.8 ± 4.7
Underlying comorbidity	
CAD	75 (16.8)
CHF	60 (13.4)
CVA	89 (19.9)
COPD	46 (10.3)
DM	134 (30)
CRI	171 (38.3)
ESRD	60 (13.4)
Organ transplantation	6 (1.3)
Liver cirrhosis	23 (5.1)
Pancreatitis	33 (7.4)
Solid tumor	207 (46.3)
Hematological malignancy	31 (6.9)
Collagen vascular disease	15 (3.4)
Conditions within previous 30 d	
ICU admission	232 (51.9)
Operation	145 (32.4)
Antacid use	296 (66.2)
Chemotherapy	73 (16.3)
Immunosuppressive therapy	69 (15.4)
Colonization	198 (44.3)
Albumin (g/dL, mean ± SD)	2.64 ± 0.62
Neutropenia	36 (8.1)
Thrombocytopenia	227 (50.9)
Shock	196 (44.0)
Procedures	
Hemodialysis	77 (17.2)
Nasogastric tube usage	312 (69.8)
Mechanical ventilation	186 (41.6)
Nontunneled CVCs	295 (66.1)
Removal of nontunneled CVCs	214 (72.8)
Tunneled CVCs	150 (33.6)
Removal of tunneled CVCs	46 (30.7)
Arterial line	129 (28.9)
Parenteral nutrition	221 (49.4)
TPN	122 (27.3)
PPN	163 (36.5)
Urinary catheters	238 (53.2)
Surgical drainage devices	130 (29.1)
Previous antifungal agents exposure	39 (9.3)
Concurrent bacteremia	79 (17.7)

Data are n (%) or mean ± SD unless otherwise indicated. CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRI = chronic renal insufficiency; CVA = cerebrovascular accident; CVC = central venous catheter; DM = diabetes mellitus; ESRD = end stage renal disease; ICU = intensive care unit; LOS = length of hospital stay; PPN = peripheral parenteral nutrition; SD = standard deviation; TPN = total parenteral nutrition; TTP = time to positivity.

Table 2 Identification of yeast species

Species identification	Number of isolates (%)
C. albicans	258 (57.7)
C. tropicalis	67 (15)
C. parapsilosis	58 (13)
C. glabrata	37 (8.3)
Others	27 (6)
Candida spp. unidentified	11
Yeast unidentified	4
C. famata	3
C. lusitaniae	2
C. krusei	1
Trichosporon asahii	3
Cryptococcus neoformans	3

In the logistical regression model of multivariate analysis, variables including SOFA scores, albumin level, TTP for yeast, and use of total parenteral nutrition (TPN) achieved statistical significance among the three NAC species compared with *C. albicans* (Table 4). Compared with that of *C. albicans*, a longer TTP for yeast was more frequently observed in *C. parapsilosis* and *C. glabrata*, while a shorter TTP was observed *C. tropicalis*. A lower SOFA score, higher albumin level and more prevalent usage of TPN were associated with *C. parapsilosis* candidemia, while less association with TPN was noted for *C. tropicalis* candidemia.

Discussion

Overall 30-day crude mortality in patients with candidemia was 48.2%, which was not significantly different from *C. albicans* and other NAC groups. Although Moran *et al.* reported that an increased mortality rate and cost was noted in an adult population with NAC candidemia in the USA,[14] several other studies failed to identify a difference in the mortality rate between patients with *C. albicans* or NAC candidemia.[17,23,24] Oversimplifying categorization method for different species into a single NAC group may explain the different conclusions among these studies and may indicate differences in both incidence and species distribution between geographic regions and institutions.[6,8,25] As described in the ARTEMIS DISK surveillance study, the distribution of *C. glabrata* with potential fluconazole resistance was less common in the Asia-Pacific region (12.6%) than in North America (21.1%).[12] The fluconazole susceptibility rate among *Candida* species presented here is similar to that reported in the ARTEMIS DISK surveillance study. Thus, identifying invasive candidiasis on an individual basis would enable more precise conclusions in different clinical settings.

The TTP for yeast showed significant differences between species before final species identification. The TTP for yeast was similar to the natural growth speed of each *Candida* species, as described previous reports.[26–28] A recent report by Ben-Ami e*t al.* also revealed the TTP to be

Table 3 Univariate analysis of risk factors among the four common *Candida* species

Variable	*C. albicans*	*C. tropicalis*	*C. parapsilosis*	*C. glabrata*	*p*
	$n = 258$	$n = 67$	$n = 58$	$n = 37$	
Age (years)	70 ± 16	67 ± 15	63 ± 16	72 ± 14	0.011*
30-day mortality	134 (52)	39 (58)	15 (26)	15 (41)	0.001*
TTP for yeast (hours)	58.4 ± 18.2	50.6 ± 13.9	71.3 ± 26.9	90.7 ± 36.5	<0.001*
APACHE II score	25.2 ± 8.6	26.0 ± 8.4	20.8 ± 7.7	26.0 ± 9.1	0.002*
SOFA score	6.9 ± 4.7	7.9 ± 4.7	4.7 ± 4.1	7.2 ± 4.7	0.001*
Underlying comorbidities					
Hematological malignancy	12 (5)	7 (10)	7 (12)	2 (5)	0.049*
Conditions within previous 30 days					
ICU admission	127 (49)	41 (61)	26 (45)	25 (68)	0.049*
Antacid use	165 (64)	52 (78)	35 (60)	28 (76)	0.076
Colonization	119 (46)	38 (57)	15 (26)	22 (60)	0.002*
Albumin (gm/dl)	2.69 ± 0.62	2.60 ± 0.64	2.91 ± 0.54	2.53 ± 0.59	0.006*
Thrombocytopenia	127 (49)	46 (69)	20 (35)	18 (49)	0.002*
Procedures					
Nasogastric tube usage	185 (72)	46 (69)	32 (55)	30 (82)*	0.035*
Arterial line	74 (29)	19 (28)	12 (21)	17 (46)	0.068
TPN	71 (28)	12 (18)	25 (43)	10 (27)	0.019*
Fluconazole susceptibility rate	237 (97)	59 (92)	53 (93)	0	<0.001*
MIC50 (mg/L)	<1	<1	<1	4	
MIC90 (mg/L)	<1	2	2	16	
MIC range (mg/L)	<0.25–>128	0.25–>128	<0.25–4	<0.25–32	

* $p < 0.05$.
Data are *n* (%) or mean ± SD unless otherwise indicated.
ICU = intensive care unit; MIC = minimal inhibitory concentration; SD = standard deviation; TPN = total parenteral nutrition; TTP = time to positivity.

Table 4 Multivariate analysis of the relative risk among different species compared with *C. albicans*

Variable	OR (95% CI) in *C. tropicalis*	OR (95% CI) in *C. parapsilosis*	OR (95% CI) in *C. glabrata*
SOFA scores	1.06 (0.99–1.14)	0.90 (0.84–0.98)*	0.97 (0.88–1.07)
Albumin	1.14 (0.68–1.93)	2.55 (1.33–4.88)*	0.80 (0.38–1.70)
TTP for yeast	0.96 (0.94–0.98)*	1.04 (1.02–1.05)*	1.06 (1.04–1.07)*
Use of TPN	0.43 (0.20–0.92)*	3.01 (1.46–6.23)*	2.22 (0.82–6.03)

* $p < 0.05$.
TTP = time to positivity; TPN = total parenteral nutrition.

an early indicator for catheter-related candidemia.[26] This information may be used to guide antifungal therapy before final species identification in patients with candidemia who are in critical condition. Further studies examining the clinical significance of TTP for yeast are necessary.

Between the two scoring systems used to determine the severity of acute illness, the SOFA score is easier to determine in clinical field and showed more statistical significance in multivariate analysis compared to the APACHE II score. A linear association was observed between the SOFA score and APACHE II score according to the logistical linear regression model ($p < 0.001$). However, unlike APACHE III, no further age grading was available for those older than 65 years, and no dynamic grading was available for urine output in the APACHE II scoring system.[19,29] Thus the APACHE II score should show a smaller difference than the SOFA score among species examined in our study population.

Among patients with *C. parapsilosis* candidemia, a lower SOFA score, higher albumin level and more frequent TPN usage were common associated clinical characteristics. These factors may suggest a less virulent nature for the *C. parapsilosis* infection as a previous report in an animal model.[30] The slow growing rate and lower fluconazole nonsusceptibility percentage of *C. parapsilosis* may explain the lower patient mortality rate, lower APACHE II and SOFA scores, and higher albumin level determined through univariate analysis.[31] Similar to the results of previous studies, *C. parapsilosis* candidemia was associated with a more prevalent TPN usage.[13,32] Although the virulence of non-*albicans* species remains unclear, biofilm formation and parenteral hyperalimentation may be risk factors for identifying *C. parapsilosis* candidemia in susceptible hosts. A less significant association with TPN usage was noted for *C. tropicalis* candidemia.

A lower mortality rate was observed in patients with *C. glabrata* candidemia compared to those with *C. albicans* candidemia. The first line antifungal agent for treating candidemia was 400 mg/day fluconazole at a dosage of after an 800 mg loading dosage at our hospital during the study period, rather than treatment with echinocandin or amphotericin B. Similar to the fluconazole-nonsusceptible rate, 30-day crude mortality in patients with *C. glabrata* candidemia was 40.5%, which is not as high as that reported previously (range 40% to 70%).[5,33,34] Moreover, several studies have indicated that candidemia caused by *C. glabrata* is not associated with an increase in mortality or length of hospital stay, but it is associated with higher treatment cost for antifungal therapy.[7,35,36] Therefore, *C. glabrata* virulence may not be as toxic as expected because of its slow growth rate, and the adverse outcome related to *C. glabrata* candidemia may be related to an increased probability of azole-resistance, underlying multiple comorbidities,[25,28,35,37] or higher prevalence of intensive care unit admission. However, a healthy worker effect may exist due to the retrospective design of this study for the decreased mortality rate among patients with *C. glabrata* candidemia. Further *in vitro* studies of *C. glabrata* are necessary to establish the clinical significance of this infection and to determine virulence factors in addition to intrinsic fluconazole-nonsusceptiblity.

In conclusion, categorizing different *Candida* species into a single NAC group may not be a sufficient approach for determining treatment due to the heterogeneity that exists among species and to different species distributions among institutes and geographic areas. Identifying associated factors for each species may be a better approach than using simple NAC grouping, while the TTP for yeast may be helpful in guiding antifungal therapy measures.

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Conflicts of interest

All contributing authors declare that they have no conflicts of interest relevant to this article.

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