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Associated clinical characteristics of patients with candidemia among different Candida species

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KEYWORDS
Candidemia; Non-albicans Candida species; Time to positivity; 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,
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.

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. 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) and sequential organ failure assessment (SOFA) scores 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.

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 $\geq 15$ 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.
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 in 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.

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

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

* 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.

### 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, several other studies failed to identify a difference in the mortality rate between patients with C. albicans or NAC candidemia. 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. 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%). 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. A recent report by Ben-Ami et al. also revealed the TTP to be...
an early indicator for catheter-related candidemia.\textsuperscript{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.\textsuperscript{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 \textit{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 \textit{C. parapsilosis} infection as a previous report in an animal model.\textsuperscript{30} The slow growing rate and lower fluconazole nonsusceptibility percentage of \textit{C. parapsilosis} may explain the lower patient mortality rate, lower APACHE II and SOFA scores, and higher albumin level determined through univariate analysis.\textsuperscript{31} Similar to the results of previous studies, \textit{C. parapsilosis} candidemia was associated with a more prevalent TPN usage.\textsuperscript{13,32} Although the virulence of non-\textit{albicans} species remains unclear, biofilm formation and parenteral hyperalimentation may be risk factors for identifying \textit{C. parapsilosis} candidemia in susceptible hosts. A less significant association with TPN usage was noted for \textit{C. tropicalis} candidemia.

A lower mortality rate was observed in patients with \textit{C. glabrata} candidemia compared to those with \textit{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 \textit{C. glabrata} candidemia was 40.5%, which is not as high as that reported previously (range 40% to 70%).\textsuperscript{5,33,34} Moreover, several studies have indicated that candidemia caused by \textit{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.\textsuperscript{7,35,36} Therefore, \textit{C. glabrata} virulence may not be as toxic as expected because of its slow growth rate, and the adverse outcome related to \textit{C. glabrata} candidemia may be related to an increased probability of azole-resistant, underlying multiple comorbidities,\textsuperscript{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 \textit{C. glabrata} candidemia. Further in vitro studies of \textit{C. glabrata} are necessary to establish the clinical significance of this infection and to determine virulence factors in addition to intrinsic fluconazole-nonsusceptibility.

In conclusion, categorizing different \textit{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.

### Funding

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### Conflicts of interest

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

### Acknowledgments

We thank the infection control nurses at the Department of Infection Control, Taipei Veterans General Hospital, for collecting data and identifying candidemia species.

### References


#### Table 4  Multivariate analysis of the relative risk among different species compared with \textit{C. albicans}

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

* $p < 0.05$.

TTP = time to positivity; TPN = total parenteral nutrition.


