Original Article

Epidemiology and risk factors for nosocomial Non-*Candida albicans* candidemia in adult patients at a tertiary care hospital in North China

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Abstract

Nosocomial candidemia extends the length of hospital stay, increases the costs of medical care, and is associated with a high mortality rate. Epidemiological data that assist in the choice of initial therapy may help to improve the prognosis. The present study was undertaken to investigate the epidemiology of nosocomial candidemia and identify risk factors for nosocomial candidemia caused by *C. albicans* and non-*albicans* *Candida* species (NAC). A retrospective chart review was undertaken to analyze cases of nosocomial candidemia treated at the Beijing Friendship Hospital between January 2008 and December 2012. All cases of candidemia were identified using the previously published criteria. Among 106 patients analyzed, 53.8% had nosocomial candidemia caused by NAC. *Candida albicans* was the most common causative agent, accounting for 46.2% of all cases, followed by *C. glabrata* (25.5%), *C. tropicalis* (15.1%), *C. parapsilosis* (10.4%) and *C. Krusei* (0.9%). Comparison of nosocomial *C. albicans* and NAC candidemia by multivariate logistic regression showed that factors independently associated with nosocomial NAC candidemia included exposure to azole agents (odds ratio [OR]: 3.359; 95% confidence interval [CI]: 1.136–10.154; *P* = 0.031) and artificial surgical implants (OR: 37.519; 95% CI: 2.5–562.998; *P* = 0.009). A significant risk factor for nosocomial *C. albicans* candidemia was cancer surgery (OR: 0.075; 95% CI: 0.013–0.437; *P* = 0.004). Clinical and epidemiological differences in the risk factors between nosocomial candidemia caused by *C. albicans* and NAC should be considered when selecting an initial antifungal regimen for the treatment of adult patients. This should be undertaken before the availability of species identification and/or antifungal susceptibility results.

Key words: Nosocomial candidemia, non-*albicans* *Candida* species, epidemiology, risk factor.
Introduction

Nosocomial bloodstream infections (BSIs) are blood infections that occur during hospitalization and are an important cause of morbidity and mortality in hospitalized patients. Approximately 7.6–9.0% of nosocomial BSIs are due to Candida spp., which currently ranks as the fourth and seventh most common systemic pathogen in North America and Europe, respectively [1,2]. Nosocomial candidemia is not only associated with substantial mortality but also extends the duration of hospital stay and increases the costs of medical care [3,4]. Until recently, C. albicans was the predominant Candida spp. isolated from patients with nosocomial candidemia. However, in recent years, there has been an increase in the proportion of non-albicans Candida spp. (NAC) isolates, and in some European and Latin American centers it has overtaken C. albicans as the predominant cause of nosocomial candidemia [5–7]. Considering the different worldwide distribution of Candida spp., some researchers have recommended that the epidemiology of Candida infections should be studied at local levels rather than on a worldwide scale [8].

There is a consensus that to avoid mortality it is crucial that antifungal therapy is initiated before candidemia ensues [9,10]. In practice, this has to occur long before the causative Candida spp. is identified and prior to obtaining the results of antifungal susceptibility testing. Non-albicans Candida (NAC) spp. are associated with stronger biofilm production than C. albicans spp., and C. glabrata and C. krusei show less susceptibility to azole agents [11–14]. Thus, eradication of NAC candidemia is likely to require higher doses of fluconazole or other effective agents (e.g., echinocandin or amphotericin B) [15,16]. Epidemiological data that help to differentiate C. albicans from NAC infections may therefore be of value in the choice of appropriate antifungal treatment.

Only a few studies to date have sought to identify specific risk factors for nosocomial NAC candidemia. The data that are available are mostly limited to special populations, such as cancer patients or critically ill patients from Western Countries [17,18] and have predominantly focused on single species, such as C. glabrata, C. parapsilosis, or C. krusei, rather than evaluating all NAC spp. together [19]. In a European study of immunocompromised patients, nosocomial NAC candidemia was associated with medical device use or steroid therapy [18]. In nonimmunocompromised Chinese patients, nosocomial C. albicans candidemia has been associated with tracheal incubation and nosocomial NAC candidemia with head trauma and bacterial sepsis [20]. A surveillance study in China identified central venous catheter placement and poor response to fluconazole as being associated with an increased risk of 30-day mortality [21]. However, little has been reported about the epidemiology of nosocomial C. albicans and NAC candidemia in North China.

Therefore, the present study was undertaken to investigate the epidemiology of nosocomial candidemia in adult patients at a single center in North China, in an attempt to identify factors associated with nosocomial NAC candidemia.

Patients and Methods

Study design

This retrospective study was conducted at Beijing Friendship Hospital, which is a 1,300-bed tertiary care hospital located in North China. Patients with systemic Candida bloodstream infections (BSIs) were identified from an electronic microbiology laboratory database in our hospital. We evaluated all cases recorded between January 1, 2008, and December 31, 2012.

Definitions and exclusion

Candidemia was identified using the previously published criteria [22–24]. Infection was defined as at least one positive blood culture for Candida spp. in patients hospitalized for more than 48 h with signs or symptoms of infection. Pediatric patients (less than 18 years old), those without complete case files and having candidemia before admission to our center were excluded. Patients infected simultaneously with both C. albicans and NAC were also excluded.

Data collected included patient demographic characteristics; comorbidities; concomitant infections; hospital length of stay (LOS); operations; exposure to antibiotic, antifungal, and cancer therapy; total parenteral nutrition (TPN); gastrointestinal surgery; central venous catheter (CVC) use; mechanical ventilation; and in-hospital mortality. If patients had multiple candidemia episodes, data from only the first episode were included in the analysis. Previous exposure to azole agents was defined as having received azole agents within 30 days prior to the onset of candidemia (for prophylaxis or for treatment/empirical therapy). Cancer surgery was defined as having a surgery for a cancer within the past 3 months of candidemia onset.

Identification of the species

All positive cultures were manually sampled and inoculated on CHROMagar Candida medium (JinZhang, Tianjing, China) to ensure viability and purity. An aliquot was Gram-stained for preliminary identification of the microorganism. Identification of all species was confirmed with the
Vitek 2 Compact YST (bioMérieux, France) or the API 20C AUX system (BioMérieux, France). Quality control isolates included *C. albicans* (ATCC90028), *C. parapsilosis* (ATCC22019), and *C. krusei* (ATCC6258).

**Outcomes**

The 7- and 30-day mortality were used as outcomes.

**Statistical analysis**

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL, USA). Variables are expressed as mean ± standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. Categorical variables were compared using the $\chi^2$, Fisher exact tests or continuity correction [7], as appropriate. Continuous variables were compared using the Student t test. The $\chi^2$ tests for trend were performed to assess changes over the study period.

Multivariate forward stepwise logistic regression analyses were performed to identify independent variables associated with nosocomial *C. albicans* and NAC candidemia. Variables that had a statistical significance of $P<.30$ in the univariate analyses were candidates for the multivariable analysis. For all other tests, $P<.05$ were considered statistically significant.

**Results**

**Patient characteristics**

A total of 121 evaluable patients were treated for nosocomial candidemia between 2008 and 2012. Fifteen patients were excluded from the analysis: nine patients with incomplete case files, three were with candidemia before hospitalization, two who were younger than 18, and one patient with mixed candidemia due to *C. albicans* and NAC.

The analysis included 72 males and 34 females with a mean age of 68.8±18.7 years. The median duration of hospitalization was 46.3±29.7 days. Most patients (49/106: 46.2%) were treated in the intensive care unit (ICU), 38 (35.8%) were from medical wards, and 19 (17.9%) from surgical wards (Table 1). The length of time between hospital admission and candidemia diagnosis was 22.6±21.3 (range 3–121) days. The most common clinical manifestations were fever, often exceeding 38°C, together with occasional chills and low blood pressure [8]. None of the subjects had evidence of organ involvement.

The most common underlying illness and predisposing factors were broad-spectrum antibiotics (99.1%), central intravenous catheters (61.3%), cardiovascular disease (57.5%), and gastrointestinal pathology (50.0%). Lung disease tended to be less prevalent among patients with *C. albicans* candidemia (14.3% versus 28.1%), but the difference between the groups was not statistically significantly ($P = .082$) (Table 1).

Eleven patients had long-term artificial implants: six had coronary stents, two had esophageal stents, and one each had a femoral artery stent, an artificial blood vessel and a hip prosthesis. Among patients with long-term artificial implants, the median age of the artificial implants was 3 years, and the older implant was 8 years old.

**Epidemiology of Candida spp.**

*Candida albicans* and NAC spp. were responsible for 49/106 (46.2%) and 57/106 (53.8%) of nosocomial candidemia cases, respectively. The distribution of NAC spp. was: 27/106 (25.5%) for *C. glabrata*, 16/106 (15.1%) for *C. tropicalis*, 11/106 (10.4%) for *C. parapsilosis*, 1/106 (0.9%) for *C. krusei* and 2/106 (1.9%) for other less common species (1/106 *C. lusitaniae*, and 1/106 *C. guilliermondii*). There was no significant difference in species distribution pattern for NAC over the study period ($\chi^2 = 1.245$, $P = .878$). As shown in Figure 1, an upward trend was observed in the number of cases per year between 2008 and 2012, with the overall number doubling between 2009 ($n = 14$) and 2012 ($n = 28$). But, the annual rates of nosocomial candidemia in BSIs during the 5 years of the study were: 10.6%, 6.7%, 6.0%, 6.4%, and 5.9%, the difference was not statistically significant ($\chi^2 = 4.803$, $P = .309$).

**Outcome**

The overall 30-day mortality among all patients with nosocomial candidemia was 36.9%. However, the 7-day mortality rate had a tendency to be higher in patients with NAC (19.3%) compared with those with nosocomial *C. albicans* candidemia (6.1%), but the difference was not statistically significant ($P = .087$; continuity correction) (Table 1).

**Risk factors associated with nosocomial candidemia due to Candida spp.**

The significant univariate risk factors for NAC were previous exposure to azoles agents ($P = .020$) and the presence of artificial surgical implants ($P = .022$). Significant univariate risk factors for nosocomial *C. albicans* candidemia were cancer surgery and TPN ($P = .002$ and $P = .045$, respectively) (Table 1).

In multivariate analysis, the significant independent risk factors for nosocomial NAC candidemia were previous exposition to azole agents (OR: 3.359; 95% CI:
Table 1. Demographic, clinical characteristics and outcome of study populations.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N = 106</th>
<th>C. albicans N = 49 (46.2%)</th>
<th>NAC spp N = 57 (53.8%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68.8±18.7</td>
<td>69.8±17.4</td>
<td>67.9±18.2</td>
<td>.572</td>
</tr>
<tr>
<td>Male sex</td>
<td>72 (67.9%)</td>
<td>34 (69.4%)</td>
<td>38 (66.7%)</td>
<td>.765</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>46.3±29.7</td>
<td>46.5±24.8</td>
<td>38.9±26.9</td>
<td>.367</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>61 (57.5%)</td>
<td>28 (57.1%)</td>
<td>33 (57.9%)</td>
<td>.938</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>44 (41.5%)</td>
<td>18 (36.7%)</td>
<td>26 (45.6%)</td>
<td>.355</td>
</tr>
<tr>
<td>Gastrointestinal pathology</td>
<td>53 (50.0%)</td>
<td>24 (49.0%)</td>
<td>29 (50.9%)</td>
<td>.846</td>
</tr>
<tr>
<td>Lung disease</td>
<td>23 (21.7%)</td>
<td>7 (14.3%)</td>
<td>16 (28.1%)</td>
<td>.086</td>
</tr>
<tr>
<td>Renal disease</td>
<td>6 (5.7%)</td>
<td>4 (8.2%)</td>
<td>2 (3.5%)</td>
<td>.301*</td>
</tr>
<tr>
<td>Organ transplantation</td>
<td>3 (2.8%)</td>
<td>1 (2.0%)</td>
<td>2 (3.5%)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Therapeutic factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the ICU at diagnosis</td>
<td>49 (46.2%)</td>
<td>23 (46.9%)</td>
<td>26 (45.6%)</td>
<td>.892</td>
</tr>
<tr>
<td>Recent surgery (&lt;3months)</td>
<td>50 (47.2%)</td>
<td>26 (53.1%)</td>
<td>24 (42.1%)</td>
<td>.260</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>39 (38.2%)</td>
<td>20 (42.6%)</td>
<td>19 (34.5%)</td>
<td>.407</td>
</tr>
<tr>
<td>Cancer surgery</td>
<td>21 (19.8%)</td>
<td>16 (32.7%)</td>
<td>5 (8.8%)</td>
<td>.002</td>
</tr>
<tr>
<td>Cancer chemotherapy</td>
<td>11 (10.4%)</td>
<td>4 (8.2%)</td>
<td>7 (12.3%)</td>
<td>.488</td>
</tr>
<tr>
<td>Prior antibiotherapy</td>
<td>105 (99.1%)</td>
<td>49 (100%)</td>
<td>56 (98.2%)</td>
<td>.935</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>22 (20.8%)</td>
<td>10 (20.4%)</td>
<td>12 (21.1%)</td>
<td>.02</td>
</tr>
<tr>
<td>Previous exposure to azole agents</td>
<td>36 (34.0%)</td>
<td>11 (22.4%)</td>
<td>25 (43.9%)</td>
<td>.02</td>
</tr>
<tr>
<td>Invasive procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>32 (30.2%)</td>
<td>15 (30.6%)</td>
<td>17 (29.8%)</td>
<td>.349</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
<td>29 (27.4%)</td>
<td>18 (36.7%)</td>
<td>11 (19.3%)</td>
<td>.045</td>
</tr>
<tr>
<td>Presence of CVC</td>
<td>65 (61.3%)</td>
<td>34 (69.4%)</td>
<td>31 (54.4%)</td>
<td>.114</td>
</tr>
<tr>
<td>Time from CVC placement to candidemia (days)</td>
<td>19±19.4</td>
<td>17±11.6</td>
<td>21±25.4</td>
<td>.453</td>
</tr>
<tr>
<td>Artificial implants</td>
<td>11 (10.4%)</td>
<td>1 (2.0%)</td>
<td>10 (17.5%)</td>
<td>.022*</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude 30-day mortality</td>
<td>39 (36.8%)</td>
<td>17 (34.7%)</td>
<td>22 (38.6%)</td>
<td>.678</td>
</tr>
<tr>
<td>Crude 7-day mortality</td>
<td>14 (13.2%)</td>
<td>3 (6.1%)</td>
<td>11 (19.3%)</td>
<td>.087</td>
</tr>
</tbody>
</table>

Note: *Includes the following diseases: hypertension, coronary disease.
\[a\]Includes the following diseases: cholecystitis, pancreatitis, peritonitis, and hepatitis.
\[b\]Includes the following diseases: pneumonia, chronic obstructive pulmonary disease, and acute respiratory distress syndrome.
\[c\]Includes the following diseases: chronic cardiovascular disease.
\[d\]Hemodialysis or peritoneal dialysis
CVC: central venous catheter.

1.136–10.154; P = .031) and the presence of artificial implants (OR: 37.519; 95% CI: 2.5–562.998; P = .009). The significant independent risk factor for C. albicans nosocomial candidemia was cancer surgery (OR: 0.075; 95% CI: 0.013–0.437; P = .004) (Table 2).

The distribution of C. albicans and NAC spp. between patients previously exposed or not to an azole agent is shown in Table 3. Previous exposure to an azole agent affected the distribution of C. albicans (P = .020) and C. glabrata (P = .023).

Discussion
Recent studies have reported the epidemiology of the species responsible for BSI has shifted from C. albicans to NAC spp.\[5–7\]. In support of this changing pattern our analysis showed that NAC spp. (53.8%) were more frequent isolates than C. albicans (46.2%) in adult Chinese patients with nosocomial candidemia. In our study, the most common NAC spp. was C. glabrata, followed by C. tropicalis, C. parapsilosis, C. krusei and other less common species.

This species distribution pattern is consistent with studies from European countries \[18,25\] but it differs from previous studies from Shanghai \[20\], Nanjing \[21\] Chongqing, and Taiwan \[27\], which have all highlighted C. tropicalis as the most common NAC spp. C. parapsilosis or C. glabrata were isolated second most frequently and C. krusei was relatively rarely encountered. The reasons for the changing species distribution around the world remain unclear \[21\]. It may be partly explained by differences in study populations and healthcare standards \[25,28\]. Most nosocomial candidemia cases in our study were from ICU patients who were relatively elderly (aged 68.8±18.7 years). It has previously been reported that prior ICU admission and older age
both increase the risk of nosocomial candidemia caused by C. glabrata [6,29,30].

A number of comparative studies have sought to identify the risk factors that favor nosocomial NAC candidemia [14,18,20,31–33]. Our analysis identified previous exposure to azole agents as an independent risk factor for nosocomial NAC candidemia. This is consistent with previously reported findings in Australia and the United States [31,32]. This association may be partly due to the selective resistance resulting from frequent use of antifungal agents, especially fluconazole. While C. albicans is generally susceptible to fluconazole, C. krusei has been shown to be innately resistant and it has been reported that C. glabrata readily develops azole resistance [34].

Our analysis identified long-term artificial implants as a risk factor for nosocomial NAC candidemia. C. albicans, and NAC spp. were responsible for 1/11 (9.1%) and 10/11 (90.9%) cases, respectively. C. parapsilosis was the causative pathogen in 5/10 (50.0%) cases, C. glabrata in 3/10 (30.0%) cases and C. tropicalis in 2/10 (20%) cases. However, in this small sample, it is not possible to ascertain whether the surgical implants were the direct cause of nosocomial candidemia. However, our findings are in line with the distribution of pathogens reported in a European study of 56 patients with surgical implants [35]. A previous studies has also shown that urinary and venous catheters increased the risk of nosocomial candidemia due to NAC [30].

Cancer is recognized as a general risk factor for nosocomial Candida infection [4]. A previous Scandinavian study has shown that C. albicans was responsible for up to 92% of nosocomial fungemias associated with cancer surgery patients and for up to 42% of nosocomial fungemias associated with chemotherapy [36]. Our analysis also showed that nosocomial C. albicans candidemia was more prevalent among cancer surgery patients than among patients undergoing cancer chemotherapy. Multivariate analysis identified cancer surgery but not cancer chemotherapy as a risk factor for nosocomial C. albicans candidemia, which is consistent with the finding by Li et al. [37].

Previous studies have identified TPN as a risk factor for nosocomial candidemia overall [38,39]. It has also been reported [14] that TPN is a greater risk factor for nosocomial candidemia due to C. albicans than due to NAC spp, although the underlying mechanism is not clear. Other reported risk factors for nosocomial NAC candidemia include CVC [14,30], bacterial sepsis [18], female gender [33], leukocytosis [30] and immunosuppression [30]. However, findings vary significantly between studies, probably due to heterogeneity in pathogens and study populations. This further underlines the importance of local epidemiology studies.

The present analysis was limited by the retrospective design, which meant that we were unable to obtain data on corticosteroid use and underlying chronic disease status. In addition, the relatively small number of cases (n = 106) that could be followed up for 5 years and the single center design may have compromised the statistical power of the study, nevertheless, these results are in agreement with the literature, and could serve as a basis for future larger-scale studies.

**Table 2.** Independent risk factors associated with NAC spp. and C. albicans infection among patients with nosocomial candidemia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artificial implants</td>
<td>37.519</td>
<td>2.5–562.998</td>
<td>.009</td>
</tr>
<tr>
<td>Previous exposure to azole agents</td>
<td>3.359</td>
<td>1.136–10.154</td>
<td>.031</td>
</tr>
<tr>
<td>cancer surgery</td>
<td>0.075</td>
<td>0.013–0.437</td>
<td>.004</td>
</tr>
</tbody>
</table>

Note: 95% CI: 95% confidence interval.

**Table 3.** Isolates from patients with nosocomial candidemia with/without previous exposure to azole agent.

<table>
<thead>
<tr>
<th>Isolate</th>
<th>With, N = 36</th>
<th>Without, N = 70</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>11 (30.6)</td>
<td>38 (54.3)</td>
<td>.020</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>14 (38.9)</td>
<td>13 (17.8)</td>
<td>.023</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>6 (16.7)</td>
<td>10 (14.3)</td>
<td>.746</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>4 (11.1)</td>
<td>7 (10.0)</td>
<td>1.0 *</td>
</tr>
<tr>
<td>C. krusei</td>
<td>1 (2.8)</td>
<td>0 (0)</td>
<td>.340 +</td>
</tr>
<tr>
<td>C. lusitaniæ</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td>1.0 +</td>
</tr>
<tr>
<td>C. guilliermondii</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td>1.0 +</td>
</tr>
</tbody>
</table>

* Continuity correction.
+ Fisher exact test.
In conclusion, our findings suggest that previous exposure to azoles and the presence of artificial surgical implants were associated with an increased risk of nosocomial NAC candidemia. Our findings also showed that cancer surgery is associated with an increased risk of nosocomial C. albicans candidemia rather than NAC candidemia. These factors should be considered when selecting empiric antifungal treatment of nosocomial candidemia in adult patients prior to the availability of culture results.

Acknowledgments

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Authors’ contributions

JRS conceived, coordinated and designed the research; XRD performed the experiment, contributed to the acquisition, analysis and interpretation of data and drafted the manuscript; DHY contributed to data analysis; WS, ZYZ and RRS participated in Candida spp. Identification and data acquisition. All authors read and approved the final manuscript.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

References