Seven-year trend analysis of nosocomial candidemia and antifungal (fluconazole and caspofungin) use in Intensive Care Units at a Brazilian University Hospital

Infection Control Nosocomial Committee, Hospital das Clínicas, University of São Paulo, São Paulo, Brazil

Candidemia is associated with high morbidity and mortality resulting in significant increases in the length of patients’ hospitalization and in healthcare costs. Critically ill patients are at particular risk for candidemia because of their debilitated condition and frequent need for invasive procedures. The aim of this study was to characterize the incidence and epidemiology of candidemia over a seven-year period in intensive care units (ICUs) and the use of fluconazole and caspofungin in a large university-affiliated hospital. All cases of candidemia were identified by surveillance, using the Centers for Diseases Control and Prevention criteria. Demographic variables, use of antifungal (fluconazole and caspofungin) and patient outcomes were evaluated. The χ² test for linear trend was employed to evaluate the distribution of Candida spp. and the use of fluconazole and caspofungin by defined daily dose (DDD) per 1,000 patients-days during the study period. One hundred and eight episodes of candidemia were identified. The overall incidence of candidemia (P = 0.20) and incidence of non-Candida albicans Candida infections (P = 0.32) remained stable over the study period and ranged from 0.3–0.9 episodes per 1,000 catheter-days and 0.39–0.83 episodes per 1,000 patients-days. However, the use of fluconazole and caspofungin increased significantly (P < 0.001). While there were no reports of the use of fluconazole for prophylaxis in 1999, its use for this purpose increased from 3% in 2000 to 7.0% (P = 0.07) in 2006. C. albicans was the most frequent species isolated and burns and cancer were the most frequent underlying conditions. The overall mortality was 76%. There was no difference between C. albicans and non-C. albicans Candida infections when the crude and 14-day mortality rates were compared. Our data demonstrated that C. albicans is still the most frequent species causing candidemia in our intensive care units. Our rates of candidemia are lower than those reported from the region and similar to American and European hospitals. Although the incidence of blood stream infections (BSI) and candidemia remained stable, the use of fluconazole and caspofungin increased significantly over the years included in this study but had no impact on the incidence of infections caused by non-C. albicans Candida species.

Keywords Candidemia, fluconazole, intensive care unit

Introduction
Candidemia is associated with high morbidity and mortality resulting in significant increase in the duration of hospitalizations and healthcare costs [1,2]. Critically ill patients are at particular risk for candidemia because of their debilitated condition and frequent
need for invasive procedures [3,4]. The use of intravascular devices is one of the most important risk factors associated with the development of nosocomial primary bloodstream infection (BSI) and is also a risk factor for candidemia in intensive care units (ICU) [3–5].

Although Candida albicans has been the predominant etiologic agent for several decades, a substantial shift towards non-C. albicans Candida species has been observed more recently in many series [1,6–8]. Several studies have attributed these epidemiological changes to the increased use of prophylaxis with azoles, but this remains a subject of debate.

The objective of the present investigation was to characterize the incidence and epidemiology of candidemia in the ICUs and the use of antifungals (fluconazole and caspofungin) over a seven-year period in a large university-affiliated hospital.

Methods

Setting and study population

This study was performed from 1999 to 2006, in the Hospital das Clínicas of University of São Paulo. This is a tertiary care hospital with a 945 bed main building and 120 beds in 12 ICUs. The hospital has a policy of restricting the use of several antibiotics including fluconazole, voriconazole, lipid amphotericin B, echinocandins (caspofungin), as well as quinolone, 4th generation cephalosporines, piperacillin-tazobactam, vancomycin, teicoplanin, linezolid, carbapenem and polymyxins. While voriconazole is not recommended in our hospital for the treatment of candidemia, amphotericin B (conventional or lipid), fluconazole and caspofungin were, until 2006, the drugs of choice to treat this fungal infection. The latter antifungal has been available since 2003 in our hospital, but due to its higher cost in Brazil, caspofungin is recommended only in the treatment of patients with candidemia or Aspergillus spp. infections with whom amphotericin B (conventional or lipid), fluconazole, and voriconazole cannot be used. The infection control committee recommends the replacement of all central venous catheters in case of documented candidemia.

Definition of Candidemia

All cases of nosocomial candidemia were identified by concurrent surveillance, using the Centers for Diseases Control and Prevention (CDC) criteria. [9] Such an infection was defined when one or more cultures inoculated with blood samples drawn at least 48 hours after the patient’s admission to ICU yielded a yeast with no other documented source except for the central venous catheter. Repeated isolates of the same species from the same patient were recorded as one episode of candidemia.

Surveillance of Candidemia

The data were collected by the infection control team prospectively using the National Nosocomial Infection Surveillance (NNIS) system now named National Healthcare Safety Network (NHSN). Peripheral blood samples were inoculated into anaerobic and aerobic bottles (Bactec 9240 and aerobic plus bottles). Clinical information and microbiological data were recorded by the infection-control team. Blood stream infection and candidemia rates were calculated using as the denominator patient-days and catheter-days. Crude mortality and deaths that occurred during the 14 days from the first recovery of a suspected pathogen from blood specimens were evaluated. Cases of candidemia due to C. albicans were compared with those caused by non-C. albicans Candida species. The following variables were evaluated; age, sex, length of stay, underlying diseases, central venous catheter, previous use of fluconazole, and outcome.

Measure of antifungal use

To enable appropriate interpretation of the data, the quantities of antifungals used between 1999–2006 were converted to the defined daily doses (DDD) per 1,000 patients-days. The DDDs of an antifungal agent are calculated by dividing the total grams of the antifungal agent employed by the number of grams in an average daily dose of the same agent, i.e., 400 mg for fluconazole and 50 mg for caspofungin divided by 1,000 patient-days [10].

Statistics

Data were analyzed using EpiInfo 6.04 software (CDC) [11]. The χ² and Fisher test were performed to compare the categorical variables among the main microorganisms isolated, and the Wilcoxon test for the continuous variables. The χ² test for linear trend was used to evaluate the distribution of Candida spp. and the use of fluconazole and caspofungin (DDD) during the study period.
Results

Candidemia incidence

The incidence of BSI did not change significantly during the study period, ranging from 8.3 to 10.8 episodes per 1,000 patient-days and 10.2 to 15.04 episodes per 1,000 catheter-days (Fig. 1). Candida spp. accounted for 5.6% of the total BSI.

Epidemiology of Candidemia

The overall incidence of candidemia (P=0.20) and incidence of non-C. albicans Candida infections (P = 0.32) remained stable over the study period, ranging from 0.33 to 0.9 episodes per 1,000 catheter-days and 0.39 to 0.83 episodes per 1,000 patients-days. Over 7 years, 108 episodes of candidemia were detected, of which 40% were caused by C. albicans, 34% by C. tropicalis, 18% C. parapsilosis, 3% C. krusei, 1% C. guillhermondii, a similar percentage by C. glabrata and 3% due to other etiologic agents (Fig. 2).

Thirty-three cases involving Candida albicans were compared with 40 in which non-C. albicans Candida species were the etiologic agents. The main demographic and epidemiological characteristics of cases are seen in Table 1. In general, the most frequent underlying diseases among patients with candidemia were burns (11%), followed by cancer (9.5%), renal disease (9.5%), cardiovascular disease (8%), gastrointestinal disease (7%) and solid organ transplantation (7%). HIV was present in 5.5% of the cases. However, among patients with non-C. albicans Candida caused candidemia, the most frequent underlying diseases were cancer (15%), followed by burn (10%), cardiologic diseases (10%) and solid organ transplant (10%).

Central venous catheters were present in 100% of patients. There is no difference among patients with candidemia due to C. albicans with cases caused by non-C. albicans Candida spp when compared on the basis of the previous use of fluconazole (Table 1).

The mean time from admission into the ICU to the development of a BSI was 15 days for C. albicans and 18 days for non-C. albicans Candida spp. The overall mortality was 76%, the 14-day and crude mortality associated with the Candida spp. are outlined in Table 2. There is no difference in the 14-day and crude mortality between cases caused by C. albicans and non-C. albicans Candida spp. (Table 2). Crude mortality in those cases of candidemia caused by C. parapsilosis was 84%, 83% when C. tropicalis was the etiologic agent and 73% if due to C. albicans.

Discussion

Since the attack rate of hospital-acquired BSIs and candidemia varies with the type of population studied, the size of institution and ward location, and the length of the patient’s stay in the hospital [1,2,12,13], it is difficult to compare data between hospitals.

Data from the last National Healthcare Safety Network (NHSN) report showed a low rate of BSI among...
American hospitals [12]. However, rates of BSI in Latin America are higher than those reported from the United States (US) and Europe, ranging from 11.3 to 23 cases per 1,000 catheter-days [13–15]. The rates of candidemia also varied over the world, ranging from less than 1 to over 3 episodes per 1,000 patients-days [1,2,16,17].

A number of reports indicate a substantial increase in Candida infections in US and Europe during the last years [1,16]. Candida spp. have been shown to be the fourth most common cause of nosocomial BSI in the US [1]. The most recent data from the SCOPE (Surveillance and Control of Pathogens of Epidemiologic Importance) project revealed that the most common pathogens causing nosocomial BSI were CNS (31%), followed by Staphylococcus aureus (20%), enterococci (9%) and Candida species (9%) [1]. Our results show that the overall incidence of candidemia and BSI due to non-\textit{C. albicans} Candida spp. remained unchanged over 7 years.

A study involving 11 Brazilian hospitals that detected 712 cases of candidemia, showed an overall incidence of 2.49 cases per 1,000 admissions and 0.37 cases per 1,000 patient-days [18]. The 30-day crude mortality was 54%. \textit{C. albicans} was the most common etiologic agent (40.9%), followed by \textit{C. tropicalis} (20.9%) and \textit{C. parapsilosis} (20.5%) [18]. Another recent study in Brazilian hospitals showed that the incidence rate of candidemia was 1.66 candidemic episodes per 1,000 hospital admissions. \textit{C. albicans} was again the most frequently species isolated in all hospitals, but \textit{Candida} species other than \textit{C. albicans} accounted for 62% of isolates, including predominantly \textit{C. parapsilosis} and \textit{C. tropicalis} [19].

**Table 1** The main demographic and epidemiological characteristics of 73 patients with candidemia in ICU over a 7-year period (1999–2006) in the Hospital das Clínicas of University of São Paulo, Brazil.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total of patients</th>
<th>\textit{C. albicans} (N = 33)</th>
<th>Candida non-albicans (N = 40)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (means)</td>
<td>12–86 (51) years</td>
<td>15–86 (51) years</td>
<td>12–86 (51) years</td>
<td>NS*</td>
</tr>
<tr>
<td>Male</td>
<td>51%</td>
<td>40%</td>
<td>60%</td>
<td>NS</td>
</tr>
<tr>
<td>Central venous catheter (%)</td>
<td>73 (100%)</td>
<td>33 (100%)</td>
<td>40 (100%)</td>
<td>_</td>
</tr>
<tr>
<td>Duration of hospitalization before positive blood culture (means)</td>
<td>16,4 days</td>
<td>15 days</td>
<td>18 days</td>
<td>NS</td>
</tr>
<tr>
<td>Previous use of fluconazole</td>
<td>2 (5%)</td>
<td>0</td>
<td>2 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Underlying diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burn</td>
<td>8 (10.9%)</td>
<td>4 (12.1%)</td>
<td>4 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cancer</td>
<td>7 (9.5%)</td>
<td>1 (3.1%)</td>
<td>6 (15%)</td>
<td>NS</td>
</tr>
<tr>
<td>Renal diseases</td>
<td>7 (9.5%)</td>
<td>7 (21.2%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cardiologic diseases</td>
<td>6 (8.2%)</td>
<td>2 (6%)</td>
<td>4 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>5 (7%)</td>
<td>1 (3.1%)</td>
<td>4 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>GIT</td>
<td>5 (7%)</td>
<td>4 (12.1%)</td>
<td>1 (2%)</td>
<td>NS</td>
</tr>
<tr>
<td>HIV</td>
<td>4 (5.5%)</td>
<td>3 (9.1%)</td>
<td>1 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Neurologic diseases</td>
<td>4 (5.5%)</td>
<td>3 (9.1%)</td>
<td>1 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Trauma</td>
<td>4 (5.5%)</td>
<td>2 (6%)</td>
<td>2 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>2 (3%)</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td>–</td>
</tr>
<tr>
<td>Others</td>
<td>21 (28.4%)</td>
<td>6 (18.2%)</td>
<td>15 (37%)</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>73 (100%)</td>
<td>33 (100%)</td>
<td>40 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

*NS, not significant; **GI, gastrointestinal tract diseases.
Despite the fact that *C. albicans* has been the predominant species for several decades, a substantial shift towards non-*C. albicans* Candida species has been observed in some hospitals [1,20,21]. The association between the use of fluconazole and the increase of infection due to non-*C. albicans* Candida, however, is still controversial [21,22]. Lin *et al.* compared 68 patients with candidemia with 121 controls and showed that exposure to antibacterial agents, specifically vancomycin or piperacillin-tazobactam, but not fluconazole, was associated with subsequent hospital-acquired *C. glabrata* or *C. krusei* candidemia [22]. In another study, there was no evidence that the use of fluconazole was linked to the predominance of *C. tropicalis* as the cause of candidemia over a 18-month period [21]. In contrast, others authors have demonstrated an association between the increased use of azoles on the rates of candidemia caused by non-*C. albicans* Candida [23–26]. A recent study performed in a university hospital in Vienna with 2,200-beds, showed that the use of azoles (DDD), particularly fluconazole was correlated with the increased incidence of candidemia caused by non-*C. albicans* Candida spp. [24]. Another investigation that involved a review of all cases of candidemia over a 10-year period and data on the annual consumption of prescribed antifungal drugs (annual mean defined daily dose), provided evidence of a link between the increased prevalence of *C. glabrata* and the high level of prescription of fluconazole at prophylactic doses [25]. Finally, a recent study showed that the incidence of infections caused by most non-*C. albicans Candida* species changed substantially in concomitance with a four fold increase in the use of fluconazole. These authors found that these increases were due to the usage of fluconazole at dosage of 200–400 mg/day as part of a prophylactic strategy in high-risk patients [26]. The World Health Organization (WHO) recommends standardizing the consumption of antibiotic on the basis of 100 patient-days [27], but reports in the literature have generally reported antibiotic use as 1,000 patient-days [10]. As our study involved ICUs, we employed the DDD per 1,000 patient-days. The present investigation demonstrated that *C. albicans* remained the most frequently recovered *Candida* specie over 7-year and that the proportion of cases due to non-*C. albicans* Candida remained stable despite the significant increase of use of fluconazole. The greater use of this antifungal reflects its adoption in the prophylaxis therapy in critically ill and transplant patients reported in the literature [28–30]. However, a similar increase was found in this investigation not to be statistically significant. We also demonstrated an increased in the use of caspofungin over the study period. This is the first data regarding its use in Brazil. Unfortunately, this antifungal is expensive and is only available in a few university hospitals in the country. A recent study evaluated 469 episodes of candidemia between year 2002 and 2006 and compared

### Table 2
Comparison of 14-day mortality and crude mortality of patients with Candidemia due to *Candida albicans* and non-albicans Candida species over a 7-year period (1999–2006) in the Hospital das Clínicas of University of São Paulo, Brazil.

<table>
<thead>
<tr>
<th>Number of death/total of candidemia (%)</th>
<th>Candida non-albicans</th>
<th>Candida albicans</th>
<th>RR 95% IC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-days mortality</td>
<td>20/40 (50%)</td>
<td>15/33 (45%)</td>
<td>1.10 (0.68–1.79)</td>
<td>0.87</td>
</tr>
<tr>
<td>Crude mortality</td>
<td>32/40 (80%)</td>
<td>24/33 (72%)</td>
<td>1.10 (0.85–1.43)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

![Fig. 3](https://example.com/fig3.png)

**Fig. 3** Comparison of Incidence of Candidemia due to *Candida albicans* and non-albicans Candida species per 1,000 patient-days with use of fluconazole (DDD) in ICUs in a teaching Brazilian hospital over 7-year period. Y axis (0–200 g) refers to DDD of fluconazole per 1,000 patient-days. Secondary Y axis (0–3 episodes) refers to incidence of Candidemia by 1,000 patient-days.

* Fluconazole DDD.
the incidence of *Candida* species with the consumption of antifungal using DDD. These authors found correlations between increased caspofungin usage \( (P = 0.017) \) and an increase in *C. parapsilosis* candidemia. However, they also noted a decrease in *C. tropicalis* candidemia \( (P < 0.05) \) and a trend towards a similar decrease in cases involving *C. glabrata \( (P = 0.1) \) \[31\]. Despite the increased use of caspofungin in our hospital, the present study could not find a correlation between its use and the incidence of candidemia due to non-*C. albicans Candida* spp.

Interestingly there was no difference between patients with candidemia due to *C. albicans* and non-*C. albicans Candida* spp. related to the previous use of fluconazole. This fact could be explained by the small number of cases caused by *C. glabrata* and *C. krusei* in the present study. Our results are similar to data from others Brazilian hospitals that indicated that the incidence of specie resistance or susceptible-dose-dependent to fluconazole is rare in the country \[18,19,32\]. The direct impact of the prophylactic doses of fluconazole on the incidence of non-*C. albicans Candida* spp. infections was evaluated by Sfadar et al. \[33\]. These authors showed that the predominance of *C. glabrata* and *C. krusei* breakthrough infections in allogeneic marrow transplants patients being treated with 100 to 200 mg of fluconazole was similar to that seen with high-dose fluconazole \( (400 \text{mg}) \) prophylaxis, but there was no impact of low-dose fluconazole in terms of increased incidence of non-susceptible *Candida* species \[33\]. It seems that the increase in incidence of non-*C. albicans Candida* spp. causing candidemia in several centers could not be only explained by the increase in the use of this antifungal. It is more complex and could be related to type of the patient populations, CVC cares and perhaps local climate.

In contrast with others reports that suggested that *C. parapsilosis* is a leading cause of candidemia in South American hospitals \[18,19,32\], it was only the third most common cause of candidemia in our hospital and its incidence remained stable over the study period. Candidemia due to *C. parapsilosis* is regarded as having an external source, such as catheters or contamination of intravenous solutions and medical devices, as opposed the endogenous origins of most cases of candidemia caused by other species \[32\]. The reasons why candidemia caused by *C. parapsilosis* is so frequent in Latin America (particularly in Brazil) are not known but could be related to inappropriate central venous catheters care practices.

The mortality rate associated with nosocomial candidemia varies widely \[2,34–37\] and it is extremely difficult to differentiate between mortality directly attributable to candidemia and that caused by the patients’ underlying clinical conditions. This difficulty is compounded by the fact that previous studies included patients from general medical wards, as well as cancer and intensive care units, and thereby encompassing wide range of underlying illnesses of variable severity. In addition, candidemia due to *C. parapsilosis* has been associated with better patient outcomes \[32\]. In the present study the crude mortality of patients with such infections was not different than those caused by other *Candida* species such as *C. tropicalis* and *C. albicans*. We also found no difference with respect to 14-day and crude mortality when cases caused by *Candida albicans* with those due to non-*C. albicans Candida* spp.

Independent risk factors for death among patients with candidemia in the literature include advanced age, increased severity score such as Acute Physiology and Chronic Health Evaluation II score, and co-morbidity \[2,19,34–36\]. A limitation of the present study was that data collection was restricted to those variables routinely evaluated in the nosocomial surveillance system which did not include severity scores. Despite this fact, the presence of CVC and type of underlying diseases can be used as severity surrogates in our patient population. Candidemia in our investigation was associated with a higher overall mortality (76%) when compared with the results in other reports \[2,19,34–36\]. Perhaps this difference can be explain by the fact that our study included only patients in intensive care units, who were severely ill as a result of burns or cancer, had central venous catheter lines and had a mean of duration of hospitalization before the onset of candidemia of 16 days. Another important limitation with our investigations was the small number of patients with candidemia over the 7-year study period which could explain the reason why we could not determine risk factors associated with prognosis.

Our data demonstrated that *C. albicans* is still the most cause of candidemia in our intensive care units. Our rates of candidemia are lower than described in others reports from the region and similar to that found in American and European hospitals. Although the incidence of BSI and candidemia remained stable, the use of fluconazole and caspofungin increased significantly over years and had no impact on the incidence of infection due to non-*C. albicans Candida* spp.

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