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## Original article

# Secular trends of candidemia at a Brazilian tertiary care teaching hospital

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### ABSTRACT

**Background:** Candidemia is the most frequent invasive fungal disease in hospitalized patients, and is associated with high mortality rates. The main objective of this study was to evaluate changes in the epidemiology of candidemia at a tertiary care hospital in a 21-year period.

**Methods:** We evaluated all episodes of candidemia diagnosed between 1996 and 2016 at a University-affiliated tertiary care hospital in Brazil. We arbitrarily divided the study period in 3: 1996–2002 (period 1), 2003–2009 (period 2) and 2010–2016 (period 3). Incidence rates were calculated using hospital admissions as denominator.

**Results:** We observed 331 episodes of candidemia. The incidence was 1.30 episodes per 1000 admissions, with no significant change over time. *Candida albicans* (37.5%), *C. tropicalis* (28.1%), *C. parapsilosis* (18.4%) and *C. glabrata* (6.9%) were the most frequent species. The proportion of patients receiving treatment increased (65.5%, 79.4% and 74.7% in periods 1, 2 and 3, respectively,  $p=0.04$ ), and the median time from candidemia to treatment initiation decreased from 4 days in period 1 (range 0–32 days) to 2 days in period 2 (range 0–33 days) and 2 days in period 3 (range 0–14 days,  $p<0.001$ ). We observed a significant decrease in the use of deoxycholate amphotericin B (47.4%, 14.8% and 11.9%), and an increase in the use of echinocandins (0%, 2.8% and 49.1%;  $p<0.001$ ). The APACHE II score increased over time (median 16, 17.5, and 22,  $p<0.001$ ). The overall 30-day mortality was 58.9%, and did not change significantly over the study period.

**Conclusions:** There was an improvement in patient care, with an increase in the proportion of patients receiving treatment and a decrease in the time to treatment initiation, but no improvement in the outcome, possibly because the proportion of sicker patients increased over time.

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## Introduction

Candidemia is a serious bloodstream infection, with incidence rates between one and three episodes/1000 admissions, and crude mortality rates exceeding 40% in Brazilian tertiary care public hospitals.<sup>1–9</sup> Epidemiologic studies conducted in the region have shown that *Candida albicans*, *Candida tropicalis* and *Candida parapsilosis* account for over 80% of episodes of candidemia, and *Candida glabrata* accounts for less than 10% of cases in public hospitals.<sup>1,7</sup> However, in private hospitals the incidence of candidemia due to *C. glabrata* is higher,<sup>10,11</sup> and a trend for an increase in the incidence in one public hospital has been reported.<sup>12</sup>

Over the past 15 years, changes in the epidemiology of candidemia have been documented, including shifts in species distribution,<sup>13</sup> changes in patterns of resistance<sup>14</sup> and therapeutic practices, with an increase in the use of echinocandins as primary therapy.<sup>3</sup> In this study we sought to evaluate changes in the epidemiology of candidemia at a tertiary care teaching public hospital in Brazil over the course of two decades.

## Patients and methods

We conducted a retrospective study at University Hospital, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil. This is a tertiary care hospital with 450 beds with different medical and surgical specialties, and admits patients older than 12 years. We evaluated all episodes of candidemia diagnosed in the hospital from January 1996 to December 2016. The study was approved by the local Ethical Committee (number 30/03). Since 2010 there was a reduction in the overall number of beds in the hospital. However, the epidemiologic profile of patients did not change in the study period. Throughout the study period the decision of the choice of the antifungal drug for the treatment of candidemia and catheter management were at the discretion of the attending physicians.

An episode of candidemia was defined as the first isolation (incident candidemia) of *Candida* species from a blood culture in a patient with signs of infection. If a new blood culture was positive within 30 days from the day of the incident candidemia, it was considered part of the same episode. However, if there was a new positive blood culture that was obtained beyond 30 days from the incident candidemia, this new positive blood culture was considered as a new episode of candidemia.

A case of candidemia was identified by looking at the records of the microbiology laboratory. Once a case was identified, patients were followed for 30 days from the date of the incident candidemia. All data were collected prospectively, using a standardized case report form, with the help of a dictionary of terms containing all definitions of the variables collected. The following data were collected: age, gender, date of hospitalization, medical ward, underlying medical condition, co-morbidities (liver, lung, cardiac, neurological or renal disease), receipt of transplant, hemodialysis, parenteral nutrition, mechanical ventilation, surgery (of any type requiring any anesthesia other than local anesthesia within the 3 months prior to the incident candidemia),

neutropenia (<500 neutrophils/mm<sup>3</sup>), central venous catheter (CVC), receipt of corticosteroids, H2 blockers, antibiotics or antifungal agents (in the previous 2 weeks), APACHE II score on the day of the incident candidemia, hypotension or receipt of vasoactive drugs in the previous 2 days, fever, antifungal treatment, and the outcome (alive or dead 30 days after the incident candidemia).

Blood cultures were collected by clinical indication, and processed using the automated system Bactec (Becton Dickinson, NJ, USA) in 1996 and 1997, and BactAlert (bioMérieux, Marcy-l'Étoile, France) from 1998 to 2016. Isolates were identified according to their microscopic morphology on cornmeal Tween 80 agar, complemented by biochemical tests using the ID 32C system (BioMérieux AS, Marcy l'Étoile, France) or Vitek 2 cards (BioMérieux AS, Marcy l'Étoile, France).

In order to evaluate epidemiologic trends of candidemia, we arbitrarily divided the 21-year study period in 3: 1996–2002 (period 1), 2003–2009 (period 2) and 2010–2016 (period 3). In the analysis, we defined three age categories: children ( $\leq 18$  years), adults (19–59 years) and elderly ( $\geq 60$  years). Incidence rates were calculated using hospital admissions as denominator. Comparisons of categorical variables were undertaken using Fisher or Chi-square test as appropriate, and for continuous variables we used the Kruskal–Wallis test. The incidences of candidemia in the three periods were compared by the chi-square test for trend. *P* values <0.05 were considered statistically significant. All statistical analyses were performed in the SPSS software (version 15, SPSS, Inc.).

## Results

During the study period we observed 331 episodes of candidemia in 324 patients. The median age of the 324 patients was 56 years (range 12–92), and 52.7% were males. The overall incidence of candidemia was 1.30 episodes per 1000 admissions, and did not change significantly in the three study periods: 1.05 per 1000 admissions in period 1, 1.50 in period 2, and 1.38 in period 3 ( $p=0.58$ ).

Table 1 shows the characteristics of the 331 episodes in the three study periods. The median age increased slightly over time, from 52.5 years in period 1 to 56.5 years in period 2 and 60.5 years in period 3 ( $p=0.06$ ). On the other hand, there was a statistically significant increase in the APACHE II score over time (16, 17.5 and 22, in periods 1, 2 and 3, respectively,  $p<0.001$ ). Other significant changes comparing periods 1, 2 and 3 included an increase in the proportion of patients with chronic renal failure ( $p=0.02$ ), cardiac disease ( $p=0.03$ ), receiving dialysis ( $p=0.003$ ), corticosteroids ( $p<0.001$ ), vasoactive amines ( $p<0.001$ ), and on mechanical ventilation ( $p=0.02$ ). The proportion of patients with liver disease increased from period 1 to 2 and decreased in period 3 ( $p=0.02$ ). Of note, the proportion of patients in intensive care unit (ICU) did not change significantly.

The most frequent etiologic agent of candidemia was *C. albicans* (124 episodes, 37.5%), followed by *C. tropicalis* (93 episodes, 28.1%), *C. parapsilosis* (61 episodes, 18.4%) and *C. glabrata* (23 episodes, 6.9%). The remaining 30 episodes were caused by *C. pelliculosa* (7 episodes), *C. krusei* and *C. famata* (6 episodes each), *C. guilliermondii* (5 episodes), *C. kefyr* (3

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