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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.[1–9] 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.[1,7] However, in private hospitals the incidence of candidemia due to *C. glabrata* is higher,[10,11] and a trend for an increase in the incidence in one public hospital has been reported.[12]

Over the past 15 years, changes in the epidemiology of candidemia have been documented, including shifts in species distribution,[13] changes in patterns of resistance[14] and therapeutic practices, with an increase in the use of echinocandins as primary therapy.[3] 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, neurologic 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^3), 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'Etolie, 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 lÉtoile, France) or Vitek 2 cards (BioMérieux AS, Marcy lÉtoile, 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 (≤18 years), adults (19–59 years) and elderly (≥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*

Table 1 – Characteristics of 331 episodes of candidemia in three periods, 1996–2002 (period 1), 2003–2009 (period 2) and 2010–2016 (period 3).

Variable	Period 1 N = 116	Period 2 N = 136	Period 3 N = 79	p value
Gender Male:Female	63:53	72:64	39:40	0.79
Age, median (range)	52.5 (12–89)	56.5 (14–92)	60.5 (21–91)	0.06
Time (days) from admission to candidemia, median (range)	18.5 (0–255)	16 (0–99)	21 (0–295)	0.07
Admission in an ICU	27 (23.3)	41 (30.1)	28 (35.4)	0.17
APACHE II score, median (range)[a]	16 (2–36)	17.5 (4–60)	22 (10–43)	<0.001
Cancer	44 (37.9)	50 (36.8)	29 (36.7)	0.98
Hematologic malignancy	21 (18.1)	22 (16.2)	16 (20.3)	0.75
Solid tumor	23 (19.8)	28 (20.6)	13 (16.5)	0.75
Diabetes	21 (18.1)	36 (26.5)	16 (20.3)	0.25
Renal failure	50 (43.1)	69 (50.7)	46 (58.2)	0.11
Chronic renal failure	14 (12.1)	27 (19.9)	22 (27.8)	0.02
Dialysis	18 (15.5)	35 (25.7)	29 (36.7)	0.003
Liver disease	12 (10.3)	27 (19.9)	6 (7.6)	0.02
Neurologic disease	9 (7.8)	20 (14.7)	15 (19.0)	0.06
Transplant	10 (8.6)	23 (16.9)	7 (8.9	0.08
Cardiac disease	39 (33.6)	66 (48.5)	38 (48.1)	0.03
Lung disease	10 (8.6)	16 (11.8)	11 (13.9)	0.49
Surgery	57 (49.1)	57 (41.9)	31 (39.2)	0.33
Abdominal surgery	26 (22.4)	28 (20.6)	12 (15.2)	0.45
Other surgery	31 (26.7)	29 (21.3)	19 (24.0)	0.42
Mechanical ventilation	41 (35.3)	64 (47.1)	44 (55.7)	0.02
Parenteral nutrition	16 (13.8)	20 (14.7)	13 (16.5)	0.88
Central venous catheter	108 (93.1)	126 (92.6)	75 (94.9)	0.80
Neutropenia	16 (13.8)	13 (9.6)	7 (8.9)	0.45
Receipt of antibiotics	95 (81.9)	116 (85.3)	69 (87.3)	0.56
Receipt of corticosteroids	37 (31.9)	66 (47.1)	51 (64.6)	<0.001
Hypotension	43 (37.1)	70 (51.5)	46 (58.2)	0.009
Receipt of vasoactive drugs	29 (25.0)	57 (41.9)	43 (54.4)	<0.001
Fever	93 (80.2)	97 (71.3)	52 (65.8)	0.07
Previous use of fluconazole	11 (9.5)	19 (14.0)	5 (6.5)	0.21
Candida species (more frequent)				
C. albicans	44 (37.9)	49 (36.0)	31 (39.2)	0.89
C. tropicalis	33 (28.4)	31 (22.8)	29 (36.7)	0.09
C. parapsilosis	18 (15.5)	31 (22.8)	12 (15.2)	0.23
C. glabrata	9 (7.8)	9 (6.6)	5 (6.3)	0.91

Numbers in parenthesis represent percentage unless specified. APACHE, acute physiologic and chronic health evaluation.

[a] APACHE II score available for 113 patients in period 1, 132 in period 2, and 63 in period 3.

(6 episodes each), *C. guilliermondii* (5 episodes), *C. kefyr* (3 episodes), and *C. zeylanoides*, *C. lipolytica* and *Pichia ohmeri* (1 episode each). There was no significant difference in species distribution during the three periods (Table 1). Previous exposure to fluconazole was associated with a higher proportion of candidemia due to *C. glabrata* or *C. krusei* (20.7% with vs. 9.7% without previous exposure to fluconazole), but the difference was not statistically significant ($p = 0.10$ and $p = 0.06$, respectively).

Table 2 shows the antifungal agents used as primary therapy of candidemia. Overall, antifungal treatment for candidemia was given in 243 episodes (78.1%). The proportion of patients receiving treatment in periods 1, 2 and 3 was 65.5%, 79.4%, and 74.7%, respectively ($p = 0.04$). Among patients who received treatment, the median time from the date of the incident candidemia to the start of antifungal therapy reduced 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, $p < 0.001$). Primary therapy differed significantly in the three periods, with a sharp reduction in the use of deoxycholate amphotericin B (47.4% in period 1, 14.8% in period 2 and 11.9% in period 3), an increased use of echinocandins (0% in period 1, 2.8% in period 2 and 49.1% in period 3), whereas the use of azoles increased in period 2 (from 48.7% to 64.8%) and decreased in period 3 (39.0%, $p < 0.001$).

Patients who did not receive treatment were more likely to be older (61 years, range 15–92 vs. 56 years, range 11–92, $p = 0.03$), to have renal failure (60.2% vs. 46.1%, $p = 0.02$), solid tumor (28.4% vs. 16.0%, $p = 0.01$), to be on mechanical ventilation (55.7% vs. 41.2%, $p = 0.02$), hypotensive (69.3% vs. 40.3%, $p < 0.001$) to receive vasoactive drugs (59.1% vs. 31.7%, $p < 0.001$), to have higher median APACHE II score (22, range 3–53 vs. 16, range 2–60, $p = 0.001$) and to have candidemia due to *C. glabrata* (15.9% vs. 3.7%, $p < 0.001$). By contrast, no treatment was less frequent in candidemia due to *C. parapsilosis* (10.2% vs. 21.4%, $p = 0.02$). Seventy-five of the 88 patients who did not receive treatment died, at a median of 2 days from the date of the incident candidemia (range 0–20). Among the 13 patients who did not receive treatment and survived, nine occurred in period 1, three in period 2, and one in period 3.

Table 2 – Antifungal therapy and the outcome in 331 episodes of candidemia in three periods, 1996–2002 (period 1), 2003–2009 (period 2) and 2010–2016 (period 3).

Variable	Period 1 N = 116	Period 2 N = 136	Period 3 N = 79	*p* value
Received treatment	76 (65.5)	108 (79.4)	59 (74.7)	0.04
Agent[a]				<0.001
Azole[b]	37/76 (48.7)	70/108 (64.8)	23/59 (39.0)	
Deoxycholate amphotericin B	36/76 (47.4)	16/108 (14.8)	7/59 (11.9)	
Echinocandin	0	3/108 (2.8)	29/59 (49.1)	
30-day mortality	69 (59.5)	78 (57.4)	48 (60.8)	0.88

[a] In 22 episodes a blind drug from a randomized trial comparing an echinocandin with liposomal amphotericin B was given.
[b] Fluconazole in all but one episode in period 1, treated with voriconazole.

Five episodes were caused by *C. parapsilosis*, and four occurred in patients with hematologic malignancies.

The overall 30-day mortality rate was 58.9% and did not change significantly over time (59.5% in period 1, 57.4% in period 2 and 60.8% in period 3, $p = 0.88$). The death rate in the three age categories was 41.7% in children, 51.5% in adults, and 68.8% in elderly patients ($p = 0.004$).

Discussion

We evaluated trends in the epidemiology of candidemia in a 20-year period, and observed that: (a) the incidence of candidemia did not change significantly over time; (b) there was a slight increase in the median age of patients with candidemia; (c) the occurrence of some factors such as mechanical ventilation and the use of vasoactive amines and corticosteroids increased over time (d) the severity of illness increased; (e) species distribution did not change over time, with *C. albicans*, *C. tropicalis* and *C. parapsilosis* accounting for over 80% of cases of candidemia; (f) the proportion of patients receiving antifungal therapy increased significantly between periods 1 and 2, and the time from candidemia to the initiation of treatment decreased over time; (g) we observed a change in therapeutic practices, with a reduction in the use of deoxycholate amphotericin B and an increase in the use of echinocandins as primary therapy; and (h) the mortality was high, and did not change significantly in the three study periods.

The epidemiology of candidemia in Brazil was first characterized in a study that analyzed 145 episodes from 6 hospitals in the 1990s. In that study, *C. albicans*, *C. tropicalis* and *C. parapsilosis* accounted for the majority of cases, most patients received deoxycholate amphotericin B as primary therapy, and the mortality rate was 50%.[15] The same epidemiologic characteristics were reported in a larger study from the same group, evaluating 712 episodes of candidemia from 11 centers in 2003 and 2004,[1] and in a study in 25 centers from 8 Latin American countries.[7] The characteristics of patients in the present study are quite similar to those reported in these studies.

Epidemiologic trends of candidemia in Brazil were evaluated in five studies. The first analyzed 73 episodes of candidemia in ICU patients in a 7-year period in a teaching hospital. While no change in the incidence or species distribution was observed, there was an increase in the use of fluconazole and an echinocandin.[16] Another study evaluated epidemiologic trends of candidemia in 10 years in a private hospital in São Paulo. Incidence rates and species distribution did not change, but a decrease in the use of deoxycholate amphotericin B and an increase in the use of echinocandins was observed. The mortality rate was 44.2%.[17] Other study evaluated trends in the epidemiology of candidemia in 2 tertiary care hospitals in Cuiabá, and found an increase in the incidence comparing 2 periods of 3 years.[5] Another study analyzing 388 episodes of candidemia in two periods (1994–1999 and 2000–2004) also noted an increase in the incidence of candidemia over time. In addition, patients in period 2 were older, and had more comorbidities. No change in species distribution or mortality was observed.[18] The latter study evaluated 647 episodes of candidemia in ICU patients from 22 public and private Brazilian hospitals in two periods: 2003–2007 and 2008–2012. In period 2 there was an increase in the prior exposure to fluconazole and candidemia due to *C. glabrata*, and a reduction in the use of deoxycholate amphotericin B and an increase in the use of an echinocandin as primary therapy.[3] Many of the trends reported in these studies were observed in the present study, including the stable incidence and species distribution, increasing age, more co-morbidities and a shift from deoxycholate amphotericin B to an echinocandin in the primary therapy of candidemia.

Over the course of the three periods, we observed some important improvements in patient care, including a higher proportion of patients receiving treatment, a shorter time between the date of the incident candidemia and the initiation of therapy, and an increase in the use of echinocandins, which is associated with better outcomes.[19] These improvements should have resulted in a decrease in 30-day mortality. However, the mortality rate did not differ over time (59.5%, 57.4% and 60.8% in periods 1, 2 and 3, respectively). The most likely explanation for this observation is that these improvements in patient care may have been counterbalanced by the fact that over time the proportion of sicker patients increased, as shown by an increase in the median APACHE II score and in the proportion of patients under mechanical ventilation, hypotensive, and receiving vasoactive drugs.

Although the proportion of patients receiving treatment increased, between 20 and 25% of patients still do not receive treatment. An analysis of the characteristics of these patients suggests that these are very sick patients, with high APACHE II scores, on mechanical ventilation and vasoactive drugs. Indeed, the majority of untreated patients died (85.2%), at a median of two days from the incident candidemia. These data suggest that by the time blood cultures became positive the

patient was already dead. Interestingly, 13 patients did not receive treatment and survived. The large majority (9 episodes, 69%) occurred in period 1, and only one in period 3. Over the past 15 years many changes have occurred in the care of candidemia, including active laboratory-based search for cases of candidemia, consulting and educational measures. These measures may have contributed to better patient care.

The overall mortality in the present series was high (58.9%), with an increase in death rate in the three age strata. Compared to large series published in the region, our mortality rate was much higher. This may be explained by the fact that the median age in the present study (56 years) was higher than in other studies (41 years in the second Brazilian study,[1] and 26 years in the Latin American study[7]), because while in other studies patients from all ages (including neonates) were enrolled, our study was conducted in a hospital that admits only patients older than 12 years.

Our study has some limitations. While data were collected prospectively, the retrospective analysis was limited to the variables already collected. Likewise, there was some heterogeneity in the methods for processing blood cultures and species identification.

In conclusion, the incidence and species distribution of candidemia was similar to other studies conducted in Brazil, and did not change significantly over the 20-year period. There was a change in therapeutic practices, with a decrease in the time to treatment initiation and a change in primary therapy, from deoxycholate amphotericin B and fluconazole to an echinocandin. However, the 30-day mortality rate did not change, possibly because the proportion of sicker patients increased over time.

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Conflicts of interest

The authors declare no conflicts of interest.

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