

Candidemia in a Brazilian tertiary hospital: microbiological and clinical features over a six-year period

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Abstract: Yeasts are becoming a common cause of nosocomial fungal infections in immunocompromised patients. Such infections often develop into sepsis with high mortality rates. The aim of this study was to evaluate some of the numerous factors associated with the development of candidemia. Medical records were retrospectively analyzed of 98 *Candida* spp. patients. Results showed that the most prevalent risk factors for developing candidemia were: antibiotics and antifungal agents (93.9% and 79.6%, respectively); the use of central venous catheter (93.9%); mechanical ventilation (73.5%); and parenteral nutrition (60.2%). The main species of *Candida* found were: *C. parapsilosis* (37.76%), *C. albicans* (33.67%); and others (28.57%). *C. glabrata* showed the highest mortality rate (75%), followed by *C. tropicalis* (57.1%) and *C. albicans* (54.5%). The elevated mortality rate found in this study indicates that preventive measures against candidemia must be emphasized in hospitals.

Key words: candidemia, mortality, associated factors, *Candida albicans*.

INTRODUCTION

Several authors have reported a global increase in yeast infections over the past 20 years. *Candida* species can be found in the gastrointestinal tract of 20 to 80% of healthy adults, becoming pathogenic when host immune conditions are altered by offending factors (1). Of the invasive infections caused by *Candida* spp., blood infections, also known as candidemias, are the most clinically relevant (2). *Candida* spp. is currently one of the five main causes of blood infections in hospitals, and an increase in candidemia cases has been reported mainly in patients using antibiotics, under immunosuppressive therapy or parenteral nutrition, and in patients exposed to multiple invasive procedures (3, 4). Candidemia is one of the most common blood infections in tertiary hospitals; it has also been associated with long stay in hospitals and high mortality (5-8).

Although *Candida albicans* is the most frequent species isolated in patients with fungemia, cases of infections caused by other *Candida* species have increased (9-15). The frequency of *C. albicans* and other *Candida* species found in patients depends, among other factors, on the analyzed population and used therapy (16-19). The most commonly found species in Brazilian candidemia patients are *C. albicans*, *Candida parapsilosis*, and *Candida tropicalis* (20).

MATERIALS AND METHODS

We analyzed 98 yeast samples from different patients admitted to Botucatu Medical School University Hospital (HC-FMB) between 2000 and 2006 along with their medical records (obtained from the Statistical Medical Service – SAME, owned by HC-FMB). These patients developed symptoms of candidemia and samples were

isolated from hemocultures (Bactec Aerobic, Peds or Myco/F BD – Becton Dickinson, USA) by the Microbiology Sector of the Clinical Analysis Laboratory. Samples included in the present study had records with all clinical data evaluated and legible; also, the yeast strain had to have been isolated between 2000 and 2006. Samples which did not meet the criteria were excluded, as were samples without records or with nonviable strains.

We analyzed the records and collected data on candidemia factors associated with development, including: gender; length of hospitalization; death and cause of death; use of antifungal agents; use of antibiotics; nosocomial infection; diabetes mellitus; liver disease; chronic bowel disease; neoplasia; kidney disease; neutropenia; immunosuppressive therapy; bowel surgery; central venous catheter; parenteral nutrition; positive HIV serology test; use of corticosteroids; prematurity; and mechanical ventilation.

Sample size was calculated using the Fisher and Belle formula, with a 95% confidence interval and 5% precision for expected prevalence of fungemia patients. Beck-Sagué and Jarvis (21) study was used as reference, which had 10.4% fungemia patients.

Samples employed in this study were stored in nutrient broth with crioprotective agent at -70°C , in the Culture Collection of the Department of Microbiology and Immunology (Botucatu Biosciences Institute, UNESP). Yeast species were identified according to morphological and biochemical characteristics. Yeast samples were inoculated into plates with chromogenic growth medium Chromagar *Candida* (Difco, USA), for isolation and preliminary identification. Germ tube tests were then performed to assess filament and chlamydoconidia production and biochemical assays performed to check for carbohydrate production and assimilation. We used Vitek I (Durham, USA) for automated identification, which employs a plate with 40 different carbohydrate and amino acid tests, incubated at 35°C for 24 to 48 hours.

Data were sorted into charts and frequency and association tables. Numeric variables were presented as mean and standard deviation, when variables presented symmetrical (normal) distribution, or median and percentiles, in cases of asymmetrical distribution. Categorical variables were expressed by number and rate of

events and evaluated by the chi-squared test or Fisher's exact test (if $n < 10$). Normal distribution variables were evaluated by the Student's t test and non-normal variables by the Wilcoxon-Mann-Whitney test. ANOVA (analysis of variance) was used to compare the three groups. Results were considered significant if $p < 0.05$. The concordance test was used to analyze laboratory assays.

This study was approved by the Research Ethics Committee of Botucatu Medical School, UNESP, on October 2nd, 2006 (protocol number 490/2006).

RESULTS

Of the 98 evaluated candidemia cases, 33.67% were caused by *C. albicans* and 66.33% by other *Candida* species. *C. parapsilosis* had the highest percentage rate (37.7%). Only 12.2% of all samples were identified as *Candida* spp. due to technical difficulties in identification, even using different methods (Table 1).

When analyzing *Candida* species in relation to patient age, we can observe that other *Candida* species have a higher incidence in premature patients than *C. albicans*. Only 11.36% of patients aged less than one year presented candidemia caused by *C. albicans*, and *C. parapsilosis* was the most frequent cause of candidemia, affecting 56.8% of these patients (Table 2). Other *Candida* species were a little more frequent in younger patients whilst *C. albicans* infections prevailed in patients over 60 years (Figure 1).

Mortality rate in this study was 53.1% (Figure 2). Mortality distribution by species shows *C. guilliermondii* as the only species with less than 50% mortality rate; *C. glabrata* had the highest mortality rate (75%). However, both species had a small number of cases, compromising data analysis. *C. albicans* and *C. parapsilosis* had more adequate numbers of cases (54.2% and 58.4%) for analysis.

If age-specific mortality is analyzed, it is noticeable that the highest percentage of deaths was in patients aged more than 60 years (83.4%) (Table 3). Other age ranges did not present significant differences between the number of patients who died or lived.

Candidemia is one of the main causes of death provoked by infections in neonatal intensive care units (NICU), varying from 15 to 59%. *Candida* spp. is the third most common cause of late sepsis

Table 1. Identification of *Candida* species isolated from candidemia patients admitted to Botucatu Medical School University Hospital

<i>Candida</i> species	Number of cases	%
<i>C. albicans</i>	33	33.67
Other <i>Candida</i> species	65	66.33
<i>C. parapsilosis</i>	37	37.7
<i>C. tropicalis</i>	7	7.1
<i>C. glabrata</i>	4	4.1
<i>C. guilliermondii</i>	3	3.1
<i>C. lusitaniae</i>	2	2.1
<i>Candida</i> spp.	12	12.3
Total	98	100.0

Table 2. *Candida* species in patients under one year of age admitted to Botucatu Medical School University Hospital

<i>Candida</i> species	Number of cases	%
<i>C. parapsilosis</i>	25	56.8
<i>C. albicans</i>	5	11.4
<i>C. tropicalis</i>	2	4.5
<i>C. glabrata</i>	2	4.5
<i>C. lusitaniae</i>	2	4.5
<i>C. guilliermondii</i>	1	2.3
<i>Candida</i> spp.	7	15.9
Total	44	100.0

in NICU (22). In the present study we found a mortality rate of 50% in NICU patients (Table 3).

Factors Associated with Candidemia Development

Main factors

In the current study the most frequently factors associated with candidemia development were use of central venous catheter (93.9%); use of antibiotics (93.9%) and antifungal drugs (79.6%); mechanical ventilation (73.5%); and parenteral nutrition (60.2%) (Table 4). Transplant, HIV positive, and neutropenia were the factors least frequently associated with candidemia, which does not mean they were less significant, as there was no control group.

Candida albicans x other *Candida* species

In the present study, the main factors

associated with candidemia caused by *C. albicans* were surgery, solid cancer, bowel disease, diabetes mellitus, immunosuppressant therapy, and higher age range. Other studies also showed that *Candida* infection is more frequent in adults (23, 24). The main factors associated with candidemia caused by other *Candida* species in the current work were age under one year, prematurity, use of antifungal drugs, and parenteral nutrition (Table 5). Such data are corroborated by other studies that indicate other *Candida* species as the leading causes of candidemia in patients born prematurely or under one year old (25).

Mortality-associated factors

Factors significantly connected with death ($p \leq 0.05$) were mechanical ventilation and solid cancer or chemotherapy; prevalence was higher among women. None of the other factors studied showed an association with patient mortality

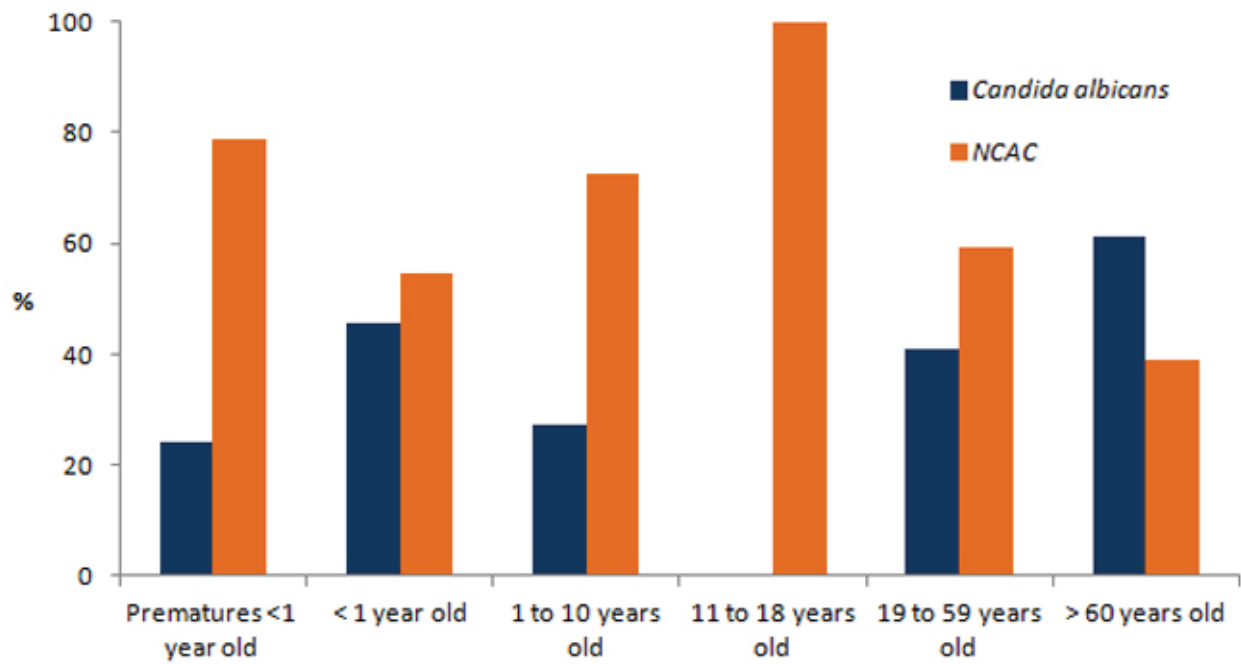


Figure 1. Percentage of *Candida albicans* and other *Candida* species by age.

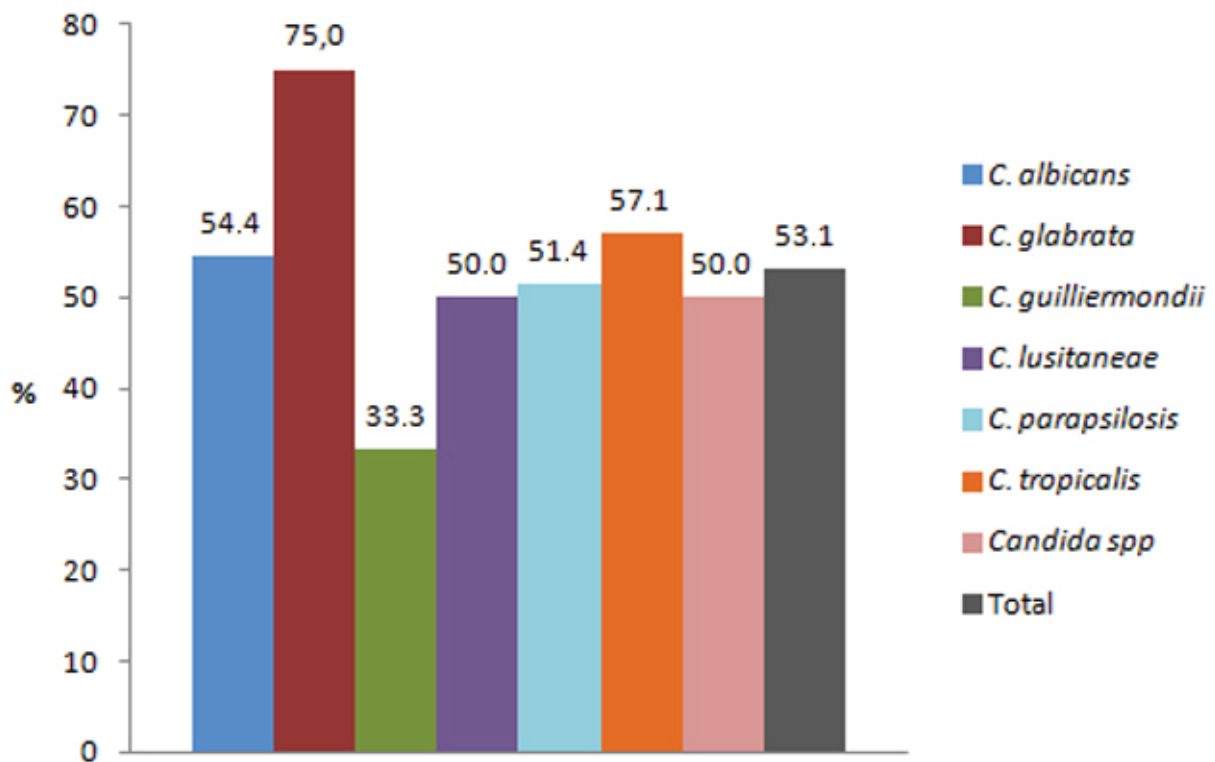


Figure 2. Mortality distribution by species.

Table 3. Age-specific mortality rate in candidemia patients admitted to Botucatu Medical School University Hospital

Age (years)	Number of cases	Mortality
< 1	44	50.0%
1-10	11	36.4%
11-18	3	0.0%
19-59	22	50.0%
> 60	18	83.4%

Table 4. Main factors associated with candidemia development in patients admitted to Botucatu Medical School University Hospital

Factor	Number of cases	%
Central venous catheter	92	93.9
Use of antibiotics	92	93.9
Use of antifungal drugs	78	79.6
Mechanical ventilation	72	73.5
Parenteral nutrition	59	60.2
Prematurity	36	36.7
Surgery	34	34.7
Less than one year of age	44	44.9

Table 5. Factors associated with candidemia caused by *C. albicans* (CA) and other *Candida* species (OCS) in patients admitted to Botucatu Medical School University Hospital

Factor	CA (%)	OCS (%)	p
Less than one year of age	15.1	60.0	< 0.001
Prematurity	9.0	50.8	< 0.001
Mean age (years)	40.9	14.8	< 0.001
Surgery	51.5	26.2	0.01
Solid cancer or chemotherapy	24.2	6.2	0.01
Use of antifungal drugs	66.6	86.2	0.02

Table 6. Mortality rates and factors associated with candidemia in patients admitted to Botucatu Medical School University Hospital

Factor	Death		p
	n	%	
Mechanical ventilation (n = 72)	51	70.8	< 0.001
Female (n = 47)	33	70.2	0.002
Solid cancer or chemotherapy (n = 12)	10	83.3	0.05
Central venous catheter (n = 92)	51	55.4	0.06
Use of antifungal drugs (n = 78)	38	48.7	0.08
Parenteral nutrition (n = 59)	36	61.0	0.08
Prematurity (n = 36)	23	63.9	0.1

Table 7. Factors associated with candidemia in patients over 60 years old admitted to Botucatu Medical School University Hospital

Factor	Number of cases	%
Central venous catheter	18	100.0
Use of antibiotics	16	88.9
Surgery	9	50.0
Solid cancer	6	33.3
Diabetes	5	27.8
Death	15	83.3

Table 8. Factors associated with candidemia in patients under one year old admitted to Botucatu Medical School University Hospital

Factor	Number of cases	%
Central venous catheter	42	95.5
Parenteral nutrition	39	88.6
Use of antibiotics	41	93.2
Bowel disease	8	18.2
Prematurity	33	75.0
Death	22	50.0

rate. As 70.8% of patients on mechanical ventilation died, it is suggested to avoid the use of mechanical ventilators or get patients off the ventilator at the earliest possible time (Table 6). Mechanical ventilation was also an important factor associated with candidemia development (Table 4).

Age-associated factors

Several factors associated with the development of candidemia were more common in some age ranges than others. In patients over 60 years of age, the most frequently associated factors were, once again, use of central venous catheter (100%) and antibiotics (88.9%) (Table 7).

In patients under one year old the most frequently associated factors were use of central venous catheter, parenteral nutrition, and use of antibiotics (Table 8). We found a 50% mortality rate in these patients, and prematurity alone can be considered an important associated factor.

DISCUSSION

An increase in invasive infections caused by *Candida* species other than *C. albicans* has been

reported in recent years, which is corroborated by our findings (20, 26, 27). There are also significant geographical variations in the etiological pattern of invasive infections caused by *Candida* species other than *C. albicans* reported in different regions: in Latin America *Candida tropicalis* and *Candida parapsilosis* are more prevalent, whereas in the USA and many European countries the most frequent species is *Candida glabrata* (25, 28).

Candidemia caused by *Candida* species other than *C. albicans* is more common in children than adults; almost 60% of the affected patients were children. *C. parapsilosis* is also more common in children, mainly premature patients in NICU (29, 30). The present results agree with other studies that show *C. parapsilosis* as the most prevalent species in premature patients. This species provokes exogenous infections, since it colonizes the skin – especially the hands – of healthcare professionals, glycosylated solutions for hospital use, and central venous catheters, being associated with total parenteral nutrition (31).

The current study shows a different *Candida* spp. prevalence when compared to other research,

even Brazilian studies. We observed that the incidence of *C. parapsilosis* (38%) was higher than other *Candida* species found, possibly due to the high number of studied patients under one year old and premature infants, in which *C. parapsilosis* frequency was over 50%.

Mortality rates in the present study are similar to those found by Colombo *et al.* (15). High mortality in patients over 60 years old could be explained by comorbidities found in this age range, such as kidney disease, bowel disease, diabetes mellitus, and solid cancer. Additionally, these patients had also been exposed to other predisposing factors for candidemia development, such as surgical procedures, mechanical ventilation, use of central venous catheter and antibiotics.

Factors Associated with Candidemia Development

Use of central venous catheter is one of the main factors associated with candidemia found in the present study (especially when combined with parenteral nutrition). Administration of multiple antibiotics for long periods is also an important variable. Both factors in addition to mechanical ventilation are also reported by Colombo *et al.* (15), who evaluated risk factors in four tertiary hospitals in São Paulo. In that same study, however, parenteral nutrition was only found in 30% of candidemia patients, while in our study it was found in 60.2%. This could be explained by the elevated number of premature and under one year old patients in our study, whereas Colombo only studied adults.

In Table 5, the greater incidence of *Candida* species other than *C. albicans* is evident, specifically in patients under one year old. It is important to notice that the risk factors associated with these patients – prematurity, parenteral nutrition and use of antifungal drugs – may explain the present findings. Infections by *C. albicans* are more frequent in adults, and the risk factors associated with them are: being older, surgery, solid tumors, bowel diseases, diabetes mellitus, and immunosuppressant therapy. Therefore, we must keep in mind the greater incidence of *C. parapsilosis* in patients under one year old and of *C. albicans* in adults.

Central venous catheter, antifungal treatment, and parenteral nutrition were the most frequent associated factors. However, they did not

significantly affect patient mortality rate. Only the use of central venous catheter presented some significance, which could indicate the need for correct prophylactic measures concerning this condition. The same can be said about solid cancer, which presented statistical significance, requiring extra care. Higher mortality rates in women and elderly over 60 years can be explained by the comorbidities more frequently found in these patients, such as diabetes mellitus in women and impaired immune system in elderly patients.

Candidemia is a serious condition in the neonatal period, in which it is associated with high mortality rates, especially in very low birth weight newborns. Advances in intensive neonatal care have improved survival rates of newborns born under 1500 g or seriously ill, who are subjected to invasive procedures and thus at higher risk of nosocomial infections, including fungemia. Preventing hospital infection in this situation is challenging, since the immune system of these infants is immature and the skin barrier is ineffective and unprepared (32).

Based on present findings, it is suggested that invasive procedures such as use of central venous catheter, mechanical ventilation, and parenteral nutrition, as well as antibiotics and antifungal drugs should be administered with caution and removed as soon as clinical conditions allow (33). The use of antibiotics is also one of the factors which increases intestinal colonization by *Candida* species potentiating translocation. Therefore, they should be employed wisely as an effective candidemia preventive measure (33, 34).

CONCLUSION

The high mortality rate found in the current study allows us to conclude that preventive measures against candidemia must be emphasized in hospitals, mainly regarding the rational use of antibiotics and appropriateness of invasive therapeutic measures.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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ETHICS COMMITTEE APPROVAL

This study was approved by the Research Ethics Committee of Botucatu Medical School, UNESP, under protocol number 490/2006-CEP.

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