

Candidemia and it's Epidemiology at Hospital México

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Abstract

Background: Invasive *Candida* infections are frequent and exhibit high mortality in clinical practice. There are few published data in our country. This retrospective observational study intends to provide new knowledge about the local epidemiology of candidemia.

Methods: 136 patients older than 17 years were included when they had their first episode of candidemia during hospitalization at the Hospital Mexico, in the time period between 2007 and 2010. Descriptive and temporal analysis was performed and the risk factors associated with *C. parapsilosis* and survival were evaluated.

Results: An average of 34 episodes of candidemia were recorded per year (range 27-51) and the cumulative incidence was 1.1 cases/1,000 admissions. The non-albicans *Candida* species accounted for 62% of the isolated yeasts, *C. parapsilosis* (41%) was the predominant yeast isolated in 3 out of the 4 years analyzed, except for 2009, followed by *C. albicans* (38%). Strong association between *C. parapsilosis* bloodstream infection, the presence of a central venous catheter (2.6 to 403.8, $p < 0.001$ OR = 19.6, 95% CI) and use of parenteral nutrition ($p=0.014$) was established. The 30-day mortality was 46%, with *C. albicans* displaying the highest and *C. parapsilosis* the lowest. Patients who did not receive antifungal treatment had significantly higher mortality.

Conclusions: the unusually high incidence of candidemia due to *C. parapsilosis* is directly related to the use of central venous catheters and parenteral nutrition; the marked reduction observed in 2009 needs further investigation to find out the causes of this change.

Keywords: *Candida parapsilosis*, candidemia, fungemia, sepsis, systemic inflammatory response syndrome.

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Invasive infections by *Candida* species have become a major cause of nosocomial infection, particularly in Intensive Care Units.¹⁻³ Overall, *Candida* species account for almost 80% of all pathogenic fungi causing nosocomial infections. Candidemia is the most common form of invasive disease by this species, representing about 15% to 20% of all bloodstream infections in hospitals in developed countries.⁴⁻⁷

In the last two decades significant changes have occurred in the epidemiology of candidemia, especially related to the frequency of the species involved. There has been a decrease in the incidence of *Candida albicans* from 90% in the 70, up to 50% or less at present, because of an increase of other species of non-albicans *Candida*, such as *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*.⁷ The incidence of candidemia by *C. parapsilosis* has grown progressively and recent studies place it as the third most common cause of candidemia in the world.⁸ In addition, the infection leads to high attributable mortality, prolonged hospital stay and increased costs of care.⁹

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Despite the growing importance of this disease, there are only two national publications; both from the Hospital San Juan de Dios. The first analyzed the period from 1996 to 1998 and showed that *C. albicans* was the most frequent,¹⁰ but in the second study, conducted five years later, *C. parapsilosis*¹¹ was ranked first.

The purpose of this study was to characterize the epidemiology of candidemia in the Hospital Mexico, another center of the Costa Rican social security, in order to expand the existing knowledge about the behavior and dynamics of this infection in the country.

Methods

This is a retrospective observational study conducted at the Hospital Mexico, part of the Social Security System in San Jose, Costa Rica. It include all patients over 17 years-old during the period between January 2007 and December 2010, that had, at least one blood culture positive for *Candida* spp.; only the first episode of candidemia detected per patient was analyzed. The investigation began getting a list of all blood cultures reported as positive by any *Candida* species during this period, the database Observa®, from the bacteriology identification system VITEK®2 (bioMérieux), of the Bacteriology Division of the Clinical Laboratory.

From this information, the medical records were reviewed and the following variables were studied: sex, age, date of admission to hospital, hospitalization area, use of central venous catheter (CVC), catheter-days until the time of blood culture, parenteral nutrition, mechanical assisted ventilation at diagnosis of candidemia, antifungal treatment, and mortality in the first 30 days of candidemia. The Charlson comorbidity index^{12,13} (ICC), adjusted for age was determined for each patient. Patients excluded from the study were those where he could not get all of the clinical variables studied, or the clinical record was not found.

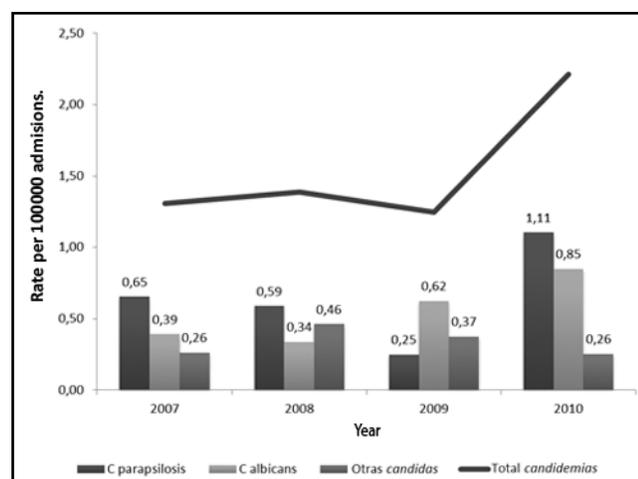


Figure 1. Cumulative incidence of candidemia for 1000 admissions, according to year and species. Mexico Hospital, 2007-2010.

Quantitative variables were described using measures of central tendency and dispersion. The comparison of averages was performed by analysis of variance or the Kruskal - Wallis test, when it was not valid to apply the first test. The qualitative variables were described using frequency distributions; and, confidence intervals at 95% for the relative frequencies were calculated, and the proportions were compared using hypothesis tests (*Student t*-test) by normal approximation. A significance level of 0.05 was established. The cumulative incidence per year was calculated per 1000 discharges and its behavior over time was plotted. The associated factors were analyzed for the presence of *C. parapsilosis* relating to other *Candida* species, using for these the calculation of odds ratio (OR) with their respective 95% confidence intervals (CI 95%). In addition, a Kaplan-Meier analysis was performed and Cox regression was used to assess survival at 30 days of patients with *C. parapsilosis*, compared with other species of *Candida* and other variables.

Microsoft Office Excel 2010 and SPSS version Version 18 were used for the statistical analysis.

The study was reviewed and approved by the Local Ethics Committee of the Hospital Mexico.

Results

145 cases of candidemia were identified, of which 136 different episodes of candidemia were analyzed and 9 cases were excluded because it was not possible to obtain all the variables studied.

Candida spp. was the sixth more frequent among the recovered microorganisms in blood during this period, corresponding to 5% of all germs isolated from blood cultures. All episodes were nosocomial candidemia.

An average of 34 different episodes of candidemia per year (range 27-51) and a cumulative incidence of candidemia for the period, from 1.1 cases per 1000 discharged patients was obtained; year cumulative incidence was 0.9, 1.0, 0.9 and 1.7, respectively (Figure 1). The increased incidence of 2010 compared to previous years, was statistically significant ($p = 0.01$).

The *non-albicans Candida* species accounted for 62% of the yeasts isolated in the episodes of candidemia studied. *C. parapsilosis* was the most frequently isolated species (41%), followed by *C. albicans* (38%), *C. tropicalis* (12%), *C. glabrata* (6%); other species accounted for 3% (Table 1).

The individual analysis of the information collected per year (Figure 1) revealed that *C. parapsilosis* was the most common species in 3 of the 4 years of the study (44% in 2007, 40% in 2008, 51% in 2010). In 2009 this was reversed,

Table 1. Demographic, clinical and therapeutic characteristics of patients with candidemia. Hospital México. 2007 - 2010

Variable	Valor por especie					
	Total General (n=136)	C albicans (n=51)	C glabrata (n=8)	C parapsilosis (n=56)	C tropicalis (n=16)	Other candida (n=5)
Age median (range)	55 (16 - 87)	62 (17 - 87)	64,5 (26 - 83)	50,5 (16 - 81)	49,5 (21 - 78)	48 (37 - 79)
Over 60 years-old (%)	57 (42)	26 (51)	6 (75)	19 (34)	4 (25)	2 (40)
Male (%)	69 (51)	24 (47)	4 (50)	30 (54)	10 (63)	1 (20)
Median in days (range) in the hospital until candidemia	21,5 (0 - 220)	24 (0 - 86)	17 (1 - 72)	18,5 (1 - 220)	22,5 (3 - 60)	22 (13 - 67)
N° of patients with:						
Charlson comorbidity index ≥ 3 (%)	63 (46)	27 (53)	6 (75)	20 (36)	7 (44)	3 (60)
Central venous line (CVC) (%)	114 (84)	37 (73)	5 (63)	55 (98)	12 (75)	5 (100)
Days median (range) with CVC until the candidemia	10 (1 - 100)	11 (2 - 24)	9 (5 - 20)	10 (1 - 100)	9 (4 - 32)	13 (4 - 20)
Parenteral nutrition (%)	63 (46)	19 (51)	3 (38)	33 (59)	5 (31)	3 (60)
Assisted mechanical ventilation (%)	55 (40)	20 (39)	4 (50)	27 (48)	2 (13)	2 (40)
Candida in other site (%)	30 (22)	13 (25)	5 (63)	9 (16)	3 (18)	0 (0)
No of patients with*:						
Prophylaxis or anticipated treatment (%)	38 (28)	12 (50)	2 (25)	22 (40)	1 (6)	1 (20)
No treatment (%)	27 (20)	10 (20)	3 (38)	10 (18)	3 (19)	1 (20)
In treatment with:						
Anfotericin b (%)	70 (52)	29 (58)	3 (38)	25 (45)	9 (56)	4 (80)
Caspofungine (%)	9 (7)	1 (2)	1 (13)	5 (9)	2 (13)	0 (0)
Fluconazole (%)	28 (21)	10 (20)	1 (13)	15 (27)	2 (13)	0 (0)
Letality at 30 days (%)	63 (46)	32 (63)	3 (38)	18 (32)	7 (44)	3 (60)

*In the case of the treatments, it was not possible to find the data of treatment in two patients, one with *C. albicans* and other with *C. parapsilosis*, so the number of patients is 134 instead of 136.

C. albicans frequency increased to 50%, and *C. parapsilosis* was reduced to 21%. The difference observed between 2009 and 2010 in the case of *C. parapsilosis* was statistically significant ($p = 0.023$).

The distribution per month showed a decrease of candidemia cases of *C. parapsilosis* throughout 2009, with a rise from January 2010; on the contrary, the other species had a stable behavior over the 4 years (Figure 1).

42% of individuals aged 60 years or older, with a median age of 55 years (range 16-87 years) there was no statistically significant difference between the age of patients and *Candida* species (Table 1).

Half of the patients (51%) was hospitalized in different surgical specialties; medical specialties accounted for 38%

of cases and intensive care 8%, the latter having a candidemia rate of 5.4 cases per 1000 discharged patients; the remaining 3% of patients was detected in emergency departments and obstetrics and gynecology.

When evaluating the comorbidity of patients, it was determined that 46% of them had an ICC of 3 or more points (estimated 10-year survival of 77% or less). 75% of patients with *C. glabrata* had an ICC greater or equal to 3, while in patients with *C. parapsilosis* this percentage was 36% (Table 1). Patients had a diverse variety of pathological conditions, but the most frequent were cancer (32%), postoperative intestinal fistula (29%), diabetes mellitus (21%) and multiple trauma (16%). No statistically significant association between these conditions and the species of *Candida* isolated in blood was found.

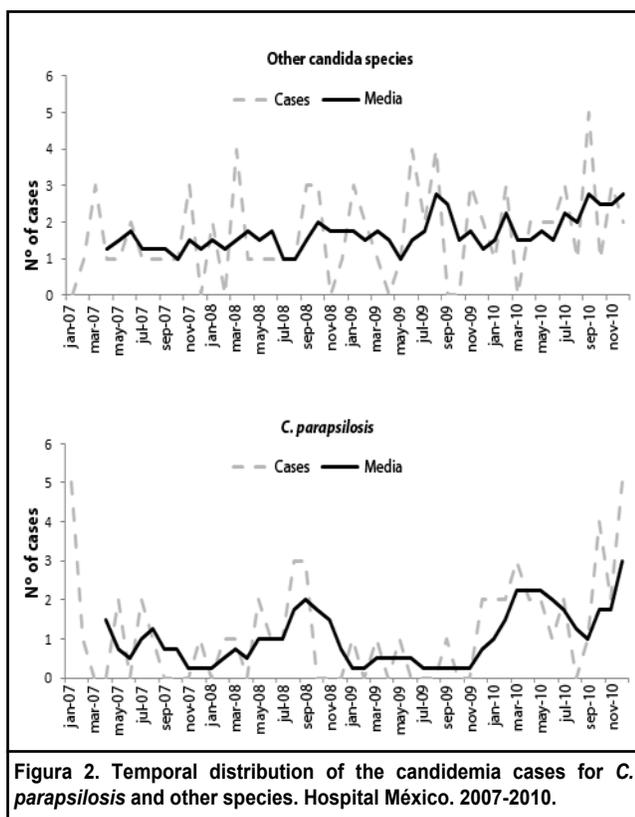


Figura 2. Temporal distribution of the candidemia cases for *C. parapsilosis* and other species. Hospital México. 2007-2010.

The median number of days of hospitalization until candidemia was 21.5 days, with no statistically significant difference between *Candida* species (Table 1). When analyzing this variable according to the hospitalization department, the median stay in the surgical specialties was higher (25 days) than in the medical (15.5 days) or in intensive care (10 days), a difference that was statistically significant ($p < 0.001$).

84% of patients had a CVC when candidemia occurred; in individuals with *C. parapsilosis* this occurred in 98%, while in patients with *C. albicans* this percentage was 73%. A strong association between the presence of candidemia and CVC was observed for *C. parapsilosis*, compared with other species of *Candida* (OR = 19.6, 95% CI 2.6 to 403.8, $p < 0.001$) (Table 2). By studying the number of days between the placement of the CVC and the diagnosis of candidemia, a significant difference between *Candida* species (Table 1) was found.

46% of patients were receiving parenteral nutrition at the time of candidemia (Table 2) and a greater likelihood that the species associated was *C. parapsilosis* (OR = 2.4, 95% CI 1.1 to 5.1, $p = 0.014$).

In relation to the treatment of candidemia, 20% of patients did not receive antifungal treatment, 28% had prophylaxis or treatment was initiated due to clinical suspicion without blood culture results (Table 1), and the remaining 52% received treatment once the report of the blood culture was obtained. The most commonly used drug was amphotericin B followed by fluconazole and

casposungin, there was no difference in the choice for each species (Table 1) or associated comorbidity (ICC). Those who did not receive antifungal therapy had a significantly higher risk of death at 3, 7, 30 days, when compared with patients who did receive antifungal (HR = 34.7, $p < 0.001$; HR = 17.7, $p < 0.001$; HR = 3.1, $p < 0.026$, respectively). Of the 18 patients who received no treatment and died, 13 they died before or the day of the blood culture report with *Candida*.

The 30-day mortality was 0.52 per 1,000 discharges, equivalent to 46% of patients. *Candida* species with longer survival were *C. parapsilosis*, with 70.4% (95% CI 56.3 to 80.7%) (Figure 3); conversely, *C. albicans* had the lowest survival rate, with 38.8% (95% CI 25.3 to 52.0%). By Cox regression we found that patients with *C. parapsilosis* had a lower chance of dying in relation to other species of *Candida* (HR = 0.5, 95% CI 0.3 to 0.8, $p = 0.01$) (Figure 2). People over age 60 had a lower survival (HR = 2.2, 95% CI 1.3 to 3.7, $p = 0.004$). Factors such as the ICC, department in which they were hospitalized, CVC, parenteral nutrition, mechanical ventilation and presence of *Candida spp.* in another anatomical site, did not demonstrate to have a statistically significant association with mortality at 30 days.

Discussion

In a similar way to other centers, the *Candida* species are among the most frequently isolated microorganisms from blood cultures¹⁴ The rate of candidemia in the hospital is within the range reported in the literature (0.2 - 2.8 cases / 1000 expense)¹⁵ and is similar to other Latin American hospitals,^{16,17} but higher than described in hospitals in developed countries.¹⁶

Contrary to the findings of other researchers^{18,19} most cases came from surgical specialties, not intensive care. This

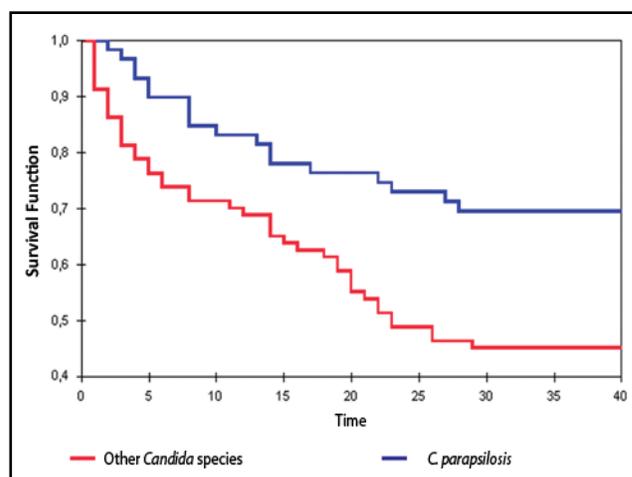


Figure 3. Kaplan - Meier estimation on survival of patients with candidemia for *C. parapsilosis* and other species. Hospital Mexico. 2007-2010.

Table 2. Univariate analysis of risk factors for candidemia presented by *C. parapsilosis*. Hospital México. 2007 - 2010

Variable	Other <i>Candidas</i>		<i>C. parapsilosis</i>		OR	IC 95%	valor de p
	n	%	n	%			
CVC*							
Absent	21	26	1	2			
Present	59	74	55	98	19,6	2,6	403,8 <0.001
NPT†							
Absent	50	63	23	41			
Present	30	38	33	59	2,4	1,1	5,1 0,014
ICC‡							
0 a 2	38	46	38	63			
>= 3	45	54	22	37	0,5	0,2	1,0 0,039

*Central venous line; † Total parenteral nutrition; ‡ Charlson comorbidity index.

situation could be due to factors specific to the Hospital, such as the large number of high-risk patients who are cared outside of this unit and with the size and complexity of the Hospital (2% of the beds).

Candida species other than *C. albicans* accounted for 62% of cases of candidemia in the Hospital Mexico, which is consistent with that reported in other centers in Latin America and the world^{16,17, 20-22} However, when analyzing the incidence by species, surprisingly, *C. parapsilosis* was the most common cause of candidemia, and their predominance in 3 of the 4 years analyzed, displayed as an endemic problem in the Hospital. This phenomenon differs from that described in most reports in the literature, including Latin America,^{16,17,21,25} where *C. albicans* is the most common species and *C. parapsilosis* takes second or third place, with an incidence ranging between 10% and 25%.^{11,23,24} There are isolated reports in the international literature where *C. parapsilosis* is the most common species, from 8,26 to 29 with isolated outbreaks in specific departments of a hospital, or in pediatric hospitals.

The significant decrease in cases of candidemia by *C. parapsilosis* in 2009, requires a detailed analysis in the future the factors involved in this phenomenon, which would help determine the reasons why the species has been the most common in the Hospital Mexico, and could indicate the actions to be implemented to modify the endemic nature of this infection.

Our data indicate that the major gateway to the bloodstream of *C. parapsilosis* is the presence of a CVC, as a strong association between both was demonstrated, a hypotheses that coincides with those published by other investigators.^{26,30,31} This is partly explained by the ability of this species to adhere to synthetic materials and form a

growth plate (biofilm) in the CVC.³²⁻³⁵ In addition, the composition of parenteral nutrition solutions that are infused by CVC, favor the growth of this species and thus facilitate blood invasion,³⁵⁻³⁷ association that was proved in the study. It should be noted, in relation to what happened in 2009, no changes occurred in the frequency of use of CVC, or parenteral nutrition during the year, which could explain the change in the distribution of *Candida* species.

The 30-day mortality found in the study is described in the literature,³⁸ but higher than that reported in most developed countries,¹⁸ although in the serie *C. parapsilosis* was the most frequent and the lowest mortality species. This high mortality may be due to one-fifth of the patients, which received no antifungal treatment. In addition, only 3 out of 10 patients received antifungal empirically or anticipated, therefore, most had to wait until the results of blood culture, which on average was higher than two days, reason why valuable time was lost to initiate antifungal therapy, and it has been demonstrated that the delay in starting treatment negatively influences survival.³⁹⁻⁴²

A weakness of the study is that a period of four years was analyzed alone, the ability to better assess temporal changes and the behavior of this infectious disease is limited. A larger number of patients would have been better.

In conclusion, the study shows that in the Hospital Mexico there is a predominance of the species *C. parapsilosis* as a cause of candidemia, unlike described in the rest of the world. The relationship established between CVC and *C. parapsilosis* indicates the need to implement local guides for installation, use and optimal handling of the CVC, and this could be a key element in reducing the high incidence of infection. In addition, the rational use of parenteral nutrition may also influence on the frequency of this species, although there are other critical factors that should be involved in this dynamic, as suggested by the change in the incidence of *C. parapsilosis* in 2009. Better understand the dynamics of candidemia, identifying patients at high risk of developing it as well as an early start of antifungal treatment, represent the best opportunities to change the high mortality of this infection in this hospital.

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