Evaluation of Blood Stream Infections by *Candida* in Three Tertiary Hospitals in Salvador, Brazil: A Case-Control Study

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Invasive infections caused by *Candida* spp. are an important problem in immunocompromised patients. There is scarce data on the epidemiology of blood stream candidiasis in Salvador, Brazil. This study evaluates the risk factors associated with candidemia, among patients admitted to three tertiary, private hospitals, in Salvador, Brazil. We conducted a case-control, retrospective study to compare patients with diagnosis of candidemia in three different tertiary hospitals in Salvador, Brazil. Patients were matched for nosocomial, acquired infections, according to the causal agent: cases were defined by positive blood cultures for *Candida* species. Controls were those patients who had a diagnosis of systemic bacterial infection, with a positive blood culture to any bacteria, within the same time period (± 30 days) of case identification. The groups were compared for the main known risk factors for candidemia and for mortality rates. A hundred thirty-eight patients were identified. Among the 69 cases, only 14 were diagnosed as infected by *Candida albicans*. *Candida* species were defined in only eight cultures: *C. tropicalis* (4 cases), *C. glabrata*, *C. parapsilosis*, *C. guillermondi*, *C. formata* (1 case each). The main risk factors, identified in a univariate analysis, were: presence of a central venous catheter (CVC), use of parenteral nutrition support (PNS), previous exposure to antibiotics, and chronic renal failure (CRF). No association was detected with surgical procedures, diabetes mellitus, neutropenia or malignancies. Patients were more likely to die during the hospitalization period, but the rates of death caused by the infections were similar for cases and controls. The length of hospitalization was similar for both groups, as well as the time for a positive blood culture. Blood stream infection by *Candida* spp. is associated with CVC, PNS, previous use of antibiotics, and CRF. The higher mortality rate for cases probably better reflects the severity of the underlying diseases, than as a direct consequence of Candidemia.

Key Words: Invasive candidiasis, risk factors, bacteremia.

Candida species are the most common cause of fungal infections worldwide. They can cause a great variety of infections, including simple, mucocutaneous processes, but they also provoke severe, invasive infections that can involve virtually any organ. Blood stream infections by *Candida* are increasingly common, and often are associated with high mortality rates [1,2]. Recently, we have seen an important increment in the frequency of non-albicans species of *Candida*, such as *C. glabrata, C. krusei, C. tropicalis,* and *C. parapsilosis*, as causes of fungemia [3,4].

Invasive candidiasis is a severe, life-threatening infection, with a mortality rate comparable to that observed in septic shock patients (40%-60%), and it occurs mostly in immunosuppressed patients. This is particularly true for bone marrow transplant recipients, and those under chemotherapy, in which the mortality rate is as high as 80%.

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Candida species causing invasive infections seem to vary according to the world region. Risk factors, sensitivity pattern, and outcomes can differ widely, depending on the region we analyze [5,6]. Colombo, in 2003, published the results of a multicenter, randomized study, which included 239 adult patients, from 20 countries, in five continents. *Candida albicans* was the most frequently isolated species in all regions, accounting for 45% of the total [7]. However, non-albicans species were more common. In the USA, *C. glabrata* was the second most commonly isolated species. In contrast, *C. parapsilosis* and *C. tropicalis* were responsible for 55% of cases in Latin America.

The first well-documented case of deep organ infection (brain) by *Candida* was described by Zenker, in 1861 [8]. The first report of disseminated candidiasis in an adult patient was published in 1937, by Bogden and Kessel [9]. In 1940, endocarditis by *Candida* was also reported for the first time [10]. A review of such cases, performed by Hurley, in 1964 detected 16 reports on disseminated candidiasis [11]. The reports on *Candida* isolation from the blood stream became more frequent after the introduction of antibiotics use as a usual practice, in 1940 [12].

Nowadays, *Candida* spp. is known as the 4th most frequently isolated pathogen from the blood stream, among hospitalized patients in North American hospitals [13,14].

Disseminated candidiasis is a consequence of medical progress. Invasive fungal infections are more prevalent due to the increasing number of high-risk patients, with different degrees of immunosuppression. Underlying diseases or chronic conditions, like cancer, bone marrow transplantation, AIDS, and chronic use of corticosteroids, are risk factors for fungal infections, and surgical procedures, extended use of catheters, and extended spectrum antibiotics are frequently associated with severe fungal diseases [15].

Candida spp. were rarely identified before 1960. However, these pathogens are now recognized as among the most important pathogens causing nosocomial infections, according to the National Nosocomial Infections Surveillance System [16]. They are one of the leading causes of blood stream infections, with a mortality rate of 40%. The incidence of such infections nearly doubled from 2.0 to 3.8/1000 patients discharged in American hospitals [17]. The main increase occurred in internal medicine and surgical clinics, but not in oncology or transplantation units. This suggests that fungal infections are no longer limited to immunosuppressed patients [18].

The reasons for this increase in fungal infections are multifactorial: better clinical evaluation, and diagnosis, greater survival for patients with malignancies, chronic diseases, increasing number of transplants, complex surgical procedures, catheters, implants and use of wide spectrum antibiotics [19]. There is little information on *Candida* infections in Bahia. We designed this study to evaluate the risk factors and outcomes of patients presenting with blood stream *Candida* infections in three private hospitals in Salvador, Brazil.

Material and Methods

Study design. This was a case-control, retrospective, multicentric study to evaluate risk factors, clinical characteristics and outcomes for patients who had *Candida* spp. isolated from the blood stream in three different private hospitals, in Salvador, Bahia, Brazil. Cases were defined as patients with a blood stream, hospital acquired infection caused by *Candida* spp., in the last eight years. Controls were defined as patients admitted at the same period of time as the cases (or within a three week interval), who had a diagnosis of nosocomial bacterial blood stream infection. We recorded data on age, gender, time of hospitalization before infection diagnosis, previous use of antibiotics and its duration, underlying disease, and final outcomes.

Settings. The study was conducted at three different hospitals in Salvador. The first one, Hospital Espanhol (HE) is a tertiary, private, 300 bed-hospital. The HE has a 25 bed Intensive Care Unit (ICU), and a neonatal ICU with 12 beds. The second hospital, Hospital Aliança (HA), is also a private, tertiary care, 160 bed-hospital, with a 15 bed general ICU, and a 6 bed cardiac ICU. The third institution is Hospital Santo Amaro (HAS), a tertiary, private, 150 bed hospital, with a 5 bed ICU and a neonatal ICU with 15 beds.

Data collection. We reviewed all laboratory reports from the three hospitals made during the previous eight years. The positive blood stream cultures for *Candida* spp. were recorded, and these cases were paired with other presenting bacterial infections at the same site, within a three-week interval of *Candida* isolation. The data were stored in a database, using the software SPSS for windows, version 12.0. The statistical analysis was also performed with this computer program.

Results

A total of 138 patients were enrolled in the study (69 cases). The distribution by hospital showed a greater number of enrolled patients at HA (58), followed by HAS, and HE (40 patients each). The gender frequency was identical for cases and controls (50% each). Mean age in years was also similar for cases (51.6 ± 31.9) and controls (53.4 ± 29.2, p=0.1). The number of positive blood cultures was also similar for both groups, although we have found a trend for a greater number of positive blood cultures for cases, when compared to controls (73% of cases had three positive blood cultures compared with only 27% of controls, p=0.08, chi-square test). Also, there was a trend towards more frequent isolation of *Candida* among patients in ICUs (62.6%), than blood stream bacterial infection (49.2%, odds ratios (OR)=1.79; 95% confidence interval (CI): 0.87 – 3.4, p=0.08, Fisher exact test).

The identification of *Candida* species was only available for 25 samples: 14 were classified as *Candida albicans*, 4 as *C. tropicalis*, and 3 as non-albicans species (without identification). *Candida glabrata*, *C. parapsilosis, C. formata* and *C. guilliermondi* were identified in one culture each. Forty-four cultures had the final resulted released as *Candida* spp. Table 1 shows the frequency of bacterial infection identified among the controls.

Surgical procedures were not associated with *Candida* infection: cases were more likely to report a previous surgical procedure (55.7%) than controls (42.4%), but this difference was not significant (relative risk (RR)=1.71; 95% CI: 0.82 – 3.58, p=0.16). In addition, report of previous use of antibiotics was significantly associated with *Candida* infection: it was reported by 58.4% of cases and by only 41.6% of the controls (RR=4.91; 95% CI=0.88 – 35.99, one-sided p=0.03). Nevertheless, the duration of antibiotic use was similar for both groups (13.4 *versus* 15.9 days, for cases and controls, respectively, p=0.5) as was the number of drugs used by each group of patients.

Another risk significantly associated with *Candida* infection was use of central venous catheters (CVC). The frequency of that device use was 72% for cases, against 56% for controls (OR=2.0; 95% CI: 0.99 – 4.12, one-sided P value: 0.037, by the Fisher exact test). In addition, the use of parenteral

Table 1. Frequency of bacterial agents isolated among controls

Bacteria	Number of positive cultures
Acinetobacter baumannii/haemolytic	1
Acinetobacter baumannii	1
E. aerogenes	1
E. aglomerans	1
E. gergoviae	1
Klebsiella oxytoca	1
Ralstonia picckettii	1
S. agalactiae	1
S. viridans	1
Serratia marcescens	1
Staphilococcus hominis	1
Staphylococcus auricularis	1
Staphylococcus sp.	1
Streptococcus alfa-hemolytic	1
Streptococcus sp.	1
P. fluorescens/putida	2
Pseudomonas fluorescens	2
S. haemolyticus	2
Acinetobacter linoffii	3
Enterobacter cloacae	3
S. hominis	3
Stenotrophomonas maltophilia	3
E. coli	6
K. pneumoniae	6
S. epidermidis	6
P. aeruginosa	8
S. aureus	10
Total	69

nutrition (PN) was also strongly predictive of *Candida* infection (OR=3.3; 95% CI: 1.5 – 7.1, p=0.02). An association was also detected between fungal infection and use of corticosteroids (OR: 1.55; 95% CI: 1.08 – 2.22, p=0.049), and for patients with diagnosis of chronic renal failure (OR=1.95; 95% CI: 1.5 – 2.5, p=0.004). On the other hand, diagnosis of malignancies, neutropenia and diabetes mellitus, as the underlying disease, were not associated with development of *Candida* infection. Table 2 displays the main risk factors and their association with Candidemia.

A consistent association was detected between candidemia and death during the hospitalization period: patients presenting blood stream infection by *Candida* were more likely to die during hospitalization (OR=2.24; 95% CI: 1.05 – 4.81, p=0.03). However, this tendency was not detected when we analyzed only the deaths directly attributable to the infections (OR=2.4; 95% CI: 0.48 – 12.1, p=0.2).

The mean hospitalization period in days was similar for cases and controls (73.2 ± 7.1 *versus* 61.2 ± 8.1, p=0.3). The time in days till detection of fungemia (cases) after hospital admission was longer (32.6 ± 26.7) than that for detection of bacteremia among controls (26.4 ± 38.9), but the difference was not significant.

We performed a multivariate analysis, including all significant risk factors detected in the preliminary evaluation, but the resulting model showed considerable overlapping of the variables associated with candidemia. This fact generated an unstable model, which could not identify any single significant risk factor, due to the low number of samples in the

Table 2. Risk factor for invasive Candidiasis in three different hospitals, in Bahia, Brazil

Risk factor	Cases N (%)	Controls N (%)	OR (95% CI)	p value
Gender				
Male	40	40 -	NS	
Female	29	29		
Mean duration of Hospitalization (days ± sd)	73,2 ± 58.8	61.1 ± 67.0	NS	
Time in hospital before a positive culture	32.7 ± 26.7	26.4 ± 38.9	NS	
Previous use of antibiotics	58 (84.1)	44 (63.8)	4.91 (0.88 – 35.99)	0.03 (one sided)
Parenteral Nutrition	30 (43.4)	13 (18.8)	3.31 (1.53 – 7.14)	
Previous surgery	44 (63.8)	35 (50.7)	1.71 (0.87 – 3.38)	0.08
CVC	50 (72.4)	39 (56.5)	2.0 (0.99 - 4.12)	0.037
Use of corticosteroids	11 (15.9)	4 (5.8)	1.56 (1.09 – 2.22)	0.049
Neutropenia	0 (0)	3 (4.3)	NS	
Malignancies	10 (14.5)	4 (5.8)	0.56 (0.23 – 1.34)	NS
Chronic renal failure	10 (14.5)	1 (1.5)	11.5 (1.43 – 92.71)	0.004
Diabetes mellitus	12 (17.4)	12 (17.4)	1.0 (0.41 – 2.41)	NS
Death	34 (49.3)	21 (30.4)	2.24 (1.05 – 4.80)	0.03
Death related to the infection	29 (42.0)	16 (23.9)	2.42 (0.39 – 16.02)	NS

study, and the prevalence of multiple conditions associated with the main risks that were initially detected.

Discussion

Candida species are the most common causes of fungal infection. In Brazil, several reports have shown that non-albicans species of *Candida* are more prevalent in tertiary hospitals [20]. In Bahia, there is no previous epidemiological information on the characteristics of Candidemia. Our report confirms some previously described findings from Brazilian hospitals, but it also reveals some important differences: We detected a predominance of non-albicans species in three tertiary hospitals, but the species definition was possible for only part of the patients. In Bahia, there is no specialized mycology laboratory, and the routine procedure is to classify the non-albicans species as *Candida* spp. Recently, we have seen some changes in this practice, with a greater effort of some private hospital laboratories to properly identify the species of *Candida* promoting infection in hospitalized patients. Since our work was performed in a retrospective manner, there was no chance to precisely discriminate albicans and non-albicans species of *Candida*, unless it had already been done during the isolation procedures. Nevertheless, we detected a large proportion of non-albicans species, (here reported as spp.), and we were able to identify the main risk factors associated with such infections.

In a similar way to that reported by various other authors, we found that candidemia was significantly associated with antibiotic use (but not with the duration of its use), presence of a central venous catheter, use of parenteral nutritional support, and chronic renal failure [21]. No association was detected with other recognized risks for invasive candidiasis, such as diabetes mellitus, neutropenia, and malignancies. The relatively low number of some of these conditions in our sample may explain such discrepancies (for instance, only three patients presented with neutropenia), but for the remaining, it could mean a real lack of association between such conditions and *Candida* infection in our hospitals. It could represent a distinctive pattern of risk for acquisition of invasive candidiasis in Bahia, or only a different at-risk population in our hospitals.

The results from our study reinforce the evidence for the already recognized risk of invasive candidemia in chronic renal failure patients. These individuals are often submitted to invasive procedures, are much more exposed to antibiotics than the general population (due to the higher risk of bacterial infections), and are considered to be immunocompromised patients. In addition, the need for maintenance of ready access to dyalitic procedures increases the risk for acquiring bacterial infections (blood stream infections, peritonitis, etc). The consequent greater use of antibiotics is a potential risk factor for the selection of resistant bacterial infections, and for the acquisition of fungal infections [22].

The same rationale may explain the higher risk found for patients using parenteral nutrition support. These individuals are frequently severely ill, and they are often affected by debilitating diseases, which increases the chance of use of antibiotics, invasive procedures, and the use of corticosteroids [23,24]. All patients with severe disease usually need a central vascular access line. Thus, the finding of CVC as a risk factor for candidiasis is also expected, and it may be related to the catheter itself, but, conversely, it could also be a marker of the severity of the underlying disease.

Candidiasis is a life-threatening infection, with mortality rates often reaching 50%, or higher [25]. There is also some evidence suggesting that non-albicans species could be associated with a poorer prognosis. In our study, candidemia was associated with a higher mortality rate, but when we analyzed the mortality attributable to infection, there was no difference between cases and controls. This suggests that invasive candidiasis, in our study, was a better marker for disease severity, than an independent risk for mortality during the course of infection.

The choice of controls presenting with blood stream, nosocomial bacterial infection made it possible to avoid other potential confounding factors, since most of these patients had a similar diagnosis, a similar length of hospitalization, and similar time to acquire the blood stream infection. Also, the gender distribution and mean age were almost identical for both groups. This approach differs from other studies, where patients were compared to controls without candidemia, but not presenting nosocomial infections, which could lead to potential bias in the analysis of risk factors.

In conclusion, candidemia is associated with well-known risk factors in tertiary hospitals in Salvador, Brazil. There was a higher prevalence of non-albicans species, but the characterizations of these isolates was not performed, which does not allow us to define the exact profile of such infections in our hospitals. However, the finding of *C. tropicalis* in three of seven species-identified samples suggests that this species could be moere prevalent in Salvador.

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