

Original Research Article

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## Prevalence of *Candida* in Blood Cultures from in patients at a Teaching Hospital in Brazil

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### ABSTRACT

Candidemia is a serious public health problem and is associated with high morbidity and mortality rates. This study aimed to determine the prevalence of *Candida* species isolated from inpatients with candidemia at a teaching hospital in Brazil; characterize patients; correlate the risk factors and investigate the use of antibiotics. Medical records of 54 hospitalized patients from October 2013 to July 2015 were evaluated. The species identification was performed by automated system Vitek ® 2. In this period there were 19,962 hospitalizations, observing a frequency of 2.7 cases per 1,000 admissions. The prevalent species were *Candida albicans* (29.6%), *C. tropicalis* (29.6%), and *C. parapsilosis* (29.6%). Neonatal sepsis was the clinical condition more related to candidemia. The highest incidence of *Candida* species was observed in patients undergoing invasive procedures. All subjects studied were submitted to prolonged antibiotic therapy. The greatest diversity of *Candida* species was isolated from the Intensive Care Unit (ICU) and adult wards. The mortality rate found was 51.0%, of which 78.0% were ICU patients. These results reinforce the need to follow the clinical course of hospitalized patients for *Candida* infection through epidemiological surveillance in order to contribute to the action plan

#### Keywords

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### Introduction

*Candida* spp. is the most common cause of fungal infections in hospitalized patients. They are also frequent pathogens in blood infections, and are associated with high morbidity and mortality (Yesilkaya *et al.*,

2017). In the last two decades, there has been an increase in occurrence of infections by species of *Candida* (Bailly *et al.*, 2016).

This increase has been attributed, in part, to the increase in susceptible patients, such as patients with neoplasia or degenerative

diseases, HIV seropositives, patients in intensive care units, receiving immunosuppressing therapies associated with transplants and broad-spectrum antibiotics therapies. All of this makes *Candida* infection a problem in medical practice in hospitals (Ala-Houhala *et al.*, 2019).

The frequent usage of antibiotics, central venous catheters and other invasive devices, abdominal surgery and prolonged stays in Intensive Care Units (ICU) predispose patients to a risk of infection by *Candida* reflected in lower survival rates to any blood infection (Yesilkaya *et al.*, 2017).

The determining factor for the predominance of some pathology is not simply by the presence of *Candida* spp. in human microbiota, but changes in the host's defenses that alter the parasite/host balance favoring the invasion of this yeast through various mechanisms, including the translocation of *Candida* spp. to the mesenteric capillaries (Chatelon *et al.*, 2019). Changes in skin and mucous caused by this yeast, like hydration, pH e nutrient levels can alter the normal microbiota and lead to infections caused by this fungus. *Candida albicans* is the main species detected on incidences of candidemias but some studies indicate an increase of candidemia due to other species, such as *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei*, representing a new challenge to empirical therapy and prevention strategies (Lin *et al.*, 2018; Pinto-Magalhães *et al.*, 2019).

The incidence of infections by *Candida* spp. have been increasing considerably in the last years, thus health professionals have an important role to play in acquiring knowledge of necessary steps for diagnosis, control and treatment of invasive infections by these pathogens. It is then essential to accomplishment blood cultures for diagnosis

of fungemias, as it is an exam of great value for laboratorial diagnosis and infection prevalence (Ezenwa *et al.*, 2017).

Therefore, the aim of this study was to detect the number of cases of blood cultures positive for *Candida* spp. from inpatients at Santa Casa de Misericórdia of Sobral (SCMS), a teaching hospital focused on tertiary care, a reference in the North of the state of Ceará – Brazil; and characterize the patients for associated risk factors, use of invasive devices and prior usage of antibiotics.

## Materials and Methods

A retrospective observational study was carried out from October 2013 to July 2015, to analyze the prevalence of *Candida* spp. in blood cultures at SCMS, reference hospital for 61 municipalities in the Macro-Region of Sobral, covering approximately 2 million inhabitants, with 92.0% of its total installed area at the service of the Unified Health System.

Candidemia cases were considered in adult patients or neonates with at least one positive blood culture for any *Candida* species during a single hospitalization for more than 30 days, or with an invasive device for over 15 days.

The patients analyzed in this study were selected from the analysis of results of blood cultures generated by SCMS's microbiology laboratory. The candidemia patients' clinical and epidemiological data were gathered from revision of medical records and stored in databases using Microsoft Excel 2007 version 9.0.2812. The information of interest obtained from the records were the patients' age, gender, mycological diagnosis, reason for admission, prior exposures to antibiotics, length of hospital stay, invasive procedures performed during the stay and other risk factors for candidemia.

The present study was conducted according to the Declaration of Helsinki, and the protocol was approved by the Institutional Ethics Committee of the State University of Vale of Acaraú, Sobral, Ceará, Brazil (Protocol n ° 644,365).

The biological samples were collected at SCMS by hospital professionals from its Laboratory for Clinical Analysis. The samples were immediately transported to the institution's microbiology laboratory, where they were identified.

Phenotypic identification and susceptibility to antimicrobials were determined by the VITEK®2 automated system (BioMérieux, Marcy-l'Etoile, France) at SCMS microbiology laboratory.

## Results and Discussion

For the time period chosen for the study a total of 19,962 were admitted to SCMS, 54 of which presented blood cultures positive for *Candida* spp., revealing an incidence rate of 2.7 cases per 1,000 inpatients. The yeasts identified were of the following species: *C. albicans* (29.6%), *C. tropicalis* (29.6%), *C. parapsilosis* (29.6%), *C. famata* (5.0%), *C. lusitaniae* (1.8%), and other species. Most of the candidemias were diagnosed in patients aged 0 to 14 years (44.4 %), the frequency of cases among men being 46.3% and 53.7% among women. The most documented reasons for hospitalization prior to candidemia diagnosis were neonatal sepsis (16.6%), pneumonia (16.6%) and Traumatic Brain Injury (TBI) (14.8%) (Table 1).

The frequency of isolation of *Candida* species varied with gender, patients' age and underlying diseases. *C. albicans* was isolated with greater frequency in female (68.7%), aged 0 to 14 years (50.0%), in patients stricken with pneumonia (44.4%) and with

TBI (37.5%). On the other hand, for patients diagnosed with neonatal sepsis, *C. parapsilosis* was detected in 55.5% of candidemia cases and *C. tropicalis* was isolated in 80.0% of patients with respiratory disorders. All patients studied had been submitted to antibiotics therapy prior to candidemia diagnosis (Table 1).

The distribution of *C. albicans* and *non-albicans Candida* by different risk factors associated with the patients is presented in table 2. Among the observed patients, 24 presented some risk factors, particularly anemia and trauma for all fungal species found, with incidences of *C. tropicalis* (37.5%), *C. parapsilosis* (37.5%) and *C. albicans* (12.5%) in patients with anemia and *C. tropicalis* (33.3%), *C. parapsilosis* (33.3%) and *C. albicans* (16.6%) in patients with trauma. However, the greater incidence of *C. albicans* (60.0%) was detected in prematurity (Table 2).

*C. albicans* was the most isolated species of patients with candidemia undergoing invasive procedures. Among these procedures orotracheal intubation, nasogastric tube and tracheostomy had higher prevalence of isolated strains, as indicated in table 3.

Among the data obtained from exposure prior to antibiotic treatment in patients with candidemia, of the 17 distinct antibiotics used, the most frequent were vancomycin (17.1%), meropenem (11.4%), oxacillin (9.2%) cefepime (8.5%), and imipenem (7.8%). In relation to *Candida* spp. more prevalent in candidemias after antibiotic therapy, *C. albicans* was isolated in 50.0%, 45.4%, 41.6%, and 38.4% of cases of candidemia after the use of meropenem, imipenem, vancomycin, and oxacillin, respectively. While *C. tropicalis* occurred in 50.0% of candidemias after the use of cefepime (Table 4).

In graph 1, we may observe the distribution of species of *Candida* by hospital sector. It shows a high percentage of *C. albicans* isolation in all hospital sectors except in the nursery. In general, the highest diversity of *Candida* spp. was isolated in the adult ICU and the infirmary.

The mortality rate observed was of 51.8%, of which 78.5% were adult ICU, neonatal or pediatric patients (42.8%, 14.3% and 21.4%, respectively). Among these patients the most common species was *C. tropicalis* 46.4%, and 53.5% of them were treated with antifungal agents (fluconazole or amphotericin B). The reasons for lack of treatment for some patients were hospital transfers, death before a final diagnostic and for some there was no documented reason in their records. A direct correlation between candidemia and the cause of death of these patients can't be drawn due to multiple associated pathologies (Table 5).

Some studies have shown that incidences of candidemia have been on the rise for many hospitals throughout the world (Colombo *et al.*, 2013; Vibhor *et al.*, 2014; Israel *et al.*, 2019), but in some metropolitan regions of the USA the number of cases is decreasing (Cleveland *et al.*, 2015). In our research, we encountered a rate of 2.7 cases per 1,000 hospitalizations, similar to what is reported by studies conducted in other regions of Brazil (Motta *et al.*, 2010; Colombo *et al.*, 2013; Wille *et al.*, 2013). Incidences of candidemia have been reported in some countries like Denmark (0.41 cases per 1,000 hospital admissions) (Arendrup *et al.*, 2011), Israel (0.50 cases per 1,000 admissions) (Rennert *et al.*, 2000), China (0.53 cases per 1,000 admissions) (Li *et al.*, 2013), India (7.76 cases per 1,000 admissions) (Vibhor *et al.*, 2014), and USA (0.14 cases per 1,000 admissions) (Cleveland *et al.*, 2015). In Brazil, studies conducted in public hospital centers from the South and Southeast regions and from Federal

District indicate rates between 1.2 and 2.4 cases per 1,000 hospital admissions (Motta *et al.*, 2010; Colombo *et al.*, 2013; Wille *et al.*, 2013) and in the Northeast region a higher rate of 3.9 cases per 1,000 admissions (Hinrichsen *et al.*, 2008). The different rates between the aforementioned countries may reflect demographic and socioeconomic differences, variations in healthcare practices, different diagnosis and different prolonged antibiotic usage patterns (Epelbaum and Chasan, 2017).

Newborns and children have historically been populations with some of the highest rates of candidemia (Shetty *et al.*, 2005; Chang *et al.*, 2008; Roilides, 2011; Ezenwa *et al.*, 2017) similar to what was observed by this study, in which children under 14 years old represented 44.4% of patients stricken with candidemia.

In this research *C. albicans*, *C. tropicalis* and *C. parapsilosis* were predominant and the three yeast species had the same frequency (29.6%). For most of the world, *C. albicans* accounts for 40% to 70% of cases of candidemia (Bassetti *et al.*, 2006; Horn *et al.*, 2009; Dutta and Palazzi, 2011; Al-Rawahi and Roscoe, 2013). However, this distribution has been changing over the last decade, with reports of an ever-increasing percentage of *C. non-albicans* cases, probably due to changes in antifungal therapy and the increase in the usage of azoles for prophylaxis or empirical treatment (Lortholary *et al.*, 2011; Epelbaum and Chasan, 2017). This distribution of species varies according to the countries, thus *C. glabrata* and *C. albicans* were the most commonly isolated species in Portugal and Canada, whereas *C. albicans* and *C. parapsilosis* were the most common in Spain (St-Germain *et al.*, 2008; Labbé *et al.*, 2009; Ortega *et al.*, 2011). This variation is probably the result of reductions in susceptibility and the emergence of resistant strains. In general, however, the three most prevalent species of *Candida* are *C. albicans*, *C. tropicalis* and *C.*

*parapsilosis* (Al-Rawahi and Roscoe, 2013) as was also observed by our study.

Most cases of candidemia are believed to be endogenously acquired through translocation of *Candida* into the gastrointestinal tract (Allert *et al.*, 2018). However, haematogenous

infections by *Candida* spp. can also occur exogenously, through contact with health professionals who have patients with central catheters, implants of contaminated prosthesis, as well as through parenteral administration of contaminated solutions (Epelbaum and Chasan, 2017).

**Table.1** Characteristics of patients and prevalence of candidemia

	Total	<i>C. albicans</i>	<i>C. tropicalis</i>	<i>C. parapsilosis</i>	Others*
	N = 54	N = 16	N = 16	N = 16	N = 6
	(100%)	(29.6%)	(29.6%)	(29.6%)	(11.2%)
<b>Characteristics of patients</b>					
<b>AGE (YEARS)</b>					
<b>0-14</b>	24	08	05	09	02
<b>15-49</b>	21	06	07	05	03
<b>50-65</b>	05	01	01	02	01
<b>&gt;65</b>	04	01	03	-	-
<b>GENDER</b>					
<b>Male</b>	25	05	08	09	03
<b>Female</b>	29	11	08	07	03
<b>Reason for hospitalization</b>					
<b>Neoplasia</b>	03	-	02	01	-
<b>Meningitis</b>	02	01	01	-	-
<b>Neonatal sepsis</b>	09	02	01	05	01
<b>TBI<sup>a</sup></b>	08	03	02	02	01
<b>IH<sup>b</sup></b>	01	01	-	-	-
<b>Respiratory dysfunction</b>	05	01	04	-	-
<b>Pneumonia</b>	09	04	01	03	01
<b>Polytrauma</b>	01	-	-	01	-
<b>Premature birth</b>	02	02	-	-	-
<b>IE<sup>c</sup></b>	01	01	-	-	-
<b>Liver disease</b>	01	01	-	-	-
<b>Exposure to antibiotic</b>					
<b>Exposed</b>	54	16	16	16	06
* <i>Candida lusitanae</i> , <i>C. famata</i> and other yeasts.					
<sup>a</sup> Trauma Brain Injury, <sup>b</sup> Intracranial Hypertension, <sup>c</sup> Ischemic Encephalopathy.					

**Table.2** Risk factors in patients with candidemia

Riskfactors	<i>C. albicans</i>	<i>C. tropicalis</i>	<i>C. parapsilosis</i>	Others*	Total
Diabetes	01	-	01	-	02
Pneumonitis	-	01	-	-	01
Trauma	01	02	02	01	06
TransplantPregnant	01	-	-	01	02
Prematurity	03	-	01	01	05
AnemiaImmunosuppression	01	03	03	01	08
<b>Total</b>	<b>07</b>	<b>06</b>	<b>07</b>	<b>04</b>	<b>24</b>

\**Candida lusitanae*, *C. famata* and other yeasts.

**Table.3** Invasive procedures performed in patients with candidemia

Invasive procedures	<i>C. albicans</i>	<i>C. tropicalis</i>	<i>C. parapsilosis</i>	Others*	Total
Central catheter	03	03	05	02	13
Dialysis catheter	02	03	02	-	07
Urinary catheter	03	03	03	01	10
Nasogastric tube	07	06	06	01	20
Thoracic drainage	01	-	-	-	01
Lumbar puncture	01	01	01	01	04
Endotracheal intubation	08	03	04	01	16
Tracheostomy	04	-	02	01	07
<b>Total</b>	<b>29</b>	<b>19</b>	<b>23</b>	<b>07</b>	<b>78</b>

\* *Candida lusitanae*, *C. famata* and other yeasts.

**Table.4** Prior exposure to antibiotics and *Candida* species isolated

Antibiotics	<i>C. albicans</i>	<i>C. tropicalis</i>	<i>C. parapsilosis</i>	Others*	Total
Cefepime	01	06	04	01	12
Imipenem	05	02	03	01	11
Ceftriaxone	03	03	02	-	08
Polymyxin	02	01	02	01	06
Vancomycin	10	04	08	02	24
Meropenem	08	03	04	01	16
Oxacillin	05	04	02	02	13
Penicillin	04	01	03	01	09
Gentamicin	04	-	03	01	08
Clindamycin	01	02	04	01	08
Others**	08	06	09	02	25
<b>Total</b>	<b>51</b>	<b>32</b>	<b>44</b>	<b>13</b>	<b>140</b>

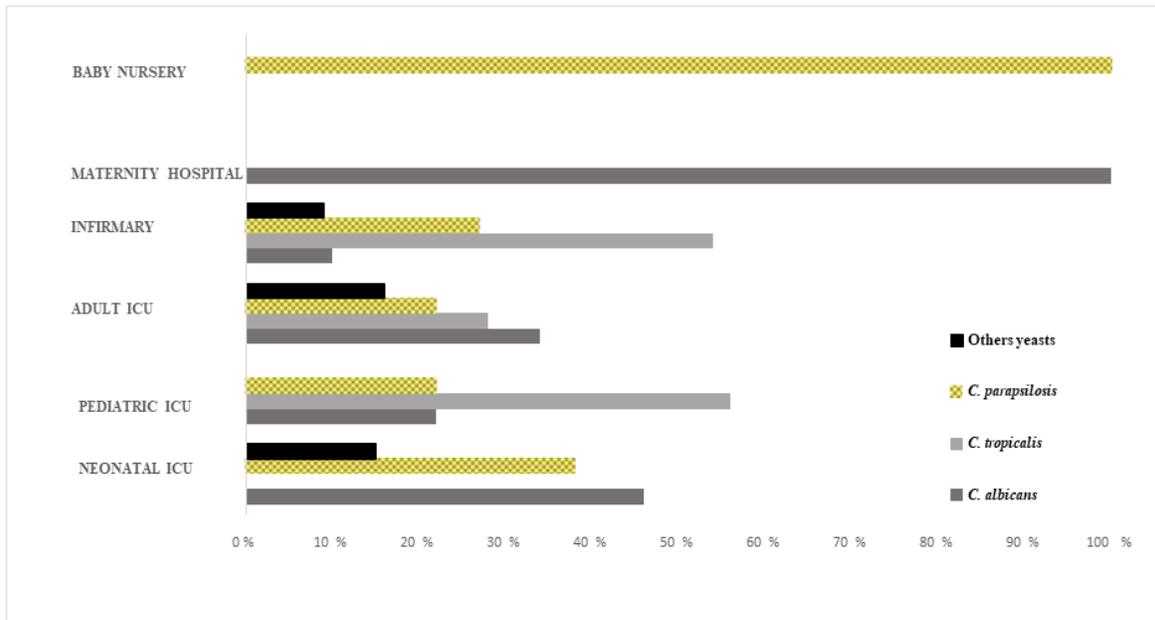
\* *Candida lusitanae*, *C. famata* and other yeasts.

\*\*Tazocin, Ampicillin, Cephalothin, Metronidazole, Clindamycin, Teicoplanin, Cefotaxime, and Ciprofloxacin.

**Table.5** Factors associated with mortality in candidemia patients

Variable	After 30 days of hospitalization	
	Survived (n = 26)	Death (n = 28)
<b>Gender (male:female)</b>	02:04	05:03
<b>Adult ICU</b>	06	12
<b>Neonatal ICU</b>	09	04
<b>Pediatric ICU</b>	04	05
<b>Infirmery</b>	05	06
<b>Maternity hospital</b>	01	-
<b>Baby nursery</b>	01	01
<i>C. albicans</i>	10	06
<i>C. tropicalis</i>	03	13
<i>C. parapsilosis</i>	09	07
<i>Others*</i>	03	03
<b>Treatment with antibiotics</b>	26	28
<b>Treatment with antifungals**</b>	17	15
<i>*Candida lusitanae, Candida famata and other yeasts.</i>		
<i>** Fluconazole and Amphotericin B.</i>		

**Graph 1.** Distribution of *Candida* species according to the hospital sector



The predisposing factors for development of candidemia observed in our research corroborate the aforementioned studies (Rennert *et al.*, 2000; Chang *et al.*, 2008; Arendrup *et al.*, 2011; Israel *et al.*, 2019). Vibhor *et al.*, (2014) have shown that the presence of bladder catheter, nasogastric tube, central catheter or dialysis, as well as prior administration of antibiotics were the main conditions associated with an increased risk. Most of the infected patients in our study used a bladder catheter or nasogastric tube and central catheter, and antibiotics were used in all who were sick before the development of candidemia. Berdal *et al.*, (2014) also presented in their study antibiotic therapy prior to candidemia in 87.0% of patients, characterizing it as a risk factor for incidences of cases of infection by *Candida* spp.

Fungi have a high capacity to attach themselves to surfaces (devices, probes and catheters) forming a biofilm, and to protect themselves against antifungal agents and immune responses. These mechanisms may in fact explain the common association of infections by *Candida* spp. and the use of probes and catheters, procedures involving intubations, and tracheostomy. Something else to consider is prolonged hospital stays as an important risk factor as observed in our study.

In this research we analyzed the prognosis for patients with candidemia, and verified a high mortality rate (51.8%), superior to those in hospitals in China (26.0 – 33.3%) (Wu *et al.*, 2011; Li *et al.*, 2013), Europe (37.9%) (Tortorano *et al.*, 2004), but inferior to hospitals in Saudi Arabia, where the mortality rate is 72.0% (Al-Tawfiq, 2007). We also observed that *C. tropicalis* was the species associated with the highest mortality rate (46.4%), corroborating the results encountered by Chung-Fang *et al.*, (2013). The severity of the underlying medical conditions will have certainly influenced the mortality rate

considerably among the population in study. It is also important to note that the hospital in this research is an institute of reference in the region for polytrauma patient care, who represent 16.6% of the deceased patients.

The main limitation of this study were the incomplete records, which made it impossible to faithfully collect data on some risk factors such as tobacco use, alcoholism, diabetes, etc.

Another point to consider is the lack of a protocol from the hospital to request microbiological tests for the cases that fit the criteria for inclusion in this study, and we can't therefore guarantee that all the cases that corresponded to our criteria had fungi cultures requested for them. Possible causes for this problem are the scarcity of resources for public hospitals in our country, as well as the unfamiliarity with this issue (candidemia) among nonspecialists.

In addition, the difficulty to put into practice consecrated procedures for the prevention of hospital infections, such as hand hygiene, to avoid transmission through the colonized hands of the team providing care to patients, as well as an insufficient number of health care professionals in critical areas, especially in the intensive care units, should also be considered.

The results of this research highlight the need to evaluate the impact of prolonged hospitalizations, indiscriminate use of broad-spectrum antibacterials, comorbidities prior to hospitalization, patient age, and the presence of invasive devices in the incidence of nosocomial candidemia. Furthermore, epidemiological studies can also contribute to action plans for the improvement of hospital environments and therapy conducts.

Finally, this study points to the need to find ways to avoid invasive infections by *Candida*

spp., which are rising rapidly in our region and throughout the world, and which also, represent a significant negative influence on the prognosis of the patients.

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