Original Research Article

Candida bloodstream infection and antifungal susceptibility over three years in a single center from Medinah, Saudi Arabia

Abstract

In the healthcare setting, *Candida* bloodstream infections significantly increase morbidity and mortality. There is little proof that invasive infections in Saudi Arabia are brought on by *Candida* spp. To identify *Candida* species that cause bloodstream infections, as well as to ascertain the clinical outcome and risk factors for mortality in a Saudi Arabian tertiary hospital. This retrospective analysis covered all instances in which patients hospitalized to Ohud hospital, a tertiary care facility in Madinah, Saudi Arabia, between January 2019 and December 2021, had positive blood cultures for *Candida*. Anaerobic and aerobic Bactec bottles were inoculated with blood samples, and they were then incubated at 35°C for five days. Identification-YST card kits from VITEK II (~~Biomerieux~~BioMérieux, France) for yeast and yeast-like organisms. Testing for antifungal susceptibility was done using AST YS07. A total of 78 patients (71% men, 29% women) were found to have candidemia. *Candida albicans* (51.3%), *Candida parapsilosis* (16.7%), and *Candida tropicalis* (16.7%) were the three *Candida* spp. that were most frequently isolated. Those with Saudi (51%; P = 0.500), leukopenia (40%; P = 0.001), neutrophilia (92%; P = 0.638), and thrombocytopenia (42%; P = 0.374) had a higher incidence of candidemia. Fluconazole sensitivity in non-albicans*Candida* species ~~ranged from~~ was 39.5%. Nonetheless, caspofungin was effective against all species. This study discovered an epidemiological shift toward more non-albicans *Candida* spp. in Saudi Arabia as well as a changing pattern in the *Candida* spp. causing bloodstream infections.

Keywords:

Candidemia, *Candida albicans*, *Candida* non-albicans, Antifungal, and Echinocandins.

1.Introduction

Although *Candida* spp. is a normal component of human skin and mucosa, reports of it as a pathogen have increased as a result of risk factors like excessive use of a wide range of antibiotics, prolonged hospital stays, organ transplantation, HIV infection, underlying malignant diseases, and exposure to invasive procedures ~~(Messer et al., 2006 and Richardson et al., 2008).~~[1,2]. One of the pillars of goal-directed sepsis management is early infection control with the right administration of antibiotics, as

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the survival rate of untreated sepsis patients drops by the hour (Wisplinghoff et al., 2004).

Bloodstream infections (BSIs) and disseminated candidiasis are just two of the many illnesses that *Candida* spp. can cause. Despite improvements in the identification and management of candidiasis, *Candida* ranks fourth in the United States and seventh in Europe among the infections responsible for BSI (Wisplinghoff et al., 2004 and Sievert et al., 2013). Only a few studies from India have documented candidemia rates (6–18%) and an increase in the isolation of *non-albicans* ~~*Canddia*~~*Candida* from BSIs. (Magill et al., 2006; Kothari and Sagar., 2009; ~~) (~~Shivaprakasha et al., 2007 and Chakrabarti et al.,2009).

A recent study found that 7.5% of ICU patients taking antifungal medication also had a candidemia incidence rate of 6.9 per 1000 patients in the critical care unit (ICU) (Kett et al., 2011 and Azoulay et al.,2012). Nosocomial candidiasis is linked to a crude mortality rate of over 60%, while the attributable mortality rate may be as high as 49% (Lark et al., 2000 and Gudlaugsson et al., 2003). Despite these findings, there are still many unresolved issues surrounding the treatment of candidiasis.

Azole, allylamine, polyene, and echinocandin are the only antifungal medications approved to treat systemic and invasive candidiasis. Healthcare providers should be extremely concerned about the dramatic rise in *Candida* spp. resistance to antifungal treatment over the past few decades. Clinical management solutions for this issue can be determined with the use of research on infection prevalence and antifungal susceptibility testing. Our goals were to identify the *Candida* spp. that cause bloodstream infections and to look into the antifungal susceptibility patterns of these species.

2 . Materials and methods

2.1Patients

This retrospective, observational study was carried out from January 2019 to December 2021 in the Ohud hospital's microbiology lab in Madinah, Saudi Arabia. Prior to the study, permission from the ethics committee was obtained (IRB 22-070). Only 78 *Candida* spp. were recovered from blood cultures out of a total of 1256 positive blood cultures. Hospitalized patients with a fever (>37^{o}C), a respiratory rate (>20 breaths/minute), and a white blood count (WBC) of more than 12,000/mm3 or less than 4000/mm3 were all required for the study. Patient demographic data, such as age, nationality, and gender.

2.2Sample Collection

2.2.1Isolation and identification of *Candida*

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The automated blood culture system Bactec FX (Becton Dickinson, Sparks, MD) was used to collect clinical isolates of *Candida* spp. from blood cultures. Anaerobic and aerobic Bactec bottles were inoculated with blood samples, and they were then incubated at 35°C for five days. Gram-stained bottles were examined, and afterward, subcultures were created. Standard bacteriological tests were used to identify bacterial isolates from positive bottles (Magill et al., 2006).

2.2.2Antifungal susceptibility testing

Identification-YST card kits from VITEK II (~~Biomerieux~~BioMérieux, France) for yeast and yeast-like organisms. Testing for antifungal susceptibility was ~~done on~~ performed using VITEK II ~~using~~ AST YS07 Kits. The Clinical and Laboratory Standards Institute approach was used to establish minimum inhibitory concentrations and resistance rates. Control organisms included *C. albicans* (ATCC 1023), *C. ~~topicalis~~ tropicalis*(ATCC 13803), and *C. glabrata* (ATCC 2001). Guidelines from the Clinical and Laboratory Standards Institute (CLSI) were used to interpret the data (Al-Jasser and Elkhizzi., 2004).

2.3 Data analysis

The statistical analysis was carried out using the statistical package for the social sciences (SPSS) version 24.0 software from SPSS Inc. in Chicago, Illinois, USA. All nominal variables, including demographic information, were calculated as frequencies and percentages. We used the Chi-square test x2 and Fisher's exact test to compare the *C. albicans* and *Candida non-albicans* groups on all nominal variables. Results with a p-value less than 0.05 (P<0.05) will be considered significant.

3. Results

Ages of the patients ranged from one year to 72 years. both cases *Candida albicans* and non-albicans*Candida*species amongpatients older than 60 had the highest frequency of *Candida*-positive cultures in both the *C.albicans* and non-albicans groups, followed by patients between the ages of 41 and 50 and those aged 1 to 10, while patients between the ages of 11 and 20 had the lowest frequency of *Candida*-positive samples. Only the age group older than 60 years (P=0.026) had significant differences according to statistical analysis (Chi-square test and Fisher's exact test) (Table 1).

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Table 1: Shows the prevalence of *Candida* species other than *C. albicans* in various age groups.

	Total number (n = 78)	Percent	*C.albicans* (n = 40)	non-albicans *Candida*species (n = 38)	p-value
1-10 years	11	14.1 %	5 (12.5 %)	6 (15.8 %)	0.677
11-20 years	1	1.3 %	1 (2.5 %)	0 (0 %)	0.513
21-30 years	2	2.6 %	0 (0 %)	2 (5.3 %)	0.234
31-40 years	5	6.4 %	2 (5 %)	3 (7.9 %)	0.475
41-50 years	11	14.1 %	5 (12.5 %)	6 (15.8 %)	0.677
51-60 years	10	12.8 %	3 (7.5 %)	7 (18.4 %)	0.135
>61 years	38	48.7 %	24 (60.0 %)	14 (36.8 %)	0.041
Total	78	100 %	40 (100 %)	38 (100 %)	

Of ~~of~~ the 40 patients with *C. albicans* isolates, 14 (~~or~~ 35%) were female and 26 (~~or~~ 65%) were male. Although 29 (76.3%) of the patients with non-albicans *Candida* isolates were men and 9 (23.7%) were women. Also, the risk variables for positive candidemia mentioned in Table 2 were examined. Blood culture positives for the *C. albicans* group and the *Candida* non-albicans group were found in 40 and 38 specimens, respectively (Table 2). These results show that white blood cells from patients with *C. albicans* are more likely to be *Candida* positive in cultures than from patients with *Candida* non-albicans, and that this difference is statistically significant (P=0.001).The incidence of *Candida*-positive cultures was also greater (72–92%) among neutrophilic individuals than neutropenic individuals (6–8%), however this difference was not statistically significant (P=0.638). Incidence of *Candida* blood culture-positive bacterial infection and platelet count (27.52% versus 21.24%, P=0.146) did not differ significantly, as reported in Table 2.

Table 2: Association of various candidemia risk factors

Risk factor	*C.albicans* (n = 40)	non-albicans *Candida*species (n = 38)	p-value
Gender Male	26 (65 %)	29 (76.3 %)	

Female	14 (35 %)	9 (23.7 %)	0.273
Nationality			
Saudi	22 (55 %)	18 (47.4 %)	
Non-saudi	18 (45 %)	20 (52.6 %)	0.500
WBCs			
<3000/mm	2 (5 %)	5 (13.2 %)	
3000-5000/mm	25 (62.5 %)	5 (13.2 %)	
1500/mm	13 (32.5 %)	18 (47.4 %)	0.001
Neutrophil			
<1500 cells/mm	3 (7.5 %)	3 (7.9 %)	
>1500 cells/mm	37 (92. 5 %)	35 (92.1 %)	0.638
Bacterial infection			
Positive	25 (62.5 %)	14 (36.8 %)	
Negative	15 (37.5 %)	14 (36.8 %)	0.305
Platelet			
<20000	3 (7.5 %)	3 (7.9 %)	
20000-100000	11 (27.5 %)	16 42.1 %)	
>100000	26 (65 %)	19 (50.0 %)	0.374

On both blood agar and Sabouroud dextrose agar, all 78 *Candida* spp. that tested positive for the presence of *Candida* spp. by microscopy and culture were taken into consideration. *Candida* non-albicans were present in 38 (48.7%) of the 78 samples, of which *C. albicans* was recovered from 40 (51.3%). The remaining *Candida* non-albicans isolates are shown in Table 3, with the highest frequency being shared by *Candida* ~~*parasilosis*~~*parapsilosis*13 (16.7%) and *Candida tropicalis* 13 (16.7%), followed by *Candida glabrata* 3 (3.8%).

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Table 3: The frequency (%) of isolated *Candida* spp. according to ~~Vitak~~ VitekII's identification.

Candida spp.	Total number (78)	Percent
C. albicans	40	51.3 %
C. glabrata	3	3.8 %

C.~~parasiolosis~~parapsilosis	13	16.7 %
C.auris	6	7.7 %
C. tropicalis	13	16.7 %
C.krusei	1	1.3 %
C.famata	2	2.6 %
Total	78	100 %

Table 4: Gram stain method and direct method sensitivity, specificity, and positive predictive value of direct blood culture investigation.

Types of test	sensitivity	Specificity	Positive predictive value
Direct method	97.4 % (76/78)	100 %	76 (100 %)
Gram stain	98.7 % (77/78)	100 %	77 (100 %)

As shown in Table 5, Gram stain examination of 78 blood cultures revealed *Candida* only form in 29 (37.2%), *Candida* with bacteria Gram positive in 31 (39.7%), and *Candida* with bacteria Gram negative in 18 specimens (23.1%), with no special observations.

Table 5: Shows the microorganisms found using the direct gram stain microscopic method.

Organisms	Direct examination (78)	Percent
***Candida* only**	29	37.2 %
***Candida* with bacteria**	31	39.7 %

(~~gram~~Gram-positive)		
***Candida* with bacteria (~~gram~~Gram-negative)**	18	23.1 %

Candida spp. susceptibility pattern to fluconazole (FLU), voriconazole (VOR), flucytosine (5FC), amphotericin B (AMP), micafungin (MIC), and caspofungin is shown in Table 6. (CAS). Fluconazole resistance was found in 7.5% of all *C. albicans*. *C. albicans* was found to be completely sensitive to VOR, 5FC, AMP, MIC, and CAS.

Resistance to FLU, VOR, 5FC, AMP, MIC, and was found in 39.5%, 13.2%, 15.8%, 10.5%, and 2.6% of *Candida* non-albicans cases, respectively. *C. albicans* had the highest number of sensitive cases to FLU, which is statistically significant (P=0.001), whereas *Candida non-albicans* spp. have 100% sensitivity to caspofungin, which may help healthcare professionals treat *Candida* infections caused by*Candida* non-albicans in the near future.

Table 6: Compares *C. albicans* and *Candida non-albicans* susceptibilities to fluconazole, voriconazole, flucytosine, amphotericin B, micafungin, and caspofungin.

Antifungals	**~~Classified as~~=Resistance or susceptibility patterns**	***C. albicans*** **(n = 40)**	**non-albicans *Candida*species (n = 38)**	**p-value**
Fluconazole	S I R	37 (92.5 %) 0 (0 %) 3 (7.5 %)	23 (60.5 %) 0 (0 %) 15 (39.5 %)	0.001
Voriconazole	S I R	40 (100 %) 0 (0 %) 0 (0 %)	33 (86.8 %) 0 (0 %) 5 (13.2 %)	0.024
Flucytosine	S I R	40 (100 %) 0 (0 %) 0 (0 %)	32 (84.2 %) 0 (0 %) 6 (15.8 %)	0.011
Amphotericin B	S I R	40 (100 %) 0 (0 %) 0 (0 %)	34 (89.5 %) 0 (0 %) 4 (10.5 %)	0.052
Micafungin	S I R	40 (100 %) 0 (0 %) 0 (0 %)	37 (97.4 %) 0 (0 %) 1 (2.6 %)	0.487
Caspofungin	S	40 (100 %)	38 (100 %)	0.999

	I R	0 (0 %) 0 (0 %)	0 (0 %) 0 (0 %)	

S, susceptible; I, intermediate; R, resistant

4.Discussion

The sixth most prevalent isolated microbial ~~species~~ genereat Ohud hospital was *Candida*. According to Sheevani et al. (2013), *C.albicans* is the sixth most common cause of nosocomial infections. Age, gender, country, and laboratory tests (Tables 1 and 2) that determined which patients were infected were the variables taken into account in this study. Patients aged > 60 and under 1 year old frequently experienced it. Accept the findings of other researchers despite blood cultures demonstrating *Candida* infection (Kothalawala et al., 2019). According to the study by Furnaleto et al. (2011), it was generally found that ICU patients, elderly people, and people under one year old were more likely to get a *Candida* spp. infection. Our study's age and gender distribution are consistent with other Saudi Arabian researchers' observations (Bukharie HA., 2002, Al-Jasser AM, Elkhizzi ., 2004, and Ahmed NJ., 2020).

Following *C. albicans* (40, 51.2%), *C. parasilosis* (13, 16.7%), *C. tropicalis* (13, 16.7%), *C. auris* (6, 7.7%), and other species (6, 7.7%), *C. albicans* was the most frequently isolated species. Thus, 48.7% of non-albicans species were present overall. These results support earlier studies from another researcher (Al-jasser and Elkhizzi, 2004). Similar to Saudi Arabia, Italy, and Sir Lanka (Kothalawala et al., 2019), *C. ~~parasilosis~~parapsilosis*and *C. tropicalis* were the second most prevalent species there as well (Al-jasser and Elkhizzi, 2004)

In our study, *C. albicans* infection is on the rise, despite the fact that it has historically been the primary cause of candidemia worldwide. According to another study, non-albicans *Candida* infections of the bloodstream were more prevalent than those caused by *C. albicans*, particularly in Asia, South Europe, South America, and the Indian subcontinent (Falagas et al., 2011 & Chakrabarti., 2002).*C. parapsilosis* and *C. tropicalis* are non-albicans that account for 33.4% of instances of candidemia in those over 60 and in newborns. It was prevalent in our study among newborns, where the prevalence was comparable to that of *C. albicans*.

Also prevalent in the ICU were *C. parapsilosis* cases in both children and adults. Neoplastic patients and adults both frequent contract *C. tropicalis* (Tortorano et al., 2013). Similar to that, it was kept separate from patients with malignancies in our study. Contrarily, patients with leukemia and those who are neutropenic are more likely to contract *C. tropicalis* (Tortorano et al., 2013). After *C. albicans*, *C. tropicalis* was more prevalent in our study among neutropenic individuals. *C. parapsilosis* is a prevalent pathogen in catheter-related infections and has the potential to produce epidemics since it colonizes the skin.

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Particularly concerning is the high prevalence of antifungal resistance among clinical isolates of *Candida* that are non-albicans. Fluconazole resistance was present in all strains of non-albicans *Candida* generating candidemia in our cohort (39.5%), while amphotericin B resistance was virtually 2.6%. Since none of the isolates exhibited caspofungin resistance from the outset, it is clear that this class of antifungals is frequently still a viable option for treating invasive *C. glabrata* and *C. auris* infections. However, our discovery of an instance of emerging caspofungin resistance is concerning and should spur additional studies to prevent jeopardizing viable treatment choices for this potentially multidrug-resistant yeast.

The majority of the discovered resistant strains, according to Saha et al. (2008) study, are non-albicans, highlighting their greatest propensity to develop fluconazole resistance for all *Candida* isolates despite their high amphotericin B susceptibility, which is consistent with our findings. Caspofungin has a 100% sensitivity pattern to non-albicans~~spp~~species. in the current investigation, which may be helpful for medical professionals to treat the *Candida* infection brought on by non-albicans *Candida*. The primary factor leading to non-albicans *Candida* dominance over *C. albicans* is the widespread use of fluconazole in a variety of clinical situations (Kothavade et al., 2010).

According to Kothavade et al. (2010) findings, all yeast isolates were susceptible to caspofungin, and there was no discernible difference in susceptibility between *C. albicans* and non-albicans*Candida* species.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of the General Directorate of Health Affairs in Madina, KSA, with reference number IRB-22-070.