Original Article

Clinical Characteristics and Outcome of Candidemia: Experience from a Tertiary Referral Center in Saudi Arabia

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Abstract

Background: *Candida* bloodstream infections cause significant excess morbidity and mortality in the health-care setting. There is limited evidence regarding *Candida* species causing invasive infections in Saudi Arabia.

Objective: To identify *Candida* species causing bloodstream infection and determine the clinical outcome and factors associated with mortality in a tertiary center in Saudi Arabia.

Materials and Methods: This retrospective study included all cases of positive blood culture for *Candida* in patients admitted to King Abdulaziz Medical City, a tertiary care center in Riyadh, Saudi Arabia, between January 1, 2013 and June 30, 2019.

Results: A total of 532 patients with candidemia were identified (male: 55.4%; mean age: 54 ± 26.2 years). The most common *Candida* species isolated was *Candida albicans* (26.7%), followed by *Candida glabrata* (22.7%), *Candida parapsilosis* (22.2%), and *Candida tropicalis* (18.4%). Non-*albicans* candidemia was more common in patients with diabetes (76.7%; $P = 0.0560$), neutropenia (89.8%; $P = 0.0062$), recent exposure to fluconazole (85.7%; $P = 0.0394$), and active chemotherapy (83.1%; $P = 0.0128$). In non-*albicans*, susceptibility to fluconazole varied from 95.9% with *C. tropicalis* to 41.5% with *C. parapsilosis*; nonetheless, all species were highly susceptible to echinocandins. The overall 30- and 90-day mortality rates were 39.9% and 56.4%, respectively. The mortality rate was nonsignificantly higher with non-*albicans* species at 30 days (41.2% vs. 35.9%; $P = 0.2634$) and 90 days (58.2% vs. 51.4%; $P = 0.1620$).

Conclusion: This study found a changing pattern in the *Candida* species causing bloodstream infections and an epidemiological shift toward more non-*albicans* Candida species in Saudi Arabia.

Keywords: Candidemia, *Candida albicans*, invasive candidiasis, nonalbicans, Saudi Arabia, susceptibility

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INTRODUCTION

Candidemia is a common etiology of nosocomial bloodstream infection: in the United States, it is fourth most common etiology.[1] Advancement in surgical interventions and use of new antifungal agents have not only contributed to prolonged survival of critically ill patients but also increased the incidence of invasive candidiasis and candidemia.[2-5] The burden of candidemia in health-care settings in terms of excess mortality, morbidity, length of hospital stay and costs is significant. Mortality rates directly associated with candidemia have been reported to range from 19.6% to 61%.[6-8]

Candida species distribution differs worldwide. Nonetheless, *Candida albicans* is the historically predominant *Candida* species, and at least 15 other species are known to contribute to human diseases. However, recent trends have shown an increase in infections being caused by non-*albicans Candida* species.[4,7,9-12] Chemotherapy, previous surgery, and treatment with antibiotics (such as aminopenicillins, carbapenems, and glycopeptides) have been identified as possible risk factors for this trend.[13] Recent systemic antifungal exposure is also reported as an independent risk associated with non-*albicans Candida* bloodstream infection. Specifically, chronic liver disease, neutropenia, and male gender were established as independent risk factors for *Candida tropicalis* candidemia.[14] A very recent study also revealed malnourishment as an independent factor associated with a higher risk of all-cause 28-day mortality in patients with non-*albicans* candidemia.[15]

Limited available evidence from Saudi Arabia has shown that *Candida* infections are increasingly being caused by non-*albicans Candida* species.[12,16,17] Of these, one of the more concerning species is *Candida auris*, which is an aggressive pathogen and is difficult to treat.[18,19] However, there is scarcity of data regarding the current candidemia trends in Saudi Arabia. This study was conducted with the aim of evaluating the trends of *Candida* species causing bloodstream infection in a tertiary center in Saudi Arabia and to determine the clinical outcome and factors associated with mortality.

MATERIALS AND METHODS

This retrospective study included all cases of positive blood culture for *Candida* in patients admitted to King Abdulaziz Medical City, a >1900-bed tertiary care center in Riyadh, Saudi Arabia, between January 1, 2013 and June 30, 2019. The study was conducted after receiving ethical approval from the Institutional Review Board (IRB) of King Abdullah International Medical Research Center, Riyadh, Saudi Arabia.

Candidemia was defined as the isolation of any pathogenic species of *Candida* at least once in a blood culture specimen along with consistent signs and symptoms of bloodstream infection. Only the first episode of candidemia was considered. Eligible patients' clinical and demographic data were obtained from electronic medical records using the local Hospital Information System (BESTCare). The primary parameters evaluated were patient characteristics, risk factors, comorbidities, duration of hospitalization, and clinical outcome in terms of mortality.

Microbiological studies

Microbiological identification of species and susceptibility profiles were performed using the VITEK® 2 system (bioMérieux). Minimum inhibitory concentrations and resistance rates were determined following the Clinical and Laboratory Standards Institute method.

Data analysis

Categorical data are reported as frequencies and percentages, and continuous data as mean ± standard deviation. Univariate analysis was conducted with outcome variables to determine factors associated with 30- and 90-day mortalities. All variables were examined for significance using the Chi-square tests and data were reported using counts and relative frequencies. No imputation method was applied for missing values. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patients

A total of 532 patients with candidemia were identified during the study period, of which 55.5% were male and the mean age was 54 (±26.2) years. The pediatric age group (i.e., aged <18 years) represented 13% of the cohort. More than half of the patients were diabetic and hypertensive (52.6% and 51.5%, respectively). The majority of the patients had recently been exposed to antibiotics (88.5%), had a central venous catheter (79.3%), and were admitted to the intensive care unit (ICU) at the time of diagnosis with candidemia (61.5%). Patients with active malignancy on chemotherapy constituted 19% of the study population, while solid organ transplant and hematopoietic stem cell transplant recipients represented 4% and 1.9%, respectively [Table 1].

Microbiology

The most common *Candida* species isolated were *C. albicans* (26.7%), *Candida glabrata* (22.7%), *Candida parapsilosis* (22.9%), and *C. tropicalis* (18.4%). In addition, another 10 non-*albicans Candida* species were isolated in smaller proportions. However, in the pediatric group, *C. albicans* (47%) was the most common species isolated followed by *C. tropicalis* (28%). While the incidence of *C. albicans* isolates was relatively stable over the study period, *C. parapsilosis* showed a steady increase in incidence rate in the last 3 years of the study period [Figure 1].

Non-*albicans* candidemia was more frequently identified compared to *C. albicans* among diabetic patients (76.8% vs. 23.2%; $P = 0.0560$), neutropenic patients (89.8% vs. 10.2%; $P = 0.0062$), those receiving active chemotherapy for malignancy (83.17% vs. 16.83%; $P = 0.0128$), and those with recent exposure to fluconazole (85.71% vs. 14.29%; $P = 0.0394$) [Table 2].

Susceptibility testing was done for all isolates with different antifungal agents. Fluconazole was the most commonly tested agent, and its susceptibility was high among *C. albicans* isolates (95.1%). Similarly, the susceptibility of fluconazole in non-*albicans C. tropicalis* and *C. glabrata* isolates was high (95.9% and 81.8%, respectively); however, it was low in *C. parapsilosis* (41.5%). The majority of the isolates were susceptible to echinocandins: no resistance was detected among *C. parapsilosis*, and only five isolates in total were resistant to one of the echinocandins tested. Amphotericin susceptibility also remained high in the isolated species [Table 3].

Table 1: Patient characteristics (*N* = 532)

Variables	*n* (%)
Age (mean±SD)	54±26.2
Male	295 (55.4)
Diabetes	280 (52.6)
Hypertension	274 (51.5)
End-stage renal disease on hemodialysis	71 (13.3)
Chronic liver disease	68 (12.7)
Malignancy on chemotherapy	101 (19)
Solid organ transplant recipient	21 (4)
Stem cell transplant recipient	10 (1.9)
Neutropenia	49 (9.2)
Use of corticosteroids	213 (40)
Previous *Candida* colonization	139 (26.1)
Central venous catheter	422 (79.3)
Urinary catheter	326 (61.2)
Total parenteral nutrition	56 (10.5)
Recent abdominal surgery	85 (15.9)
Recent antibiotic use	471 (88.5)
Recent fluconazole use	49 (9.2)
ICU admission	327 (61.5)

ICU – Intensive care unit; SD – Standard deviation

Outcome

The overall 30- and 90-day mortality were 39.9% (212/512) and 56.4% (300/512), respectively. The mortality rate was non-significantly higher with non-*albicans* species compared to *C. albicans* at both 30 days (41.3% vs. 35.9%; $P = 0.2634$) and 90 days (58.2% vs. 51.4%; $P = 0.1620$). The 30-day mortality varied among species: it was high with *C. lusitaniae* (90%), *C. kefyr* (66.7%), *C. utilis* (66.7%), and *C. dubliniensis* (61.5%), and low with *C. glabrata* (41.3%), *C. tropicalis* (40.8%), and *C. parapsilosis* (33.05%). In univariate analysis, 90-day mortality was significantly associated with patients' comorbidities, ICU admission, presence of a central venous catheter, and use of corticosteroid [Table 4].

DISCUSSION

C. albicans (26.7%) was the most frequently isolated species, which is consistent with the findings of other studies conducted in Saudi Arabia.[12,20] The study also found candidemia caused by 13 non-*albicans Candida* species, of

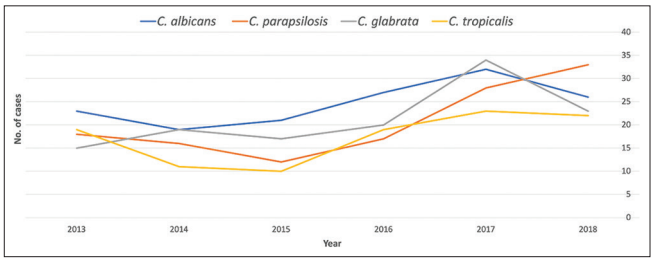

Figure 1: Distribution of the common *Candida* species causing bloodstream infection over the study period

Table 2: Clinical characteristic of patients infected with *Candida albicans* and non-*albicans*

Patient characteristics	Non-*albicans* (*n*=390), *n* (%)	*Candida albicans* (*n*=142), *n* (%)	*P*
Diabetes	215/280 (76.8)	65/280 (23.2)	0.0560
End-stage renal disease on hemodialysis	54/71 (76)	17/71 (23.9)	0.5739
Chronic liver disease	45/68 (66.1)	23/68 (33.8)	0.1546
Malignancy on chemotherapy	84/101 (83.1)	17/101 (16.8)	0.0128
Neutropenia	44/49 (89.8)	5/49 (10.2)	0.0062
Corticosteroids	168/213 (78.8)	45/213 (21.1)	0.0177
Central venous catheter	309/422 (73.2)	113/422 (26.7)	0.9304
Recent fluconazole use	42/49 (85.7)	7/49 (14.2)	0.0394
ICU admission	240/327 (73.3)	87/327 (26.6)	0.9547

ICU – Intensive care unit

which *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* were the most common. Of these, a steady increase in the incidence of *C. parapsilosis* was noted, which contrasted with the relatively stable incidence of *C. albicans* throughout the study period. Diabetes, neutropenia, active chemotherapy, and recent exposure to fluconazole were factors associated with increased risk of non-*albicans Candida* species infection. In line with this finding, increase in non-*albicans* isolates has previously been attributed to more exposure to antifungals prophylaxis, increased invasive procedures, ICU admissions and a larger population of immunocompromised patients.[21,22]

Both the 30- and 90-day mortality rates in our cohort was high (about 40% and >50%, respectively), with no statistical difference between *C. albicans* and non-*albicans*. The 30-day mortality rates varied across species: it was higher among the less commonly isolated non-*albicans* than those more commonly isolated. The high mortality rate despite the reasonable susceptibility of *Candida* species to the commonly used antifungal agents could be explained by the association of mortality with the criticality of the patients' condition and >61% of the patients in the cohort being critically ill and requiring ICU care.

In the univariate analysis, the worse 90-day mortality outcomes were associated with chronic liver disease, ICU admission, receiving total parenteral nutrition, and corticosteroids, which is considered to be usually correlated in other studies.[1,23] Patients with malignancy on active chemotherapy have significantly higher 30-day mortality ($P = 0.0004$). Higher mortality was not significantly associated with transplant recipients, which might be related to the level of the immune defect and the overall prognosis compared with patients on active chemotherapy.

There are no precise data about the incidence of candidemia in Saudi Arabia; however, dated studies have estimated the incidence to be 0.2–0.76 cases/1000 hospital discharges and 0.45–1.6/10,000 patient-days/year. Retrospective studies with small sample sizes have also been conducted over the past two decades to describe the evolving epidemiology of candidemia in Saudi Arabia. However, these reports remain scarce and difficult to generalize to the population.[12,16,24,25] It is essential to comprehend the local epidemiology and consider it during the bedside decision-making process. The selection of empirical antifungal agents in populations

Table 3: Antifungal susceptibility

Species	Antifungal agents								
	Amphotericin B	Fluconazole	Voriconazole	Itraconazole	Posaconazole	Caspofungin	Anidulafungin	Micafungin	Flucytosine
Candida albicans	139/139 (100)	135/142 (95.1)	131/139 (94.2)	54/61 (88.5)	49/54 (90.7)	142/142 (100)	56/56 (100)	133/135 (98.5)	140/142 (98.6)
Candida parapsilosis	109/112 (97.3)	49/118 (41.5)	110/113 (97.4)	39/42 (92.9)	33/33 (100)	118/118 (100)	40/40 (100)	109/109 (100)	114/117 (97.44)
Candida glabrata	115/117 (98.3)	99/121 (81.8)	108/117 (92.3)	19/51 (37.3)	36/40 (90)	120/120 (100)	45/46 (97.8)	113/113 (100)	121/121 (100)
Candida tropicalis	96/96 (100)	94/98 (95.9)	94/97 (96.9)	36/41 (87.8)	35/35 (100)	98/98 (100)	36/36 (100)	93/93 (100)	93/98 (94.9)
Candida krusei	17/18 (94.4)	2/19 (10.5)	16/18 (88.9)	6/10 (60)	7/7 (100)	19/19 (100)	9/9 (100)	17/17 (100)	1/19 (5.3)
Candida dubliniensis	13/13 (100)	12/13 (92.31)	13/13 (100)	7/7 (100)	6/6 (100)	12/13 (92.31)	6/6 (100)	12/12 (100)	6/13 (46.15)
Candida intermedia	0/0	1/1 (100)	1/1 (100)	0/0	0/0	0/0	1/1 (100)	0/0	0/1
Candida lusitaniae	9/10 (90)	10/10 (100)	10/10 (100)	6/6 (100)	5/5 (100)	10/10 (100)	5/5 (100)	9/9 (100)	8/10 (80)
Candida kefyr	1/1 (100)	2/2 (100)	2/2 (100)	0/1 (0)	0/0	3/3 (100)	2/2 (100)	2/2 (100)	1/2 (50)
Candida paratropicalis	1/1 (100)	0/1 (0)	0/1 (0)	0/1 (0)	0/0	1/1 (100)	0/0	0/0	1/1 (100)
Candida utilis	3/3 (100)	3/3 (100)	3/3 (100)	0/0	0/0	3/3 (100)	0/0	3/3 (100)	3/3 (100)
Candida rugosa	1/1 (100)	1/1 (100)	1/1 (100)	0/0	0/0	1/1 (100)	0/0	1/1 (100)	1/1 (100)
Candida orthopsilosis	1/1 (100)	1/1 (100)	1/1 (100)	0/0	0/0	1/1 (100)	0/0	1/1 (100)	1/1 (100)
Candida auris	0/0	0/1 (0)	1/1 (100)	0/1 (0)	0/0	0/0	1/1 (100)	0/0	1/1 (100)

Table 4: Univariate analysis of 30- and 90-day mortality predictors

Patient characteristics	30-day mortality (*n* = 212)		90-day mortality (*n* = 300)	
	Frequency (%)	*P*	Frequency (%)	*P*
Diabetes	117 (41.7)	0.3363	175 (62.50)	0.0027
Hypertension	112 (40.8)	0.6183	170 (62.04)	0.0067
End stage renal disease on hemodialysis	33 (46.4)	0.2203	44 (61.9)	0.3084
Chronic liver disease	38 (55.8)	0.0038	53 (77.9)	0.0001
Malignancy on chemotherapy	56 (55.4)	0.0004	71 (70.3)	0.0017
Solid organ transplant recipient	7 (33.3)	0.5337	10 (47.6)	0.4082
Stem cell transplant recipient	2 (20)	0.1956	4 (40)	0.2913
Neutropenia	28 (57.1)	0.0095	3 (63.2)	0.3085
Corticosteroids	107 (50.2)	<.0001	138 (64.7)	0.0014
Previous *Candida* colonization	58 (41.7)	0.5990	79 (56.8)	0.9023
Central venous catheter	182 (43.1)	0.0025	251 (59.4)	0.0049
Urinary catheter	137 (42)	0.1974	200 (61.3)	0.0037
Total parenteral nutrition	10 (17.8)	0.0004	20 (35.7)	0.0010
Recent fluconazole use	19 (38.7)	0.8720	28 (57.1)	0.9113
ICU admission	169 (51.6)	<.0001	232 (70.9)	<0.0001

ICU – Intensive care unit

with a high risk of non-*albicans Candida* infection should view all aspects, as this might impact the patient's outcome. The increase in infections with non-*albicans Candida* is considered a significant change in candidemia epidemiology over the past two decades.[22,26-28] Similar to our findings, the Surveillance Reports from the United States found *C. glabrata* accounted for 21% of non-*C. albicans* isolates in specific US centers and *C. parapsilosis* in other European and Latin American centers.[23]

Fluconazole susceptibility remained high among *C. albicans* isolates, reaching 95%; this is consistent with international figures where the susceptibility of isolates of *C. albicans* to fluconazole ranges from 97 to 100% at ≤8 μg/ml. Initial reports of fluconazole susceptibility among *C. albicans* in Saudi Arabia were considered low at 74.2%.[28] This discrepancy between our study and older studies from Saudi Arabia can be explained by improved microbiological susceptibility testing and the adoption of newer testing methods such as Etest, microbroth dilution, and the VITEK® 2 system.[29]

Fluconazole susceptibility among *C. glabrata* was considered low at 81.82%. This is also reported in large surveillance programs, the SENTRY 2006-2010, where 9.7% of *C. glabrata* isolates were found to be resistant to fluconazole. Fluconazole susceptibility was found to be the lowest among *C. parapsilosis* (41.5%), which is similar to the findings of international studies, including from the Middle East region.[29,30] Amphotericin susceptibility also remained high among the isolated species, with the lowest susceptibility reported in *C. krusei* (94.4%). This is similar to findings previously reported from Saudi Arabia.[21]

Limitations

Although this study reveals long-term data that would be helpful in selecting an appropriate antifungal therapy, it involves a single-center experience. The study's retrospective design is a limitation. Nonetheless, the current electronic medical records at National Guard Health Affairs, which provide digital, searchable, and continuously accessible information about each patient, ensured accuracy and completeness. The time between diagnosis and starting the antifungal therapy was not collected in this study. However, the hospital's policy includes early notification and immediate intervention for any positive blood cultures, and thus a significant delay in the initiation of antifungal therapy is not anticipated in the included patients.

CONCLUSION

This study found a changing pattern of the *Candida* species causing bloodstream infections and an epidemiological shift toward more non-*albicans* Candida species in Saudi Arabia. ICU admission, total parenteral nutrition, and malignancy were independently associated with candidemia in these species and correlated with worst outcomes. All species were highly susceptible to echinocandins, while *C. tropicalis* was most susceptible to fluconazole and *C. parapsilosis* the least.

Ethical considerations

This study was approved by the IRB of King Abdullah International Medical Research Center (Protocol no.: RC18/011) on February 4, 2018. The study adhered to the ethical principles mentioned in the Declaration of Helsinki, 2013. Requirement for patient consent was waived owing to the study design: Patient anonymity was maintained, and the study did not carry any additional risk to the patients.

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available due to privacy and

confidentiality agreements as well as other restrictions but are available from the corresponding author on reasonable request.

Peer review

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Conflicts of interest

There are no conflicts of interest.

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