

Original Article

Characteristics and clinical outcomes of patients with *Candida* bloodstream infections in a tertiary care hospital in Jordan

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Abstract

Introduction: *Candida species* are important causes of bloodstream infections, accounting for significant morbidity and mortality in hospitalized patients.

Methodology: A retrospective observational study was conducted in an academic tertiary hospital of Jordan. The medical records of patients hospitalized over a ten-year period, were reviewed and patients with candidemia were identified. Data analysis included the infecting *Candida* species, resistance to antifungals, and risk factors associated with mortality.

Results: A total of 158 cases of candidemia were identified, with an overall incidence rate of 0.48 episodes/1,000 admissions. The proportion of candidemia caused by *Candida albicans* (44.3%) was higher than that of candidemia caused by non-*albicans Candida* species (42.4%). Exposure to antibiotic therapy before hospitalization was the only independent factor associated with non-*albicans Candida* infection (OR 2.454; $p = 0.033$). The overall crude 30-day mortality was 38.7%. Central venous catheterization (OR 0.255; $p = 0.026$), mechanical ventilation (OR 0.162; $p = 0.003$), severe sepsis and septic shock (OR = 0.073; $p = 0.008$), admission to intensive care unit (OR 0.78; $p = 0.001$), *C. albicans* (OR 0.235; $p = 0.018$), length of stay (OR 1.057; $p = 0.001$), number of comorbidities (OR 0.580; $p = 0.008$) were independent risk factors for 30-day mortality.

Conclusion: This study identified several risk factors associated with blood stream infections caused by *Candida* over 10-years period. Continuous surveillance programs to monitor such types of infection are of great value to antimicrobial stewardship programs.

Key words: Candidemia; mortality; risk factors; *C. albicans*; non-*albicans Candida*.

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Introduction

Nosocomial bloodstream infections caused by *Candida* species have increased considerably in the latest years. They are associated with prolonged hospitalization time and increased mortality [1-4]. *Candida* species are estimated to be the fourth pathogen isolated in blood cultures in North America and the fifth to tenth in Europe [5,6]. In the past, the most common causative pathogen was *Candida albicans* but recent studies reported a global change in *Candida spp.* distribution toward non-*albicans Candida* species [7,8]. This change in the epidemiology of candidemia has challenged the empirical treatment strategies in infected patients. This is complicated by two factors; resistance or variable susceptibility to azole antifungals which are commonly prescribed in empirical therapy and delay in the identification of candidemia due to suboptimal sensitivity of traditional blood cultures [9-11]. Accordingly, it is of great importance the identification of risk factors and predictors of mortality in patients

with candidemia to guide empirical therapy and develop strategies to improve clinical outcomes. The aims of this study were to describe the annual incidence of candidemia over a 10-years period in a Jordanian tertiary care hospital and to identify risk factors associated with *Candida* bloodstream infection (BSI) and mortality in infected patients.

Methodology

Study Design

This was a retrospective analysis of patients with blood cultures positive for *Candida* species, admitted at King Abdullah University Hospital (KAUH), a tertiary care hospital in Jordan, between January 1, 2005 and December 31, 2014. The approval to conduct this study was granted by the ethics committee in KAUH.

Data collection

Candidemia was defined as the identification of *Candida* species in a blood culture specimen with concomitant clinical signs and symptoms of infection. The day of the first positive blood culture was considered as the onset of candidemia. If multiple episodes of candidemia occurred in the same patient during the study period, the patient was considered as one case, using only the first episode.

The following demographic and clinical parameters were obtained from electronic patients’ medical records and charts: Patient demographic characteristics, drug allergy, co-morbidities, hospitalization in the previous 90 days, previous antibiotic use (within 90 days before admission), and hospital transfer. Events that occurred during hospitalization before and after *Candida* development were also examined, including primary critical care unit admission, prior antibiotic or antifungal use, prior corticosteroids use, length of hospital stay and length of stay in critical care unit, complete blood count analysis, blood product transfusion during hospital stay, type of *Candida* isolated from blood, antifungal used for the empirical and the definitive treatment and *Candida* spp isolated from other body sites.

Neutropenia was defined as absolute neutrophil count ≤ 500 cells/mm during the previous 14 days of the onset of candidemia. Acute renal failure was defined as an increase in serum creatinine by 1.5 times or more from baseline [4]. Finally, 30-day in-hospital mortality was defined as death within 30 days of the first *Candida* positive blood culture.

Statistical Analysis

Descriptive data were presented as mean \pm SD or median and interquartile range for continuous data, whereas frequencies and percentages were used to summarize categorical data. To identify independent risk factors associated with 30-day mortality in patients

with candidemia, multivariable stepwise logistic regression analysis was conducted. Variables with a p-value of ≤ 0.10 on univariate analysis were included in the multivariable model. Odds ratio (OR) with 95% confidence intervals (CI) were calculated. The same method was used to identify risk factors of *C. albicans* vs. non-*albicans Candida species* infections. All tests performed were 2-tailed tests of significance and p-value less than 0.05 was considered significant. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) version 20.

Results

Trends in Candida Blood Stream Infections Over a 10-Years Period

A total of 158 cases of candidemia were identified during the study period. The most commonly isolated *Candida* species were *C. albicans* (44%), followed by *C. parapsilosis* (15%) and *C. tropicalis* (11%). Other *Candida* species accounted for 17% of the isolates (6% *C. glabrata*, 2% *C. krusei*, 2% *C. famata*, 1% *C. guilliermondii* and 6% other *Candida* species). The remaining isolates (13%) were mixed or unknown *Candida* species. The average time of candidemia incidence after admission was 20 ± 12 days.

The overall incidence of candidemia was 0.48 cases/1000 admissions. The incidence rate fluctuated over the study period, with the lowest incidence in 2008 (0.32 cases/1000 admissions) and the highest incidence in 2009 (0.72 cases/1000 admissions). The annual incidence rates of candidemia over the 10-year period are shown in Table 1. Overall, the resistance to antifungal agents was low over the study period. The percentage of susceptibility to fluconazole was 100.0% for *C. albicans*, *C. parapsilosis* and *C. tropicalis*. *C. glabrata* was 87.5% susceptible to fluconazole, while *C. famata* and *C. krusei* were resistant. All *C. parapsilosis* and *C. tropicalis* isolates were susceptible

Table 1. The 10-year trend in candidemia stratified by *C. albicans* and non-*albicans Candida* species, 2005–2014 (n = 158 episodes).

Year	<i>Candida albicans</i>		Non- <i>albicans Candida</i>		All <i>Candida spp</i> *	
	n	Candida/1000 admissions	n	Candida/1000 admissions	n	Candida/1000 admissions
2005	4	0.16	4	0.16	10	0.40
2006	8	0.28	5	0.17	14	0.49
2007	7	0.20	5	0.14	12	0.34
2008	5	0.16	4	0.13	10	0.32
2009	9	0.30	8	0.26	22	0.72
2010	9	0.27	6	0.18	18	0.54
2011	7	0.18	8	0.21	16	0.42
2012	7	0.19	10	0.28	18	0.56
2013	10	0.28	5	0.20	15	0.43
2014	4	0.10	17	0.44	23	0.59

*Six patients had mixed types of *Candida spp* & 15 had non-typed *Candida spp*.

to amphotericin, voriconazole, fluconazole, and flucytosine.

Clinical Characteristics and Risk Factors of Patients with C. albicans vs. non-albicans Candida BSIs

A total of 119 patients out of 158 had complete medical records and 104 patients of them had one species of *Candida* species. When patients’ baseline characteristics and clinical details stratified by two categories of *Candida species* were compared, it was shown that patients with *C. albicans* BSIs had a higher overall death rate (48%) compared to patients with non-*albicans Candida* BSIs (32%) (p = 0.008). Table 2 displays the results of the univariate and multivariable logistic regression analyses. In univariate analysis, patients with non-*albicans Candida* were more likely to

have received antibiotics in the previous 90 days (p = 0.034) and empirical or prophylactic fluconazole treatment (p = 0.091) compared to patients with *C. albicans*. However, in multivariable regression, only previous exposure to antibiotics in the previous 90-days remained independently associated with non-*albicans Candida* BSI (OR 2.454, 95% CI 1.072-5.615; p = 0.033).

Risk factors associated with the 30-day mortality of patients with candidemia

Previous antifungal therapy (prophylaxis or empirical) was administered in 22.7% of patients, while 9.24% of patients did not receive any antifungal treatment. Fluconazole was the most frequently used antifungal (59.7%), followed by amphotericin B

Table 2. Univariate and multivariable logistic regression analyses of risk factors associated with *C. albicans* vs. non-*C. albicans* BSIs (n = 104 episodes).

Risk factors	Univariate			Multivariable	
	Non- <i>C.albicans</i> n = 54 n (%)	<i>C. albicans</i> n = 50 n (%)	p value	OR (95% CI)	p value
Age					
< 1 year	18 (33.3)	18 (36.0)	0.862	-	-
1-15 years	5 (9.3)	5 (10.0)	0.901	-	-
16-65 years	21 (38.9)	16 (32.0)	0.503	-	-
Gender (male)	34 (63.0)	30 (60.0)	0.882	-	-
Previous hospitalization	29 (53.7)	23 (46.0)	0.433	-	-
Reason for hospital admission					
Medical	58 (79.5)	39(84.8)	0.354	-	-
Surgical	25 (46.3)	29(58.0)	0.234	-	-
Diabetes mellitus	15 (27.8)	18(36.0)	0.369	-	-
Cardiovascular disease	15 (27.8)	19(38.0)	0.268	-	-
Hematologic malignancy	8 (14.8)	4(8.8)	0.284	-	-
Solid tumor	6 (11.1)	9(18.0)	0.500	-	-
End stage renal disease	5 (9.3)	2(4.0)	0.298	-	-
Invasive procedure					
Mechanical ventilation	26 (48.1)	26 (52)	0.695	-	-
Foley catheter	31 (57.4)	24 (48.0)	0.338	-	-
Central venous catheterization	28 (51.9)	23 (46.0)	0.551	-	-
Nasogastric tube	12 (22.2)	13 (26.0)	0.653	-	-
Tracheostomy	16 (29.6)	11 (22.0)	0.284	-	-
Endoscopy	7 (13.0)	4(8.0)	0.415	-	-
Medications					
Previous fluconazole	16 (29.6)	8 (16.0)	0.091	-	-
Antibiotic before hospitalization	62 (84.9)	36 (78.3)	0.034	2.454 (1.072-5.615)	0.033
Dual-antibiotic therapy	8 (14.8)	3 (6.0)	0.176	-	-
Corticosteroid	50 (92.6)	43 (86.0)	0.282	-	-
Proton-pump inhibitor	26 (48.1)	23 (46.0)	0.826	-	-
Total parenteral nutrition	8 (14.8)	8 (16.0)	0.825	-	-
Others					
<u>Sepsis</u>	15 (27.8)	9 (18.0)	0.240	-	-
<u>Severe sepsis and septic shock</u>	7 (13.0)	10 (20.0)	0.335	-	-
Intensive care unit stay	39 (72.2)	37 (74.0)	0.838	-	-
Abdominal surgery	15 (20.5)	5 (10.9)	0.945	-	-
Length of hospital stay (days)	42.63 ± 5.6	46.55 ± 5.7	0.624	-	-

(23.5%) and caspofungin (10.9%). Only three patients (2.5%) received a combination therapy (fluconazole + voriconazole or fluconazole + amphotericin B). Mortality was lower if antifungal therapy was initiated within 24 hours of culture result compared to therapy after 24 hours (37.0% vs 41.3%, $p = 0.031$).

The overall 30-day crude mortality was 38.7% in 119 patients with complete medical records. In the univariate analysis, it was found that diabetes mellitus

and cardiovascular diseases were significantly higher in patients who died ($p = 0.026, 0.014$, respectively). Other variables associated with increased mortality included severe sepsis and septic shock ($p=0.001$), ICU stay ($p = 0.009$), central venous catheterization ($p = 0.019$), receiving blood during hospitalization ($p = 0.071$) or mechanical ventilation ($p = 0.001$). Table 3 displays the results of univariate and multivariable regression of mortality risk factors. The following

Table 3. Univariate and multivariate analyses of risk factors associated with 30-day mortality in patients with candidemia (n=119 episodes).

Risk factors	Univariate		p-value	Multivariable	
	Survival N = 73 n (%)	Death N = 46 n (%)		OR (95% CI)	p value
Age					
< 1 year	26 (35.6)	13 (28.3)	0.007	-	-
1-15 years	13 (17.8)	2 (4.3)	0.002	-	-
16-65 years	27 (37.0)	15 (32.6)	0.011	-	-
Gender (male)	47 (64.4)	26 (56.5)	0.392	-	-
Previous hospitalization	38 (52.1)	22 (47.8)	0.653	-	-
Delay of treatment					
≤ 24 hours	21 (28.8)	17 (37.0)	0.337	-	-
25 > hours	45 (61.6)	19 (41.3)	0.031	-	-
Reason for hospital admission					
Medical	58 (79.5)	39 (84.8)	0.467	-	-
Surgical	47 (64.4)	26 (56.5)	0.220	-	-
Diabetes mellitus	16 (21.9)	19 (41.3)	0.026	-	-
Cardiovascular disease	16 (21.9)	20 (43.5)	0.014	-	-
Hematologic malignancy	6 (8.2)	8 (17.4)	0.138	-	-
Solid tumor	9 (12.3)	8 (17.4)	0.444	-	-
End stage renal disease	5 (6.8)	2 (4.3)	0.575	-	-
Invasive procedure					
Mechanical ventilation	29 (39.7)	34 (73.9)	<0.001	0.162 (0.048-0.547)	0.003
Foley catheter	36 (49.3)	29 (63.0)	0.145	-	-
Central venous catheterization	33 (45.2)	31 (67.4)	0.019	0.255 (0.76-0.848)	0.026
Nasogastric tube	15 (20.5)	15 (32.6)	0.143	-	-
Tracheostomy	16 (21.9)	16 (34.8)	0.137	-	-
Endoscopy	10 (13.7)	6 (13.0)	0.919	-	-
Treatment					
Fluconazole prophylaxis	16 (21.9)	11 (23.9)	0.800	-	-
Corticosteroid	68 (93.2)	39 (84.8)	0.149	-	-
Blood transfusion	53 (72.6)	40 (87.0)	0.071	-	-
<u>Total parental nutrition</u>	10 (13.7)	7 (15.2)	0.813	-	-
Clinical factors					
<u>Sepsis</u>	15 (20.5)	14 (30.4)	0.224	-	-
<u>Severe sepsis and septic shock</u>	4 (5.5)	15 (32.6)	<0.001	0.073 (0.011-0.504)	0.008
ANC<500	7 (9.6)	5 (10.9)	0.821	-	-
<i>Candida</i> in urine	15 (20.5)	15 (32.6)	0.143	-	-
Bacteria in blood	33 (45.2)	19 (41.3)	0.676	-	-
ICU admission	47 (64.4)	40 (87.0)	0.009	0.078 (0.017-0.364)	0.001
Infection with <i>C. albicans</i>	37 (50.7)	17 (37.0)	0.087	0.235 (0.070-0.783)	0.018
Abdominal surgery	15 (20.5)	5 (10.9)	0.176	-	-
WBC in the 1 st day of <i>Candida</i> *	11.58 ± 1.3	12.51 ± 1.2	0.598	-	-
LOS *	28.4 ± 5.6	38.54 ± 3.5	0.011	1.057 (1.027-1.087)	<0.001
Number of antibiotics *	4.99 ± 0.28	5.0 ± 0.28	0.848	-	-
Number of comorbidities*	1.16 ± 0.16	1.93 ± 0.25	0.009	0.580 (0.338-0.868)	0.008

*mean ± SD; ANC: absolute neutrophil count, ICU: intensive care unit, WBC: white blood cell, LOS: length of stay.

factors remained independently associated with 30-day mortality in the multivariable model: central venous catheterization (OR 0.255, 95% CI 0.76-0.848; $p = 0.026$), mechanical ventilation (OR 0.162, 95% CI 0.048-0.547; $p = 0.003$), candidemia due to *C. albicans* (OR 0.235, 95% CI 0.070-0.783; $p = 0.018$), severe sepsis and septic shock (OR 0.73, 95% CI 0.011–0.504; $p = 0.008$), number of comorbidities (OR 0.58, 95% CI 0.338–0.868; $p = 0.008$) and ICU stay (OR 0.078, 95% CI 0.017–0.364; $p = 0.001$).

Discussion

This study examined the annual incidence of *Candida* BSIs and species distribution over a 10-year period in a tertiary hospital in Jordan. The overall incidence of candidemia was found to be comparable to that of other studies around the world [8, 12-16]. However, the reported incidence rate is higher in hospitals in Latin America and Italy (1.2 to 1.7 episode/1000 admission) and lower in hospitals in Northern Europe (0.01 to 0.08 episode/1000 admission) [17-19]. On regional level, the incidence rate was higher (3 episodes/1000 inpatient days) in a pediatric tertiary hospital in Egypt [20]. While in a university hospital in Saudi Arabia 4.7% of blood cultures were positive for *Candida* [21]. The incidence of candidemia was fluctuating over the study period. This fluctuation could be explained by an inconsistency in hospital's staff adherence to preventive measures and infection control practices, including hand washing, skin disinfections and removal of unnecessary catheters [22]. While *C. albicans* is still considered the most frequent species causing candidemia, trends for growing rates of non-*albicans Candida* have been reported [2,7,13,23]. The current study observed a fluctuation in non-*albicans Candida* species over the study period with the highest incidence in 2014.

In this study, previous exposure to antibiotics was found to be the only independent risk factor associated with non-*albicans Candida* BSIs. This would call attention to the importance of appropriate antibiotic use in hospitals and of antimicrobial stewardship programs in controlling and preventing unnecessary use of antibiotics [24,25]. Previous studies have identified other risk factors associated with non-*albicans Candida*, including glucocorticoids use, central venous catheter placement, candiduria, male gender, total parental nutrition and recent history of solid tumors [24-30].

The overall 30-day crude mortality was 38.7%, a finding comparable to that of other studies. In a tertiary center in the United Kingdom, the 30-day crude

mortality in patients with candidemia was 37% [13]. Similarly, the reported 30-day crude mortality in two Italian tertiary hospitals was 38.8% [3]. However, in a university hospital in Saudi Arabia, the overall mortality rate was higher (71%) [21]. In addition, 30-day crude mortality was higher in patients with *C. albicans* compared to patients with non-*albicans Candida* (48% vs.31.5%) BSI. In the US, Chow et al have reported no variation in hospital mortality among the two groups (57% versus 58%) [24]. Playford et al reported higher mortality in patients with non-*albicans Candida* compared to *C. albicans* infections (53% versus 41%) [26]. In contrast, Wang et al reported higher crude mortality with *C. albicans* BSIs (44.3% versus 29.8%) [25]. In this study, *C. albicans* was also a significant predictor of mortality. While *C. albicans* is more virulent than non-*albicans Candida* which could explain the higher mortality rate, mortality is not solely related to the virulence of the *Candida* pathogens but it is also related to the severity of the underlying illness, the comorbidities, and the integrity of the defense mechanisms of the host as has been shown previously [27]. In our study, ICU stay, central venous catheterization, mechanical ventilation, length of hospitalization, number of comorbidities, severe sepsis and septic shock were identified as predictors of mortality in patients with candidemia. These results are in agreement with previously published studies that reported risk factors for mortality in patients with candidemia [4,16,20,28,31-33].

This study has some limitations. First, it is a retrospective study performed at a single center and the results may not be applicable to other settings. Second, the severity of illness score (such as APACHE II score) was not included because of unavailable data; however, number of comorbidities was used. Third, mortality measured in this study is crude mortality which may be affected by patient's medical condition. Finally, there were limitations in data accessibility and availability.

Conclusion

This study is the first longitudinal epidemiological study of *Candida* BSIs in a Jordanian tertiary care hospital. The annual incidence of candidemia was fluctuating over the 10-year surveillance period. Previous antibiotic use was the only risk factor associated with non-*albicans Candida* BSIs and multiple underlying medical conditions were identified as predictors of 30-day crude mortality in candidemia patients. Based on these findings, continuous local surveillance programs, strict adherence to infection control measures and implementation of antimicrobial

stewardship programs should be considered to improve clinical outcomes in patients with candidemia.

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