Research Article

Candida Bloodstream Infection: Changing Pattern of Occurrence and Antifungal Susceptibility over 10 Years in a Tertiary Care Saudi Hospital

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Background. Candida has emerged as one of the most important pathogens that cause bloodstream infection (BSI). Understanding the current Candida BSI trends, the dominant species causing disease and the mortality associated with this infection are crucial to optimize therapeutic and prophylaxis measures. Objectives. To study the epidemiology and to evaluate the risk factors, prognostic factors, and mortality associated with candidemia and to compare these findings with previously published studies from Saudi Arabia. Design. A retrospective medical record review. Setting. Tertiary hospital in Riyadh. Patients and Methods. The analysis included all cases of Candida blood stream infection who are >18 years old over the period from 2013 to 2018. Continuous variables were compared using the parametric T-test while categorical variables were compared using the Chi-squared test. Main Outcome Measure. Incidence, resistance, and hospital outcomes in Candida blood stream infection. Sample Size. 324 patients. Results. Three hundred and twenty-four episodes of Candida blood stream infections were identified. Median age of patients was 49.7 SD ± 28.1 years, and 53% of patients were males. More than half of the patients had an underlying disease involving the abdomen or laparotomy, 78% had an indwelling intravenous catheter, and 62% had suffered a bacterial infection within 2 weeks prior to candidemia. Candida albicans represents 33% of all isolates with decreasing trend overtime. There was an increase in the number of nonalbicans Candida overime with Candida tropicalis in the lead (20%). Use of broad spectrum antibiotics (82%), prior ICU admission (60%) and use of central venous catheters (58%) were the most prevalent predisposing factors of candidemia. Azole resistance was variable overtime. Resistance to caspofungin remained very low (1.9%). Fourteen days crude mortality was 37% for ICU patients and 26.7% in non-ICU patients, while hospital crude mortality was 64.4% and 46.7%, respectively. Conclusion. There is an increasing trend of nonalbicans Candida blood stream infection. Fluconazole resistance remained low to C. albicans. Most isolates remain susceptible to caspofungin, voriconazole, and amphotericin B. Candida bloodstream infection is associated with high 14-day hospital mortality.

1. Introduction

Over the last two decades, Candida has emerged as one of the most important pathogens causing nosocomial bloodstream infection in both adults and children worldwide [1–6]. Candida is part of our normal flora, and more than 200 species have been described, but only 10% are known to cause human infections [7]. In hospitalized patients and especially in the critically ill patients, Candida is between the fourth and sixth most
common isolated pathogen in bloodstream infections [8–12].

As a single species, C. albicans accounts for close to 50% of overall invasive Candida infection. However, there has been a proportionate increase in the isolation of nonalbicans species of Candida [4, 13–18].

Incidence of Candida-invasive blood infection and Candida species isolated varies according to patient population and geographical locations. While some surveillance has described an increase in the incidence of candidemia, others have showed either a stable or decreasing trends [19–24].

In Saudi Arabia, candidemia incidence is not precisely known. Earlier studies revealed a low incidence in general ranging between 0.2 and 0.76 cases/1000 hospital discharges, [25–28] while more recent studies revealed a higher incidence with a median rate of 1.65 per 1,000 hospital discharges per year with a significant trend towards higher rates over time [29, 30]. Candida accounts for 2.8% of all positive blood cultures [31].

The reported mortality secondary to candidemia ranges from 30 to 60% with up to 30 days increase in the length of hospital stay for survivors [11, 12, 16, 32, 33].

Risk factors of bloodstream infections with Candida species have been extensively studied and include malignancies, neutropenia, prolonged ICU (intensive care unit) stays, Candida colonization, severe illness, diabetes, renal failure, hemodialysis, receipt of prolonged courses of broad-spectrum antibiotics, central venous catheterization, parenteral hyperalimentation, immunosuppressive drugs, and transplantation [34–38].

The current project aims to study the epidemiology and to evaluate the risk factors, prognostic factors, and mortality associated with candidemia and to compare these findings with previously published studies from Saudi Arabia.

2. Method

This is a retrospective analysis of all cases of Candida bloodstream infection over the period from 2008 to 2015 from a tertiary care hospital in Riyadh Saudi Arabia. National Guard (NGHA) hospital in Riyadh is multiple specialty hospital with a total bed capacity of more than 1200 beds.

Candida bloodstream infection is defined as at least 1 blood culture positive for Candida species for a patient who developed signs and symptoms of BSI >48 h after hospital admission. Only the first episode of candidemia was included.

Demographic and clinical data of age, gender, primary illness, comorbidities, and risk factors such as duration of antibiotic therapy, intravenous catheters, endotracheal intubation, and mechanical ventilation at the time when blood culture was positive were all collected.

When data were available, we calculated the Candida score for patients. The score consists of the following: multifocal Candida colonization (1 point), surgery on ICU admission (1 point), severe sepsis (2 points), and TPN (1 point). A cutoff of more than or equal to three was highly predictive of fungal infection. The score is created based on the four predictors of invasive fungal infection in the Estudio de Prevalencia de CANDidiasis project [39]. There was a significant linear association between higher values and invasive fungal infection especially in ICU patients, and a higher score could be used to risk stratify patients for early antifungal treatment [40]. Candida colonization data were frequently missing especially in non-ICU patients.

Candida identification was carried out via VITEK® 2 (bioMérieux, Inc. Hazelwood, MO, USA) healthcare system and bioMérieux API 20C AUX, a system for the identification of the most frequently encountered yeasts. Candida susceptibility was primarily performed with bioMérieux VITEK® 2 Fungal Susceptibility (AST-Y07). Thermo Scientific™ Sensititre™ YeastOne™ YO10 AST antifungal testing (colorimetric microplate-based assay) was occasionally used. Both methods have shown good agreement with the Clinical and Laboratory Standards Institute (CLSI) broth microdilution reference method (BMD) [39–46].

The permission of the Ethics Committee at King Abdullah International Medical Research Center (KAIMRC) was obtained.

3. Statistical Analysis

Standard descriptive statistics were used. Categorical data were reported as frequencies and percentages, while continuous variables were reported as mean ± standard deviation. Continuous variables were compared using the parametric T-test while categorical variables were compared using the Chi-squared test. Multivariate logistic regression was used to the assess Candida risk factors. Tests were performed two-tailed and considered significant when p value <0.05. All statistical tests were performed using the statistical package IBM SPSS for Windows (version 20.0: SPSS, Chicago, IL, USA).

4. Results

Over the study period, a total of 324 patients with candidemia were identified. Male-to-female ratio was 1.14 with a mean age of 49.7 SD ± 28.1. Candida albicans was the leading cause of candidemia across all years accounting for 33%. Nonalbicans strains as a group were more common representing 67% of all isolates (Table 1).

More than two thirds of candidemia episodes (67.6%) occurred in the intensive care units (ICUs) followed by medical wards (15%). There were more candidemia episodes from cardiac wards (6.5%) including CCU and medical cardiac ICU compared with surgical (5.6%) and hematology (5.2%) wards.

In the first two years of the study, there was an increase in candidemia of both nonalbicans and C. albicans groups. While the rate of candidemia due to C. albicans was stable between 2010 and 2013 and decreasing thereafter, nonalbicans candidemia continues to increase (Figure 1(a)). Candida tropicalis followed by Candida glabrata and Candida parapsilosis were the most commonly isolated in the nonalbicans group. While number of isolates due to C. tropicalis was decreasing, both C. glabrata and C. krusei were on the rise (Figure 1(b)). Nonalbicans group were more
frequently isolated in ICU patients (63.5% vs. 37.3%, \( p = 0.078 \)) crude mortality within the first two weeks after candidemia was 64% and is more observed among patients in ICU when the diagnosis is made (37% vs. 27% \( p = 0.016 \)) (Table 2). Overall hospital mortality was 59%. Crude mortality remained high for both nonalbicans and \textit{C. albicans} groups with a slightly lower rate for former overtime (Figure 2).

Patients where candidemia was diagnosed in ICU were significantly less likely to leave hospital alive (\( p = 0.002 \))

### Table 1: Patients general characteristics.

| Item                        | Identified variables          | \( N \) (%) |
|-----------------------------|-------------------------------|------------|
| Gender                      | Male                          | 173 (53.4) |
|                             | Female                        | 151 (46.6) |
| Age                         | Mean ± SD                     | 49.7 ± 28.1|
|                             | Intensive care unit (ICU)     | 219 (67.6) |
|                             | Medical                       | 49 (15)    |
|                             | Others*                       | 56 (17.3)  |
| Place of isolation          | Nonintensive care unit        | 105 (32.4) |
|                             | Prior ICU admission           | 195 (60.2) |
|                             | Neutropenia                   | 19 (5.9)   |
| Use of broad-spectrum antibiotic |                            | 264 (81.5) |
| Presence of vascular device |                              | 188 (58)   |
| Internal jugular            |                              | 98 (30.2)  |
| Risk factors                | Subclavian                    | 34 (10.5)  |
|                             | Peripherally inserted central catheter (PICC) | 33 (10.2) |
|                             | Femoral                       | 64 (19.8)  |
|                             | Parenteral nutrition          | 60 (18.5)  |
|                             | Intra-abdominal infection     | 15 (4.6)   |
|                             | Others (medications)          | 44 (13.6)  |
|                             | \textit{C. albicans}          | 108 (33.3) |
|                             | Nonalbicans                   | 216 (66.7) |
| Candida species             | \textit{C. tropicalis}        | 72 (22.2)  |
|                             | \textit{C. glabrata}          | 60 (18.5)  |
|                             | \textit{C. parapsilosis}      | 52 (16)    |
|                             | \textit{C. krusei}            | 17 (5.2)   |
|                             | Others                        | 15 (4.6)   |
| Drug susceptibility profile | Amphotericin B                | 315 (97.2) |
| (susceptible)               | Caspofungin                   | 314 (96.9) |
|                             | Fluconazole                   | 214 (66)   |
|                             | Voriconazole                  | 281 (86.7) |
| 14 days outcome             | Alive                         | 215 (66.4) |
|                             | Dead                          | 109 (33.6) |
| Hospital outcome            | Alive                         | 134 (41.4) |
|                             | Dead                          | 190 (58.6) |

* = surgical 5.6%, cardiac 6.5%, and hematology 5.2%.

![Figure 1: Trends of candidemia over time. (a) \textit{Albicans} vs non\textit{albicans}. (b) \textit{Candida} spp.](image-url)
| Identified variables | Variable | 14 days postisolation outcome | p value | Hospital outcome | p value |
|----------------------|----------|------------------------------|---------|------------------|---------|
|                      |          | Dead N (%) | Alive N (%) |              | Dead N (%) | Alive N (%) |
| Age                  | ≤18      | 15 (23.4)   | 49 (76.6)   | 0.054     | 26 (40.6)   | 38 (59.4)   |
|                      | >18      | 94 (36.2)   | 166 (63.8)  | 0.013     | 154 (63.1)  | 96 (36.9)   |
| Mean age ± SD        |          | 54.9 ± 26   | 47 ± 28.8   | <0.001    | 55.7 ± 26.2 | 41.2 ± 28.7 |
| Gender               | Male     | 60 (34.7)   | 113 (65.5)  | 0.671     | 102 (59)    | 71 (41)     |
|                      | Female   | 49 (32.5)   | 102 (67.5)  | 0.721     | 88 (58.3)   | 63 (41.7)   |
| Abdominal pathology  |          | 13 (28.3)   | 33 (71.7)   | 0.404     | 29 (63)     | 17 (37)     |
| Malignancy           |          | 86 (32.8)   | 176 (67.2)  | 0.522     | 151 (57.9)  | 111 (42.4)  |
| Trauma/surgery       |          | 4 (13.8)    | 25 (86.2)   | 0.018     | 11 (37.9)   | 18 (62.1)   |
| Sepsis/infection     |          | 40 (40.8)   | 58 (59.2)   | 0.072     | 60 (61.2)   | 38 (38.8)   |
| Kidney disease       |          | 69 (30.5)   | 157 (69.5)  | 0.869     | 130 (57.5)  | 96 (42.5)   |
| Burn                 |          | 12 (32.4)   | 25 (67.6)   | 0.521     | 22 (59.5)   | 15 (40.5)   |
| Diabetes mellitus    |          | 59 (35.8)   | 106 (64.2)  | 0.412     | 113 (68.5)  | 52 (31.5)   |
| Renal disease        |          | 50 (31.4)   | 109 (68.6)  | 0.772     | 77 (48.4)   | 82 (51.6)   |
| Cardiac disease      |          | 48 (44.9)   | 59 (55.1)   | 0.003     | 79 (73.8)   | 28 (26.2)   |
| Respiratory disease  |          | 61 (28.1)   | 156 (71.9)  | 0.731     | 111 (51.2)  | 106 (48.8)  |
| Comorbidities        |          | 24 (32)     | 51 (68.1)   | 0.003     | 55 (73.3)   | 20 (26.7)   |
| Liver disease        |          | 59 (35.8)   | 106 (64.2)  | 0.412     | 113 (68.5)  | 52 (31.5)   |
| Malignancy           |          | 60 (31.4)   | 109 (68.6)  | 0.772     | 77 (48.4)   | 82 (51.6)   |
| Recent steroid use   |          | 48 (44.9)   | 59 (55.1)   | 0.003     | 79 (73.8)   | 28 (26.2)   |
| ICU                  |          | 24 (32)     | 51 (68.1)   | 0.003     | 55 (73.3)   | 20 (26.7)   |
| Site at isolation    |          | 104 (33.7)  | 205 (66.3)  | 0.979     | 11 (73.3)   | 30 (26.7)   |
| Device related       | Non-ICU  | 81 (37)     | 138 (63)    | 0.066     | 141 (64.4)  | 78 (35.6)   |
|                      | No       | 28 (26.7)   | 77 (73.3)   | 0.066     | 49 (46.7)   | 56 (53.3)   |
| Prior ICU admission  | No       | 33 (31.4)   | 123 (68.6)  | 0.022     | 124 (64.6)  | 64 (35.4)   |
| Treatment duration   | No       | 4 (36.4)    | 7 (63.6)    | 0.846     | 4 (36.4)    | 7 (63.6)    |
| Azole therapy        | No       | 35 (35)     | 65 (65)     | 0.730     | 62 (62)     | 38 (38)     |
| C. albicans          | Yes      | 105 (33.5)  | 208 (66.5)  | 0.846     | 186 (58.4)  | 127 (41.6)  |
| (i) C. tropicalis    | No       | 4 (36.4)    | 7 (63.6)    | 0.846     | 4 (36.4)    | 7 (63.6)    |
| (ii) C. glabrata     | Yes      | 74 (33)     | 150 (67)    | 0.730     | 62 (62)     | 38 (38)     |
| (iii) C. parapsilosis| No       | 35 (35)     | 65 (65)     | 0.730     | 62 (62)     | 38 (38)     |
| (iv) C. krusei       | Yes      | 105 (33.5)  | 208 (66.5)  | 0.846     | 186 (58.4)  | 127 (41.6)  |
| Risk factors         | No       | 4 (36.4)    | 7 (63.6)    | 0.846     | 4 (36.4)    | 7 (63.6)    |
| Prior colonization   | No       | 35 (35)     | 65 (65)     | 0.730     | 62 (62)     | 38 (38)     |
| Treatment duration   | No       | 4 (36.4)    | 7 (63.6)    | 0.846     | 4 (36.4)    | 7 (63.6)    |
| Azole therapy        | No       | 35 (35)     | 65 (65)     | 0.730     | 62 (62)     | 38 (38)     |
(Table 2) Older age, candidemia in the patients with chronic liver disease, and treatment with azole therapy were all associated with worst outcome, while invasive Candida infection in trauma/surgery patients and those that are device-related have a better outcome (Table 2).

In multivariate analysis, risk factors for candidemia includes use of broad-spectrum antibiotics (81.5%) followed by ICU admission (60.2%) and use of central venous catheters (58%) (Table 3). Candida score was less or equal to 2 in 79% of patient with candidemia.

The Candida albicans group remained very susceptible to amphotericin B and echinocandin (caspofungin was the only echinocandin available in our hospital during the study period) (Table 4). Susceptibility to fluconazole remained high (77%). Among nonalbicans group susceptibility to fluconazole and voriconazole were 60% and 89%, respectively (Table 4). Although susceptibility to azoles (fluconazole and voriconazole) among the C. albicans group was trending lower during the study period, there was a significant increase in susceptibility over time in recent years in both C. albicans and nonalbicans groups (Figures 3(a) and 3(b)).

5. Discussion

Candida infection is a leading cause of invasive fungal infection worldwide [1, 2, 4, 13, 30]. Epidemiological studies have suggested that the annual incidence of candidemia in some countries might have stabilized or even decreased; however, there is a significant geographical variation [2, 4, 14, 18, 22–25, 29, 30].

Local epidemiological surveillance studies are important to guide empirical and therapeutic antifungal therapy. There is no Saudi national data on incidence and prevalence of invasive fungal infection. However, some centers have reported low and decreasing trends, while others showed an increasing rate [22–25, 30]. Candida albicans-invasive infection remains the most frequently isolated single species in our study albeit trending down frequency. Similar to other studies, BSI due to nonalbicans Candida as a group is higher with increasing frequency [29, 47, 48]. Candida tropicalis is the most frequently isolated among the nonalbicans group. In Saudi Arabia, Candida tropicalis has been the main species isolated among NAC (nonalbicans Candida) in both adult and pediatric population in most of the studies reported followed by Candida glabrata [6, 25–27, 30]. Risk factors for the emergence of nonalbicans Candida include increasing use of an antifungal regimen specially fluconazole, use of broad-spectrum antibiotics, and the increasing number of immunocompromised patients [37, 49, 50]. The decreasing trends of Candida tropicalis over time in our cohort is substituted by increasing frequency of C. glabrata and C. Krusei. This change over time may reflect patient variation and antimicrobial regimens that include more echinocandin use [51].

The European SENTRY investigators’ reported C. parapsilosis as the most frequently encountered Candida spp, while C. glabrata as the most commonly isolated NAC in US [2]. Other Candida species were more predominant in other countries. Such variability likely represents differences in populations studied and risk factors encountered [4, 32, 52].

Risk factors for invasive Candida across many studies from Saudi are consistent and similar to what is reported internationally. Use of broad-spectrum antibiotics, admission to ICU, and central vascular access were the main reported [6, 29, 30, 53].

Extensive use of broad-spectrum antimicrobial remains a very big challenge in Saudi Arabia. Ministry of health has recently launched a major campaign to combat the crisis of inappropriate use of antimicrobial in the Kingdom. More than two-third of our patients were ICU patients or with previous visit to ICU which is a major place for antimicrobial use. Vascular devices were in place in 58% of patients with candidemia. Those two factors are amenable to improvement through effective stewardship programs.

Most of the Candida spp. remains sensitive to polyene and echinocandins worldwide [11, 30, 54]. Candida albicans remains mostly sensitive to azoles. Resistance to fluconazole ranges between 0.3 and 2 percent [2, 53, 54]. However, Candida albicans with reduced susceptibility to fluconazole have been observed in many centers including Saudi Arabia [31, 55]. In our series, only 68% of Candida albicans isolates
were reported sensitive to fluconazole at the start of the study, but much higher susceptibility was observed at the end of the study (95%). Similar to other studies, resistance to fluconazole was overall predictive of resistance to voriconazole in our series [54, 56].

Candida krusei susceptibility to amphotericin B was lower than what is reported internationally but consistent with what was previously reported from Saudi Arabia (76%) [11, 29, 56].

Invasive Candida infection is associated with significant mortality especially in ICU and among older patients [1, 4, 11, 16, 30, 32, 33, 57, 58]. Both hospital and 14-day mortality in our cohort was high and was significantly higher among patients with ICU candidemia (37% vs. 26% p 0.066) and in those with candidemia related to vascular device. Patients with chronic liver disease and chronic and or acute renal failure requiring renal supportive therapy have significantly worse outcomes (p 0.017 and 0.003) Treatment for less than 48 hours and with azole therapy were also associated with worse outcome.

This study still represents single center experience which may vary according to hospital profile of admission and regional patient’s characteristics. There is a need for more comprehensive national data that should not be limited to one health care provider or geographical areas.

Table 3: A multivariate regression analysis of Candida risk factors.

| Variable                              | Infection outcome | Hospital outcome |
|---------------------------------------|-------------------|-----------------|
|                                       | 95% CI for OR     | 95% CI for OR   |
|                                       | Lower     Upper      | Lower     Upper      |
| Prior ICU admission (yes/no)          | 0.531     1.478 0.642 | 0.886     0.71 1.89 |
| Neutropenia (yes/no)                 | 0.218     1.936 0.439 | 0.65     0.29 2.01 |
| Use of broad-spectrum antibiotic (yes/no) | 0.948     3.609 0.071 | 1.849     1.74 5.77 |
| CV (yes/no)                           | 1.269     3.631 0.004 | 2.146     1.22 3.26 |
| TPN (yes/no)                          | 0.286     1.085 0.085 | 0.357     0.56 1.86 |
| Chemotherapy (yes/no)                | 0.267     2.683 0.778 | 0.847     0.33 2.61 |
| Intra-abdominal infection (yes/no)    | 0.426     3.865 0.658 | 1.283     0.37 3.43 |
| Chronic use of steroid (yes/no)       | 0.36      4.03 0.762 | 1.205     0.16 1.68 |
| Immune-modulating drugs (yes/no)      | 0.285     5.194 0.792 | 1.216     0.16 2.55 |

Table 4: Candida species susceptibility profile.

| Candida spp   | Amphotericin B N (%) | Caspofungin N (%) | Fluconazole N (%) | Voriconazole N (%) |
|---------------|----------------------|------------------|------------------|-------------------|
| C. albicans   | 106 (98.1)           | 106 (98.1)       | 83 (76.9)        | 89 (82.4)         |
| C. tropicalis | 72 (100)             | 69 (95.8)        | 52 (72.2)        | 63 (87.5)         |
| C. glabrata   | 60 (100)             | 58 (96.7)        | 29 (48.3)        | 47 (78.3)         |
| C. parapsilosis | 52 (100)           | 52 (100)         | 32 (61.5)        | 51 (98)           |
| C. krusei    | 13 (76.5)            | 16 (94)          | 4 (23.5)         | 16 (94)           |
| Others        | 12 (80)              | 13 (86.7)        | 14 (93.3)        | 15 (100)          |

Figure 3: Susceptibility trend over time.
In conclusion, the nonalbicans Candida group was the major cause of invasive candidemia and was trending higher overtime while Candida albicans were decreasing. Candida glabrata is emerging as the most frequent overtime. Most of the Candida spp. remained highly susceptible to all lines of therapy. Mortality remained high for all cases with invasive candidemia and especially among critically ill patients.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Additional Points

This study still represents single-center experience which may vary according to the hospital profile of admission and regional patient’s characteristics.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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