Taibah University

Journal of Taibah University Medical Sciences

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Original Article

A seven-year surveillance of *Candida* bloodstream infection at a university hospital in KSA

Tariq S. Al-Musawi, MD [a],[*], Wala A. Alkhalifa, MBBS [b], Norah A. Alasaker, MBBS [a], Jawad U. Rahman, MSc [c] and Amani M. Alnimr, PhD [b]

[a] *Department of Internal Medicine, King Fahad Hospital of the University, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, KSA*
[b] *Department of Medical Microbiology, King Fahad Hospital of the University, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, KSA*
[c] *Department of Microbiology, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, KSA*

الملخص

أهداف البحث: يحمل وجود المبيضات في الدم معدل وفيات مرتفعا، وقد ازدادت حالاته في السنوات القليلة الماضية. اقترحت الدراسات السابقة توزيع متغير من المبيضات بين المناطق المختلفة. وقد أجريت هذه الدراسة لتحديد الأنواع الموجودة في التهابات مجرى الدم بالمبيضات، وتحديد استجابتها لمضادات الفطريات الروتينية، مع نتائج الوفيات في مركز طبي أكاديمي.

طرق البحث: بين يناير ٢٠١٢ وديسمبر ٢٠١٨، تمت دراسة نتائج مزارع الدم الإيجابية لعدوى مجرى الدم المبيضية، وتحليلها إحصائيا لانتشار الأنواع ونمط القابلية للحساسية، ومعدل الوفيات بعد ١٤ و٣٠ و٦٠ و٩٠ يوما.

النتائج: من بين ١٥٦ حالة من حالات وجود المبيضات في الدم، كان سبب أغلبية الحالات (٦٩.٢٪) غير مجموعة المبيضات البيضاء. بعد مجموعة المبيضات البيضاء (٣٠.٨٪) كانت مجموعتا المبيضات الاستوائية والمبيضات المرطية، ثاني أكثر معزولة في كثير من الأحيان (٢٣.٧٪). واكتشفت المقاومة المكتسبة من الفلوكونازول في ١٤.٨٪ من سلالات المبيضات. ولم يتم الكشف عن أي مقاومة أخرى لمضادات الفطريات. وكانت المعدلات الإجمالية للوفيات لجميع الأنواع ٢٩.٣٪ و٤٧.٩٪ و٥٦.٤٪ و٥٨٪ في ١٤ و٣٠ و٦٠ و٩٠ يوما على التوالي. ولوحظ ارتفاع معدل الوفيات في حالات العدوى بالمبيضة الكروزية (الوفيات الخام ٧١.٤-١٠٠٪).

الاستنتاجات: لوحظ تحول كبير من المبيضات غير البيضاء للتسبب بعدوى مجرى الدم. ولكونها تهديدا خطيرا للمرضى في المستشفيات، يجب حث مختبرات علم الأحياء المجهرية على اعتماد التشخيص السريع واستعمال الحد الأدنى من الاختبارات على أساس التراكيز المثبطة للكشف عن الأنماط الظاهرية المعتمدة على الجرعة. الدراسات المستقبلية ضرورية للنظر في تشخيص عدوى مجرى الدم من قبل أنواع المبيضات المختلفة في نموذج متعدد المتغيرات.

الكلمات المفتاحية: المبيضات في الدم؛ اختبار الاستجابة لمضادات الفطريات؛ معدل الوفيات؛ التحول الوبائي؛ المبيضات غير البيضاء

Abstract

Objectives: Candidemia incidence has increased in the past few years, with high mortality. Previous studies have reported a variable distribution of *Candida* spp. among different regions. This study aimed to identify the species found in *Candida* bloodstream infections, routine anti-fungal susceptibility testing, and mortality outcomes in an academic medical centre.

Methods: Between January 2012 and December 2018, the positive blood cultures for candidemia infection were retrieved and statistically analysed for species prevalence, susceptibility pattern, and crude mortality at 14, 30, 60 and 90 days.

Results: Of 156 candidemia cases, a majority (69.2%) was caused by non-albicans *Candida* spp. After *Candida albicans* (30.8%), *Candida tropicalis* and *Candida para-psilosis* were the second and third most frequeunt isolates spp, each counting for 23.7%. Acquired resistance was detected in 14.8% of candidemia strains. No other anti-fungal resistance was detected. The overall crude

* Corresponding address: Department of Internal Medicine, King Fahad Hospital of the University, College of Medicine, Imam Abdulrahman Bin Faisal University, P.O. Box 1982, Dammam, 31441, KSA.
E-mail: Dr_tmusawi@hotmail.com (T.S. Al-Musawi)
Peer review under responsibility of Taibah University.

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mortality rates of all species were 29.3%, 47.9%, 56.4%, and 58.0% at 14, 30, 60, and 90 days, respectively. A higher mortality rate was noted in cases of *Candida krusei* infection (crude mortality 71.4−100%, $p = 0.002$).

Conclusion: In this study, a considerable shift to non-albicans *Candida* causing most bloodstream infections was observed. As such infections pose a serious threat to hospitalised patients, microbiology laboratories are urged to adopt rapid diagnostic and minimal inhibitory concentration-based testing for the detection of susceptible dose-dependent phenotypes. Prospective studies are essential to consider the prognosis of bloodstream infections by various *Candida* species in a multivariate model.

Keywords: Antifungal susceptibility testing; Candidemia; Epidemiological shift; Mortality; Non albicans

Introduction

Candida spp. are important nosocomial bloodstream pathogens with an increasing incidence over recent decades.[1,2] The diagnosis and treatment of candidemia impose a significant burden on healthcare systems. A 2019 prospective study reported that candidemia episodes in the United States led to an average 34-day increment in the length of hospital stay following diagnosis of *Candida* bloodstream infections, reflecting a $ 34,123 excess cost per case.[3] A more recent study by Zaoutis et al. on 2,000 patients showed a mean increase of $ 92,266 in the total hospital charges per patient and a mean increase of 10.1 days in the length of stay.[4] The crude mortality rate of candidemia is high and has been reported to reach up to 60%−70% in some groups.[1,5] Among various *Candida* species, *Candida tropicalis* bloodstream infections carry the worst prognosis as reported in several studies worldwide, whereas *Candida parapsilosis* shows lower mortality rates.[6−9] Other factors linked to worsening outcomes of candidemia in adults include the presence of septic shock, concurrent blood transfusion, higher APACHE II scores, older age, intensive care admission, and retained central venous lines.[7,8]

Population-based studies performed in different geographical areas suggest significant variability of *Candida* spp. in bloodstream infections worldwide. A large meta-analysis conducted by Koehler et al. in 2019 revealed considerable differences amongst candidemia species in European countries with an overall predominance of non-albicans strains.[10] In KSA, a growing body of evidence suggests that non-*albicans Candida* spp. (NAC) and *Candida albicans* contribute differently to bloodstream infections at various centres. A five-year study (1998−2002) in the Western region showed that *Candida* spp. (n = 83) was implicated in 2.8% of all culture-positive bloodstream

infections in a secondary hospital setting, with 46% attributed to *C. albicans*.[11] This was supported by two other studies in Central KSA that found *C. albicans* accounting for 38.7% and 50.7% of candidemia cases.[12,13] *C. tropicalis* was another common species in those studies and was identified as a dominant species in intensive care settings. A more recent study by Al-Dorzi et al. in a critical care unit in Central KSA identified *C. albicans* as the leading species among fungal bloodstream infections in 174 patients over four years (2012−2016).[14] In that study, the mortality rates of *C. albicans* and NAC were 61.3% and 54.9%, respectively. Most deaths occurred within 28 days of detecting a positive culture with a similar length of stay in the hospital and intensive care in both groups of species. Limited data are available for microbiological features and clinical outcomes of candidemia in the Eastern region of the Kingdom.[15] In the present study, we examined the species distribution and susceptibility patterns of *Candida* spp. amongst bloodstream infections in various age groups and the crude mortality rates at different points of time.

Materials and Methods

Research settings and participants

The study was conducted at King Fahd Hospital of the University Al-Khobar, a 550-bed secondary care and academic training centre. All patient age groups were included. Charts were individually reviewed to include cases that had clinically significant isolates. For the enrolled cases, the patients' chart data (age, sex, and location of patients when specimens were collected) and microbiological results available in the laboratory information system were evaluated. Routine testing of candidemia isolates in the laboratory included speciation by the automated VITEK 2 system (bioMe rieux Inc., Durham, NC, USA) between 2013 and 2016 and the VITEK MS (bioMe rieux Inc.) between 2016 and 2018.[16] Susceptibility testing was performed on all strains using the automated VITEK 2 system throughout the study period and was interpreted based on the FDA/CLSI breakpoints.[17] Intrinsic resistance patterns were excluded from the analysis e.g. resistance to amphotericin B in *Candida lusitaniae* and to fluconazole in *Candida krusei*. Only the first episode of candidemia per patient was included in the analysis. Two or more *Candida* species episodes per patient were counted separately. All cause crude mortality was recorded at 14, 30, 60, and 90 days.

Data analysis

The analysis was undertaken for the entire bloodstream infection study population and subgroup analyses for mortality were based on each *Candida* species alone, for aggregated NAC spp., and for adult versus paediatric age groups. GraphPad Prism software version 6.0. was used for the analysis. The normality of distribution was initially tested using the Kolmogorov−Smirnov test and data were handled as non-parametric. Cases with documented incomplete outcomes were dealt with as missing data. Continuous and categorical variables were analysed using the Mann−Whitney U test and

Fisher's exact test, respectively. A two-tailed *P* value < .05 was considered to represent statistical significance.

Results

Patient demographics

In total, 156 non-replicate candidemia episodes (51 paediatric patients and 105 adults) were included, of which 72 cases (46.2%) were female and 84 patients (53.8%) were male. Sixty-one cases (38.6%) developed fungemia within the intensive care units of adults, paediatrics, and neonates. Only one case was detected in a patient who presented to the emergency department, and the remaining 96 cases (60.8%)

were inpatients. Table 1 describes the age distribution in the identified cases (median age = 49.5 years).

Species distribution and susceptibility patterns

Six *Candida* spp. were identified from 156 bloodstream infections in the following descending order: *C. albicans, C. tropicalis, C. parapsilosis, Candida glabrata, C. krusei,* and a single case of *C. lusitaniae* isolated from a pre-term newborn. There were three patients that each had two episodes of candidemia with different species, most likely due to prolonged hospital stay, although lab misidentification of closely related spp. is a possibility. A decreasing trend was observed for *C. krusei* over the years, whereas an increasing trend was noted for *C. glabrata.* Table 2 illustrates the yearly distribution of each of the six species. The median age of infections by each of these species is shown in Table 3. Regarding antifungal susceptibility testing over seven years, only resistance to fluconazole (14.8%) was detected by VITEK 2 in *C. albicans* (16.7%), *C. tropicalis* (13.5%), *C. parapsilosis* (16.6%), and *C. glabrata* (7.7%) (Table 4).

Crude mortality

The overall crude mortality of candidemia was significantly higher in adults than in children (hazard ratio = 6.3,

Table 1: Distribution of all candidemia cases among various age groups.

Age groups in years	Number	%	Cumulative%
<1	33	21.2	21.2
1−14	18	11.5	32.7
15−44	21	13.5	46.2
45−74	66	42.3	88.5
≥75	18	11.5	100
Total	156	100.0	NA

Table 2: Frequency of isolation of *Candida species* in cases of candidemia by year (2012−2018).

Year	*C. albicans*	*C. tropicalis*	*C. parapsilosis*	*C. glabrata*	*C. krusei*	*C. lusitaniae*	Total (n)
2012	7	6	7	1	0	0	21
2013	10	7	4	1	6	0	28
2014	7	3	2	3	1	1	17
2015	4	5	4	2	0	0	15
2016	3	3	6	5	0	0	17
2017	8	6	10	8	0	0	32
2018	9	7	4	6	0	0	26
Total n (%)	48 (30.8%)	37 (23.7%)	37 (23.7%)	26 (16.7%)	7 (4.5%)	1 (0.6%)	156

Table 3: Species-specific age distribution of 156 bloodstream *Candida* strains.

Species	*C. albicans*	*C. tropicalis*	*C. parapsilosis*	*C. glabrata*	*C. krusei*	*C. lusitaniae*
Median age	43 years	54 years	6 years	65 years	53.5 years	10 days
Age range	3 days−85 years	2 days−95 years	10 days−79 years	2 days−96 years	35 years−87 years	NA
Pediatrics (n)	15	13	19	3	0	1
Adults (n)	33	24	18	23	7	0

Table 4: Antifungal susceptibility profiles of *Candida* spp. isolated from bloodstream infections by VITEK 2 system between 2012 and 2018. Breakpoints used by the system are 2 μg/ml for amphotericin B, caspofungin and micafungin, 1 μg/ml for voriconazole, 0.125 μg/ml for itraconazole, and 8 μg/ml for fluconazole.

Species and % Susceptibility	Fluconazole	Voriconazole	Flucytosine	Amphotericin B	Caspofungin *	Micafungin *
C. albicans	83.3	100	100	100	100	100
C. tropicalis	86.5	100	100	100	100	100
C. parapsilosis	83.4	100	100	100	100	100
C. glabrata	92.3 **	100 **	100	100	100	100
C. krusei	NA	100	100	100	100	100
C. lusitaniae	100 ***	100 ***	100	NA	100 **	100 **

* Denotes that the susceptibility of these drugs was only included in the panels used in period 2 (2014−2018). ** Denotes that the shown *Candida* species-antifungal testing combination is not FDA-approved for diagnostic purposes. *** Denotes that FDA approval for the shown *Candida* species-antifungal testing combination states that data about their clinical efficacy are not sufficient.
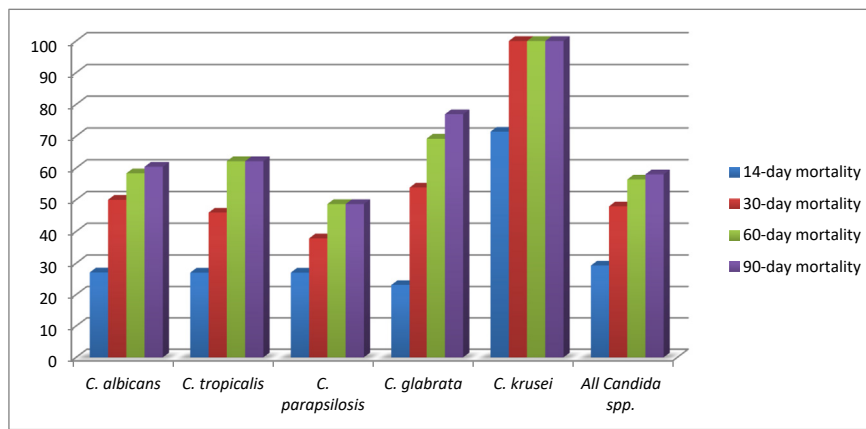
Figure 1: Crude mortality of candidemia caused by different *Candida* species in adults and pediatrics (n = 156). Note: *Candida lusitaniae*, isolated from a single case, didn't result in mortality.

95% confidence interval [CI] 4.8–13.7, $P < .0001$). Crude mortality rates observed for bloodstream infections by various *Candida* spp. at 14, 30, 60, and 90 days are illustrated in Figure 1 along with cumulative mortality by all species. When differences in crude mortality attributed to various species were assessed, only *C. krusei* bloodstream infections showed significantly worse outcomes ($P = .0024$).

Discussion

Candida spp. are known to frequently colonise hospitalised patients, especially in critical care settings.[18] Studies carried out in several countries have shown differences in the epidemiology of bloodstream infections caused by this yeast.[19] The majority of candidemia cases in the presented cohort (63.5%) originated from infants and middle-aged adults aged 45–75 years (Table 1). Most population-based studies have shown the highest incidence in very young <1 year and elderly age groups >65 years.[20,21] Our data demonstrated the frequency of distribution of bloodstream *Candida* spp. isolates in various age groups, which may not reflect true incidence. The median age of bloodstream infection by *C. glabrata* in this study (65 years) was higher than the median age in cases of candidemia by other spp., although this was not statistically significant as the species was isolated from all age groups and was previously described.[20] However, *C. parapsilosis* tended to infect younger patients and was the dominant aetiology of paediatric *Candida* bloodstream infections followed by *C. albicans* (Table 3). In a previous five-year study at the same institution, *C. parapsilosis* was the most common *Candida* species in bloodstream infections (44%), but the number of cases in that study was small (n = 32).[22] In the present study, *C. albicans* accounted for less than one-third of bloodstream infections compared to NAC spp. (69.2%), showing a changing pattern from earlier epidemiological data on candidemia from the same region,[15] even though it was the leading single species of *Candida* bloodstream infection cases in adults (Table 3). *C. tropicalis* was the second most frequent isolate from adults in this study. Similar findings were reported by Omrani et al., who evaluated 652 episodes of invasive *Candida* infections in Riyadh, with the majority being candidemia cases (82.1%),

and found 61.3% attributed to NAC spp., whereas *C. albicans* was the most commonly identified single species (38.7%) followed by *C. tropicalis* (18.9%).[12]

Each of the top three species frequently isolated in our institution had similar resistance profiles based on the automated susceptibility testing results (Table 4). Fluconazole resistance was detected in a small proportion of the isolates (14.8%) compared to previous reports in the Kingdom.[14,23,24] Species-specific antifungal clinical breakpoints have been available only recently.[25] Importantly, the susceptible dose dependent (SDD) breakpoints for azoles were not included in the previous software of automated systems. Our study included strains prior to that update and could have underestimated the resistance patterns prior to lowering the breakpoints for species that frequently fall in this category, such as *C. glabrata*.[26] Another shortcoming of automated antifungal testing, despite its ease of use, is the inability to detect the *fks* hot spot mutations that encode echinocandin resistance.[27] Currently, the lowest tested concentrations for caspofungin in those systems (0.125/0.25 µg/mL) fall at or just above the CLSI breakpoint for *C. glabrata* (0.125 µg/mL), which renders the results inaccurate for clinical decision-making in case of infections caused by this species. Thus, diagnostic microbiology laboratories need to consider adopting methods that test the susceptibility of the yeast based on minimal inhibitory concentrations (MIC), such as gradient strips, to supplement categorical automated testing. This is particularly relevant in the era of multidrug resistant yeasts such as *Candida auris,* which are increasingly being reported in bloodstream infections with uncertainty about the breakpoints for such organisms.[28] *C. auris* did not appear in any bloodstream infection in our institution until the end of the study period. The technical challenges encountered when performing antifungal susceptibility testing in the laboratory, such as the dip effect seen with echinocandins during *in vitro* testing, also need to be resolved.[29]

The high crude mortality rate found in the study (Figure 1) was previously reported in similar settings, which can be attributed to the underlying comorbidities and risk factors of patients,[23] and was also found in an intensive care-based study.[14] Notably, most of the crude mortality among our patient population was during the first 30 days after

candidemia diagnosis regardless of the *Candida* species. A study by Garey et al. found that a delay of each day to initiate effective antifungal therapy, from day 1 to day 4 or more, increased the mortality in candidemia cases in an ascending manner prospectively to 15%, 24%, 37%, and 41%.[30] Although the present study was not designed to assess the timing for initiating appropriate antifungal treatment, it still highlights the importance of rapid laboratory identification at the species level and susceptibility testing. Different *Candida* species have been implicated in worsening outcomes in various studies. Al-Tawfiq identified *C. albicans* as an independent risk factor for candidemia mortality in a multivariate analysis of 98 cases.[15] Candidemia due to *C. tropicalis* is reported to lead to higher mortality in the logistic regression analysis of a larger number of cases.[6,8] *C. glabrata* was shown to be an independent predictor of death in all age groups in an Australian surveillance of 1,095 cases.[20] The different species recognised as predictors of death in various studies suggest a possible variability in the virulence of strains circulating in these geographical areas and highlight the need for local studies. Our data suggested an increased crude mortality in *C. krusei* bloodstream infections, although the number of those cases was small (n = 7, P = .002), which needs further investigation, as this may reflect the complexities of underlying characteristics rather than an organism-specific factor.[31] *C. krusei* is intrinsically resistant to fluconazole, which may play a role in the delay to initiate effective therapy.[31–33] The observed higher mortality with age difference (HR = 6.3, P < .0001) can be attributed to several factors and further studies can elaborate on age as an independent predictor for worsening outcomes in similar patient populations.

Earlier studies from the KSA supported the predominance of *C. albicans* in fungemia cases,[13,15,23,34] whereas our data show a changing trend that is similar to subsequent studies carried out within the same time frame in the Kingdom.[12,24] This finding has clinical implications in selecting an empirical antifungal therapy in high-risk patients for optimal outcomes. The main limitations of this study were the small number of samples and the retrospective nature that limited access to information. Another point to consider is the accuracy of species identification, as the VITEK 2 system can misidentify closely related species.[35]

Conclusion

In conclusion, this study showed that non-albicans candidemia represented the majority of *Candida* bloodstream infections in the 2012−2018 cohort with an overall fluconazole resistance rate of 14.8%. The automated antifungal susceptibility testing system did not provide informative results regarding dose-dependent susceptible species. High crude mortality was noted for bloodstream infections caused by most *Candida* spp. encountered, which was more evident in adults and was mainly within 30 days of diagnosis. We observed an increased mortality in *C. krusei* infections. To verify this finding, future prospective, multi-centre studies are needed to assess the outcomes of candidemia due to different species in various age groups using a multivariate regression model considering all possible confounders.

Abbreviations: APACHE, Acute Physiology, Age, Chronic Health Evaluation; CLSI, Clinical Laboratory Standards Institute; FDA, Food and Drug Administration; HR, Hazard Ratio; MIC, Minimal inhibitory concentration; n, Number; SDD, Susceptible dose dependent; Spp., Species; NAC, non-albicans *Candida* spp.

Recommendations

We recommend that clinicians should consider Candida infection among different aetiologies of bloodstream infections in paediatric and adult patients. Also, we recommend Candidal speciation, as it is essential for treatment and prognosis stratification.

Conflict of interest

The authors have no conflict of interests to declare.

Ethical approval

This material is original, unpublished, and has not been submitted elsewhere. The study was approved by the Institutional Review Board of the University and the Ethics Committee of the affiliated Hospital (IRB-2019-01-148) on 05 March 2019. The patients' information was kept confidential.

Authors' contributions

TSM study design and conceptualisation, overall work supervision, contributed to writing the manuscript and plagiarism check. WAA, JUR, and NMA data acquisition and analysis, critical review of the manuscript, and plagiarism check. ASN study design and conceptualisation, contributed to writing the manuscript, statistical analysis, and plagiarism check. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Data availability

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

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