CANDIDEMIA AT A UNIVERSITY HOSPITAL: EPIDEMIOLOGY, RISK FACTORS AND PREDICTORS OF MORTALITY

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Background: Blood stream infection due to *Candida* species are becoming increasingly important causes of morbidity and mortality in hospitalized patients. The aim of this study was to obtain epidemiological data on candidemia in patients at King Abdulaziz University Hospital (KAUH), and to discuss the influence of several clinical variables on the development and outcome of candidemia.
Materials and Methods: Demographic information, risk factors, therapy and outcome of all patients who had candidemia at KAUH between January 1998 and December 1999 were reviewed.
Results: Thirty-one candidemic episodes were identified. All the candidemic episodes were hospital acquired. The most common risk factors to candidemia were central venous catheters (87%), stay in intensive care unit (ICU) (77%), and broad-spectrum antibiotics therapy (74%). *Candida albicans* was the most frequently isolated species (71%), followed by *Candida tropicalis* and *Candida parapsilosis* (13% each). Twenty-six patients (84%) were treated with amphotericin B, 4 (13%) with fluconazole, and one (3%) with ketoconazole. Antifungal susceptibility testing of the isolates in general revealed minimal levels of resistance to amphotericin B (3%) versus 39% resistance to fluconazole. Less than 5% of *Candida albicans* were resistant to amphotericin B, in comparison with >35% of these strains that were resistant to fluconazole. The overall mortality was 71%. Mortality was significantly associated with the presence of central venous catheters (P=0.001), stay in intensive care unit (P<0.001), and prolonged hospital stay before the onset of candidemia (P=0.05).
Conclusion: Despite antifungal treatment, the mortality of candidemia is still high. Rapid changes in the rate of infection, potential risk factors, and emerging species demand continued and close surveillance of this serious infection.
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Key Words: Candidemia, risk factors, mortality.

Candidemia is a life-threatening infection associated with an attributable mortality of 38%, and prolongation of hospital stay by as much as 30 days.[1] During the past two decades, nosocomial fungal infections have been increasingly reported in immunocompromised and other severely ill patients, such as those suffering from burns or major trauma, or those recovering from cardiac surgery.[2] Indeed, the incidence of invasive fungal infections due to *Candida* spp. has increased substantially in patients requiring intensive care.[3] More recently, the American and the European SENTRY Surveillance studies reported that 50% and 23% of candidemia episodes occurred in ICU patients, respectively.[4,5] Careful epidemiologic studies have identified intravascular catheters, broad-spectrum antibiotics therapy, mucosal colonization, neutropenia, previous surgical procedures (particularly complicated gastrointestinal surgery), total parenteral nutrition, and concomitant bacteremia or other infections as significant risk factors for invasive candidal infection.[6-9] Although *Candida albicans* remains the most frequent cause of fungemia and hematogenously disseminated candidiasis, a number of reports have documented infections caused by *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, and *C. krusei*.[10-12] Current data from the SCOPE (Surveillance and Control of Pathogens of Epidemiologic Importance) surveillance system confirm that *Candida* spp. were the fourth leading cause of bloodstream infection.[13] The aim of this work was to study candidemia at King Abdulaziz University Hospital (KAUH), its epidemiology, risk factors and predictors of mortality.

Materials and Methods

We reviewed all candidemic episodes over a 24-month period between January 1998 and December 1999 at KAUH. Patients whose blood yielded *Candida* species during the study period were identified through the records of the Microbiology Laboratory. An episode of candidemia was identified by the first isolation of any *Candida* spp. from blood culture from a patient at KAUH. For patients

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TABLE 1. *Probable risk factors for candidemia in 31 patients.*

Risk factor	No. of episodes (%)
Malignancy	5 (16)
Immunosuppressive chemotherapy	5 (16)
Corticosteroids	7 (23)
Multiple antibiotics	23 (74)
ICU stay	24 (77)
Central venous line	27 (87)
Urinary catheters	27 (87)
Neutropenia	3 (10)
Candiduria	13 (42)
Abdominal surgery	11 (36)
Hyperalimentation	11 (36)

ICU=intensive care unit.

TABLE 2. *Susceptibility pattern of* Candida *species to different antifungal agents.*

	Candida species			
Antifungal agent	*C. albicans* n=22	*C. parapsilosis* n=4	*C. tropicalis* n=4	*C. glabrata* n=1
Amphotericin B	1 (4.5)	–	–	–
Flucytosine	1 (4.5)	1 (25)	2 (50)	–
Econazole	8 (36.4)	1 (25)	3 (75)	1 (100)
Miconazole	8 (36.4)	–	4 (100)	1 (100)
Ketoconazole	4 (18.2)	1 (25)	1 (25)	–
Fluconazole	8 (36.4)	–	3 (75)	1 (100)
Nystatin	–	–	1 (25)	1 (100)

TABLE 3. *Univariate analysis of risk factors associated with mortality in 31 patients.*

Variable	Survived (n=9)	Died (n=22)	*P*-value
Age (mean in years)	39	41	0.8
Sex (M/F)	1.3:1	1.2:1	0.9
Presence of DM (%)	1 (11)	4 (18)	0.6
Presence of malignancy (%)	0	5 (23)	–
Use of chemotherapeutic agents (%)	2 (22)	3 (14)	0.09
Use of corticosteroids (%)	2 (22)	5 (23)	0.1
Use of multiple antibiotics (%)	4 (44)	19 (86)	0.01
ICU stay (%)	3 (33)	21 (96)	<0.001
Mean duration of ICU admission (days)	19	11	0.2
Presence of central venous catheters (%)	5 (56)	22 (100)	0.001
Presence of urinary catheters (%)	5 (56)	22 (100)	0.001
Neutropenia (%)	0	3 (14)	0.2
Candiduria (%)	2 (22)	11 (50)	0.1
Abdominal surgery (%)	0	6 (27)	0.08
Hyperalimentation (%)	2 (22)	9 (41)	0.3
Mean duration of hospital stay (days)	49	88	0.05

DM=diabetes mellitus; ICU=intensive care unit.

who had more than one episode of candidemia, the second episode was defined as an incident if it occurred at least 2 months after the first.

Inpatient hospital records and laboratory data of these patients were reviewed. Demographic information abstracted from the charts included age, sex, race, and hospital unit from which the *Candida* was isolated. Medical histories were reviewed for type and prognosis of underlying illness, risk factors such as use of central venous catheters, parenteral nutrition, use of antibiotics, steroids, chemotherapy, presence and duration of neutropenia, abdominal surgery, candiduria, etiologic agents of candidemia, and admission to intensive care unit (ICU). Duration of stay, treatment of the candidemia, duration of hospital stay and outcome after the first positive blood culture were also recorded.

Blood cultures were performed using the automated blood culture system (BacT/Alert Organon Teknika, USA). Ten mL of patient blood was inoculated into each bottle of blood culture, one for aerobic and the other for anaerobic growth. Culture bottles were loaded into the instrument and remained there for seven days or until designated positive. All bottles designated positive were smeared for gram stain. Culture bottles positive for yeast cells were cultured on to Sabouraud agar and the yeasts were identified with the use of the germ-tube reaction, morphology on cornmeal agar (BBL Microbiology System, Cockeysville, MD, US), Candifast (International Microbiology, France), and Vitek (Bio-Merieux, France) using YBC cards. The antifungal susceptibility testing was performed using Candifast for amphotericin B, flucytosine, fluconazole, econazole, miconazole, and ketoconazole. It was not possible in this study to use the micro- or macrobroth dilution method, which has been standardized to the National Committee for Clinical Laboratory Standards (NCCLS). Therefore, the antifungal susceptibility test was done using Candifast, a reasonable alternative with an indicative value on the interaction of the antifungal yeast pair during *in vivo* treatment.[14]

Statistical analyses were performed using the SPSS 7.5 (Statistical Package for Social Sciences). Mean±SD was determined for quantitative data, and frequency was determined for categorical variables. For continuous variables, *t*-test was used if comparing two groups. Chi-square was used to analyze group differences for categorical variables. A logistic regression model using maximum likelihood estimates was used for multivariate analysis of risk factors associated with mortality in candidemic patients. A *P*-value of <0.05 was considered significant.

Results

A total of 655 positive blood cultures were reviewed. Thirty-one episodes of candidemia were identified in 31 patients, i.e., 4.7% of total positive blood cultures, and 1/1000 admissions. All the episodes of candidemia were nosocomial and occurred 48 hours after admission to hospital. The mean duration of hospital stay before the onset of candidemia was 42 days (range 6-200 days). The median age was 41 years (range one month - 75 years). There were 17 males and 14 females, with an M:F ratio of 1.2:1. The percentage of candidemia was equally distributed between Saudi and non-Saudis. Eighteen

TABLE 4. *Multivariate logistic regression analysis for risk factor associated with mortality in candidemic patients.*

Variable	Standardized coefficient β	*t*	Significance
Age	-.306	-.977	.345
Sex	0.066	.350	.732
Diabetes mellitus	-.029	-.161	.874
Malignancy	.216	1.471	.163
Use of chemotherapeutic therapy	.119	.508	.620
Use of corticosteroid	-.169	-1.038	.317
Use of multiple antibiotics	-.007	-.040	.969
ICU stay	.701	3.358	.005
Duration of ICU admission	-.340	-1.948	.07
Presence of central venous catheters	.157	.742	.470
Presence of urinary catheters	.085	.324	.750
Neutropenia	.072	.437	.669
Candiduria	-.195	-1.584	.135
Duration of hospital stay	.597	4.217	.001
Hyperalimentation	-.245	-1.522	.150

episodes (58%) were from patients in the ICU, while 6 (19%) were from the medical unit, 4 (12.9%) from the pediatric unit and 3 (9.7%) were from the surgical unit.

Table 1 shows that indwelling central venous catheters, bladder catheters, ICU stay, and use of multiple antibiotics were the most common predisposing risk factors for candidemia. Of the 5 patients with malignancy and candidemia, 2 had hematologic malignancy and 3 had solid tumors. The mean duration of ICU stay was 17±16 days. *C. albicans* was isolated from 22 (71%) of the episodes, and was the most common species recovered regardless of the patient's underlying condition. *C. tropicalis* and *C. parapsilosis* were each recovered from 4 (13%) of the isolates, followed by *C. glabrata*, 1 (3%). The susceptibility testing to antifungal agents is shown in Table 2. Amphotericin B was the most effective agent; only 1 of the *Candida* spp. (3.2%) in general, was resistant to amphotericin, while 12 (38.9%) were resistant to fluconazole. Less than 5% (1 of 22) of *C. albicans* isolates was resistant to amphotericin B, in comparison to 8 of 22 (36.4%) isolates resistant to fluconazole. Amphotericin B (0.5 mg/kg/day) was used for treatment of candidemia in 26 (84%) patients. Twenty of those (77%) were infected with *C. albicans*, 3 (12%) with *C. parapsilosis*, 2 (8%) with *C. tropicalis*, and one (4%) with *C. glabrata*. Four patients (13%) were treated with fluconazole (200 mg/day); 2 of them had *C. albicans* infection, one had *C. tropicalis* and the other one had *C. parapsilosis*.

Only one patient with *C. tropicalis* was treated with ketoconazole (400 mg/day). The overall mortality in our study was 71% (22 of 31 patients died). Four patients (18%) died within 48 hours of the time at which initial blood culture was found to be positive for *Candida* organisms, while 18 (82%) died after more than 48 hours of candidemia. More than 50% of the patients who died were in the medical unit. The mean duration from the onset of candidemia until death was 16.45±14.24 days. Of the patients who died of candidemia, 17 (77%) had *C. albicans*, 4 (18%) had *C. tropicalis*, and one (4%) had *C. glabrata*. Univariate predictors of mortality are listed in Table 3. Hospitalization in ICU, presence of central venous catheters, urinary catheters, use of multiple antibiotics, and prolonged hospital stay were variables significantly associated with poor outcome. Of all the variables that were associated with mortality in the univariate analysis, only hospitalization in ICU and duration of hospitalization remained predictors of death in the multivariate analysis (Table 4).

Discussion

This study highlights the importance of candidemia among hospitalized patients, in addition to the well-known risk factors. Furthermore, it confirms the results of previous reports[10-12] of the increasing proportions of non-*Candida albicans* species as agents of candidemia. Approximately 30% of bloodstream infections due to *Candida* species in this study were caused by non-*C. albicans* species. The change in the pattern of nosocomial candidemia has been partly attributed to the increasing number of immunocompromised patients and the widespread use of antifungal therapy.[15] A recent multicenter study showed a dramatic shift towards non-*C. albicans* species in hematological patients, but not in solid tumor patients,[16] supporting the hypothesis of the role of immunosuppression and the prolonged use of antifungal agents.

The placement of central venous catheters, hospitalization in ICU, and multiple antibiotic courses played a major role in the development of candidemia in our hospital. This is consistent with the results reported by others.[6-9] The influence of central venous catheters and their removal on the prognosis of fungemia has been discussed in many studies.[9,16] In a prospective study, Nguyen et al.[17] found that catheter-related candidemia had a better outcome than did non-catheter-related candidemia. A strong consensus has recently emerged on the notion that intravenous lines should be withdrawn from candidemic patients whenever feasible.[18] Failure to effect complete exchange was strongly associated with the persistence of candidemia in a study by Rex et al.[19] More recently, a prospective multicenter study from a tertiary care hospital in Brazil demonstrated that non-removal of the central venous catheter, in addition to older age, were the only factors associated with an increased risk of death.[20] As in this study, we found that retaining the catheter was associated with poor outcome. Non-removal of the catheter by the attending physician could be explained by the fact that patients with an underlying disease for which the prognosis was poor were not considered good candidates for catheter removal. In this study context, non-removal of the catheter could simply reflect a high probability of death. ICU stay, with its associated invasive procedures, constituted an important risk factor of candidemia. Severity

of illness in ICU patients has been shown to be associated with impaired gut motility or ileus,[21] with subsequent overgrowth of $>10^5$ yeast cell/mL of saliva and/or gastric exocrine failure, which contributes to raising the gastric PH to >4, and promotes yeast overgrowth in ICU patients.[22] This explains our results, as more than 75% of the patients with candidemia were ICU patients. The observation that yeast is the fourth most common microorganism causing positive blood culture in some centers[23] may reflect the disturbance of the normal gut flora caused by the increased use of more potent broad-spectrum antibiotics.[24] This is in agreement with our results, where 74% of patients had received antibiotics prior to the onset of candidemia. Other studies[25] have made similar observations as well, indicating the importance of prior administration of broad-spectrum antibiotics as risk factors for developing candidemia.

Restoration of the normal gut microbial ecology is a fundamental prerequisite for the control of the fungal problems.[26,27] This requires limiting the use of antibiotics such as beta lactams and beta-lactamase inhibitor antibiotics, fluoroquinolones, and carbapenems, all known to have an impact on gut ecology. The overall resistance of *Candida* spp. to amphotericin B in this study was 3%, versus 39% against fluconazole. This is in agreement with the results of others.[28] Less than 5% of *C. albicans* was resistant to amphotericin B, in comparison with the 36% that was resistant to fluconazole. Mortality due to candidemia is high in most studies, ranging from 13% to 90%, with a median of 55%.[29,30] In our study, the mortality rate was 71%, and in only 5 patients (23%) were the isolates non-*albicans* (4 *C. tropicalis* and 1 *C. glabrata*). These data correspond well with other studies in which mortality from *C. albicans* was significantly higher than the mortality from non-*albicans Candida* spp.[31] Despite antifungal treatment, the mortality of candidemia was high (71%), which indeed may reflect the severity of the already existing underlying diseases at the onset of candidemia, as well as the direct mortality due to candidemia.

As a general rule, antifungal therapy on its own may play a limited role in the management of candidemia, as removal of central lines, withdrawal of broad-spectrum antibiotics and treating the underlying diseases are all important initial steps in the management of systemic fungal infections. Although a number of risk factors for candidemia have been identified, consensus on appropriate prevention measures has not been achieved to date. Suggested measures for management of central or peripheral intravenous catheters are still controversial.[9,16,32] Strategies such as decreasing the number of antibiotics described and initiating azole chemotherapy for a high-risk group[18] have been suggested but have not been widely implemented. The role of azole chemoprophylaxis in the development of drug resistance in *C. albicans* and in emergence of less susceptible fungal pathogens needs to be examined. Continued surveillance of candidemia will be important to document changes in its epidemiological features and antifungal susceptibilities.

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