Invasive Candidiasis in Critically Ill Patients: A Prospective Cohort Study in Two Tertiary Care Centers

Hasan M. Al-Dorzi, MD1, Hussam Sakkijha, MD2, Raymond Khan, MD1, Tarek Aldabbagh, MD1, Aron Toledo, BSN3, Pendo Ntinika, BSN4, Sameera M. Al Johani, MD5, and Yaseen M. Arabi, MD, FCCP, FCCM1

Abstract

Background: Invasive candidiasis is not uncommon in critically ill patients but has variable epidemiology and outcomes between intensive care units (ICUs). This study evaluated the epidemiology, characteristics, management, and outcomes of patients with invasive candidiasis at 6 ICUs of 2 tertiary care centers.

Methods: This was a prospective observational study of all adults admitted to 6 ICUs in 2 different hospitals between August 2012 and May 2016 and diagnosed to have invasive candidiasis by 2 intensivists according to predefined criteria. The epidemiology of isolated Candida and the characteristics, management, and outcomes of affected patients were studied. Multivariable logistic regression analyses were performed to identify the predictors of non-albicans versus albicans infection and hospital mortality.

Results: Invasive candidiasis was diagnosed in 162 (age 58.4 ± 18.9 years, 52.2% males, 82.1% medical admissions, and admission Acute Physiology and Chronic Health Evaluation II score 24.1 ± 8.4) patients at a rate of 2.6 cases per 100 ICU admissions. On the diagnosis day, the Candida score was 2.4 ± 0.9 in invasive candidiasis compared with 1.6 ± 0.9 in Candida colonization (P < .01). The most frequent species were albicans (38.3%), tropicalis (16.7%), glabrata (16%), and parapsilosis (13.6%). In patients with candidemia, antifungal therapy was started on average 1 hour before knowing the culture result (59.6% of therapy initiated after). Resistance to fluconazole, caspofungin, and amphotericin B occurred in 27.9%, 2.9%, and 3.1%, respectively. The hospital mortality was 58.6% with no difference between albicans and non-albicans infections (61.3% and 54.9%, respectively; P = .44). The independent predictors of mortality were renal replacement therapy after invasive candidiasis diagnosis (odds ratio: 5.42; 95% confidence interval: 2.16-13.56) and invasive candidiasis leading/contributing to ICU admission versus occurring during critical illness (odds ratio: 2.87; 95% confidence interval: 1.22-6.74).

Conclusions: In critically ill patients with invasive candidiasis, non-albicans was responsible for most cases, and mortality was high (58.6%). Antifungal therapy was initiated after culture results in 60% suggesting low preclinical suspicion. Study registration: NCT01490684; registered in ClinicalTrials.gov on February 11, 2012.

Keywords
intensive care, candidiasis, critical care outcomes, antifungal agents, sepsis

Background

Candida species colonizes up to 50% of critically ill patients. Translocation across the gastrointestinal mucosa and spread from invasive catheters into the bloodstream are the most common mechanisms that result in invasive candidiasis, which occurs in up to 9% of intensive care unit (ICU) patients. Candida albicans accounts for the majority of Candida infections but an increasing number of infections due to non-albicans species has been reported. This may be due to increased use of antifungal agents for prophylaxis and empirical therapy. However, there is significant variation in the epidemiology of Candida species between countries and individual ICUs.

Candida infection in critically ill patients is associated with increased morbidity and mortality. One study found that...
candidemia had a major impact on hospital length of stay with an average increase of >34 days and an estimated care cost of US$34 123 per affected Medicare patient. Another study showed that candidemia in adult hospitalized patients was associated with 14.5% increase in mortality, 10.1-day increase in length of stay, and US$39 331 increase in hospital cost. The mortality associated with invasive candidiasis is high and may be >70%.13

Most studies that evaluated Candida colonization and infection in the ICU come from Western countries. In Saudi Arabia, multiple studies evaluated Candida infections but most were retrospective, focused on their epidemiology rather than management and clinical significance, and were conducted in single centers at a hospital-wide level rather than in the ICU.17-21 Hence, the main objectives of this study were to evaluate invasive candidiasis epidemiology and susceptibility patterns in multiple ICUs, determine the risk factors for albicans versus non-albicans infections, study the practice of empirical antifungal therapy, and determine the outcomes and predictors of hospital mortality.

Methods

Patients and Setting

This was a prospective observational study conducted between August 2012 and May 2016 at the ICUs of 2 tertiary care centers in Riyadh, Saudi Arabia: King Abdulaziz Medical City (KAMC) and King Fahad Medical City (KFMC). Both centers had >1000 beds and were accredited by Joint Commission International. In KAMC, 5 adult noncardiac ICUs participated in the study (21-bed general ICU, 8-bed trauma ICU, 9-bed surgical ICU, 8-bed neuro ICU, and 14-bed step-down unit). These ICUs were closed units covered by onsite intensivists and registrars 24 hours per day, 7 days per week. In KFMC, one 35-bed closed medical-surgical ICU participated in the study. The institutional review boards of the 2 centers approved the study. Informed consents were obtained from the patients or surrogate decision makers.

All adult patients (>18 years) admitted to the ICUs of these centers for >48 hours were followed to discharge or death in ICU for occurrence of a specimen culture positive for Candida. We excluded patients with invasive candidiasis diagnosed ≥72 hours before ICU admission. For ICU readmissions with recurrent invasive candidiasis during the same hospitalization, only the first admission was counted. All decisions regarding patient management including the need to obtain cultures when sepsis was clinically suspected were left to the discretion of the treating ICU team. There was no routine surveillance for fungal colonization or infection. During the study period, β-D glucan test was not available at the 2 centers.

Classification of Candida Infection and Antifungal Therapy

Two intensivists evaluated all Candida-positive cultures and classified them as definite/proven, probable, or possible invasive candidiasis or Candida colonization. If they disagreed, a third intensivist resolved the disagreement. Briefly, definite invasive candidiasis included cases of isolated candidemia or positive specimen from a sterile site related to a specific focus on infection. Probable cases required the presence of a predisposing host factor, a clinical criterion of disseminated candidiasis, and a mycological criterion. Cases that met the criteria for a host factor and a clinical criterion but for which mycological criteria were absent were considered possible invasive candidiasis. Since multifocal Candida colonization (Candida growth in various noncontiguous foci within 5 days) is associated with relatively high invasive candidiasis incidence, it was considered as possible invasive candidiasis in the presence of severe sepsis or septic shock that could not be explained by another etiology.

Empirical antifungal therapy was defined as the initiation or modification of an existing antifungal regimen when patients suspected to have invasive fungal infection. It was considered appropriate if the cultured Candida displayed in vitro susceptibility to the antifungal therapy instituted within 24 hours of the index culture collection time. Treatment of established invasive fungal infection corresponded to the initiation of antifungal therapy after the diagnosis of proven or probable invasive candidiasis.

Antifungal Susceptibility Method

Antifungal susceptibility testing was performed using microbroth dilution method, YeastOne (Part #YO-9, Treck Diagnostics Systems, Thermo Scientific, Basingstoke, UK). It had the following antifungal agents: amphotericin B, 5-flucytosine, anidulafungin, caspofungin, micafungin, fluconazole, itraconazole, posaconazole, and voriconazole. Susceptibility testing was performed as per manufacturer’s instructions. Quality control tests were conducted on a regular basis in accordance with approved standard laboratory procedures.

Data Collection

The following data were recorded prospectively for all patients: details of Candida (such as source, species, and susceptibility to antifungal agents), demographic characteristics, location of the patient prior to ICU admission, admission category (medical, surgical, and trauma), admission diagnosis by system involvement, severity of illness on ICU admission assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II, and Sequential Organ Failure Assessment (SOFA) scores. In addition, SOFA score was calculated on day 1 (the day of diagnosing invasive candidiasis), 3, 5, 14, and 21 days of ICU stay if applicable, Candida score on the diagnosis day, Candida infection risk factors (such as diabetes mellitus, chronic renal failure, surgery within the past 3 months, antimicrobial therapy for >5 days within the past month, immunosuppression, use of total parenteral nutrition, and previous Candida colonization); use of invasive procedures; treatment of organ failures (inotropic support, hemodialysis, and
Table 1. Characteristics of Patients With Invasive Candidiasis at the ICUs of 2 Tertiary care Centers.

|                                | All Patients, N = 162 | Albicans, a n = 62 | Non-albicans, a n = 91 | P Value |
|--------------------------------|-----------------------|---------------------|-------------------------|---------|
| **Age (years), mean (SD)**     | 58.4 (18.9)           | 56.4 (19.7)         | 60.2 (17.8)             | .22     |
| **Male gender, n (%)**         | 85 (52.5)             | 32 (51.6)           | 48 (52.7)               | .89     |
| **BMI (kg/m²), mean (SD)**     | 29.3 (11.5)           | 30.0 (14.2)         | 29.0 (9.6)              | .60     |
| **Location before ICU admission, n (%)** |                      |                     |                         |         |
| Emergency department           | 82 (50.6)             | 29 (46.8)           | 48 (52.7)               | .57     |
| Ward                           | 66 (40.7)             | 29 (46.8)           | 35 (38.5)               | .47     |
| Other hospital                 | 14 (8.6)              | 4 (6.5)             | 8 (8.8)                 |         |
| **APACHE II score, mean (SD)** | 24.1 (8.4)            | 23.7 (8.5)          | 24.8 (8.4)              | .47     |
| **SOFA score, mean (SD)**      | 12.1 (3.9)            | 12.0 (4.1)          | 11.9 (3.7)              | .83     |
| **Candida score, mean (SD)**   | 1.97 (1.17)           | 1.58 (1.23)         | 2.23 (1.06)             | .01     |
| **Chronic illnesses, n (%)**   |                      |                     |                         |         |
| Cardiac                        | 17/111 (15.3)         | 9/46 (19.6)         | 8/60 (13.3)             | .39     |
| Respiratory                    | 28/111 (25.2)         | 12/46 (26.1)        | 14/60 (23.3)            | .74     |
| Renal with dialysis            | 55/161 (34.2)         | 22/62 (35.5)        | 30/90 (33.2)            | .78     |
| Hepatic                        | 17/111 (15.3)         | 6/46 (13.0)         | 11/60 (18.3)            | .53     |
| **Diabetes, n (%)**            | 107 (66.0)            | 40 (64.5)           | 59 (64.8)               | .99     |
| Insulin treated                | 48 (29.6)             | 24 (38.7)           | 21 (32.1)               | .04     |
| **Active cancer, n (%)**       | 15/114 (13.2)         | 8/46 (17.4)         | 6/63 (9.5)              | .23     |
| **Immunosuppression, n (%)**   | 12/60 (7.5)           | 4/62 (6.5)          | 6/69 (6.7)              | .94     |
| **Corticosteroids in the previous 2 weeks, n (%)** | 5/60 (3.1)           | 2/62 (3.2)          | 3/69 (3.7)              | .96     |
| **Recent neutropenia, n (%)**  | 27/159 (17.0)         | 8/61 (13.1)         | 17/89 (19.1)            | .33     |
| **Surgery in the preceding 3 months, n (%)** | 17/161 (10.6)       | 7 (11.3)            | 10 (11.1)               | .97     |
| Abdominal                      | 8/161 (5.0)           | 3 (4.8)             | 5 (5.5)                 |         |
| **Total parenteral nutrition, n (%)** | 17/160 (10.6)       | 5/62 (8.1)          | 9/89 (10.1)             | .67     |
| **Antibiotics in the preceding 5 days, n (%)** | 59 (36.4)             | 15 (24.2)           | 39 (42.9)               | .02     |
| **Recent antifungal therapy, n (%)** | 19/60 (11.9)     | 2/62 (3.2)          | 15/89 (16.9)            | .01     |
| **Azole**                      | 11/60 (1.6)           | 1 (1.6)             | 8 (16.9)                |         |
| **Echinocandin**               | 7/60 (4.4)            | 1 (1.6)             | 6 (6.7)                 |     |
| **Reason for ICU admission, n (%)** | 15 (9.3)              | 6 (9.7)             | 9 (9.9)                 | .26     |
| **Blood urea nitrogen (mmol/L), mean (SD)** | 14.8 (13.6)          | 12.4 (9.1)          | 16.9 (16.1)             | .05     |
| **Creatinine (µmol/L), mean (SD)** | 155.3 (116.9)       | 153.7 (119.7)       | 161.8 (118.8)           | .68     |
| **Lactate (mmol/L), mean (SD)** | 13.3 (3.2)            | 3.4 (3.3)           | 3.4 (3.3)               | .74     |
| **White blood cell count (10⁹/L), mean (SD)** | 3.4 (3.2)             | 3.4 (3.3)           | 3.4 (3.3)               | .74     |

(continued)
Table 1. (continued)

|                          | All Patients, N = 162 | Albicans, a n = 62 | Non-albicans, a n = 91 | P Value |
|--------------------------|-----------------------|-------------------|------------------------|---------|
| Hemoglobin (g/dL), mean (SD) | 9.0 (1.8)             | 9.1 (1.8)         | 8.8 (1.7)              | .28     |
| Platelet count (10^9/L), mean (SD) | 192 (151)             | 203 (140)         | 191 (161)              | .64     |
| INR, mean (SD)            | 1.6 (1.0)             | 1.6 (1.3)         | 1.5 (0.8)              | .46     |
| Partial thromboplastin time (seconds), mean (SD) | 49.3 (34.0)             | 51.2 (32.1)       | 47.6 (36.3)             | .54     |
| Alanine aminotransferase (U/L), mean (SD) | 108.6 (282.3)             | 104.9 (288.5)     | 96.5 (266.3)            | .87     |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; ICU, intensive care unit; INR, international normalized ratio; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

a Nine patients had Candida species not identified.

b To convert creatinine to mg/dL divide by 88.4, lactate to mg/dL divide by 0.111.

Results

Characteristics of Patients

We enrolled 162 patients with invasive candidiasis: 120 from KAMC and 42 from KFMC at a rate of 2.6 cases per 100 ICU admissions. The diagnosis was definite in 119 (73.5%), probable in 3 (1.9%), and possible in 40 (24.7%). Invasive candidiasis occurred on a median of 5 days after ICU admission (25th and 75th percentiles = 1 and 8 days, respectively) and 18 days after hospital admission (25th and 75th percentiles = 8 and 44.5 days, respectively). Most (62.5%) of the cases developed invasive candidiasis during the course of their critical illness in the ICU. Candidemia occurred in 107 patients.

The cohort characteristics are described in Table 1 and included age (58.4 ± 18.9 years), 52.5% were males, APACHE II score = 24.1 ± 8.4, and Candida score = 1.97 ± 1.17. Invasive candidiasis risk factors included diabetes (66.0%), chronic kidney disease requiring hemodialysis (34.2%), active cancer (13.2%), recent neutropenia (17.0%), recent surgery (10.6%), total parenteral nutrition (10.6%), recent antibacterial therapy (36.4%), and recent antifungal therapy (11.9%). Hyperthermia (<35°C) was present in 6.8% of patients on the diagnosis day and hyperthermia (>38°C) in 10.1%. Compared with those from KFMC, KAMC patients were generally older (60.0 ± 17.5 vs 53.5 ± 22.0 years; P = .09) with higher APACHE II scores (25.5 ± 8.3 vs 19.8 ± 7.0; P < .001).

Epidemiology

In our cohort, Candida non-albicans accounted for the majority of species causing invasive candidiasis (56.2% of all cases) as described in Figure 1A. The most frequent species were albicans (n = 62, 38.3%), tropicalis (n = 27, 16.7%), glabrata (n = 26, 16%), and parapsilosis (n = 22, 13.6%). In patients with candidemia, non-albicans species were more prevalent (74.1%; Figure 1B). Candida non-albicans was more common in KAMC compared with KFMC (77/114 [67.5%] vs 14/39 [35.9%] of Candida; P = .001).

Table 1 also describes the characteristics of albicans and non-albicans cases. The non-albicans group had higher

mechanical ventilation); clinical features on the day of positive Candida culture, antifungal therapy including timing of administration; and other treatment modifications and interventions. The primary outcome was hospital mortality. Other assessed outcomes were 28-day and ICU mortality, length of stay in the ICU and hospital, and duration of mechanical ventilation. We also noted changes in code status during ICU stay.

Statistical Methods

Frequencies and percentages were presented for categorical variables. Means with standard deviations or medians with the 25th and 75th percentiles were presented for continuous variables. The χ² test or Fisher exact test was used to evaluate differences between categorical variables and the t test to evaluate differences between continuous variables. Multivariable logistic regression analyses were performed to identify the independent predictors of non-albicans versus albicans infection and hospital mortality. Potential risk factors included in these models were clinically significant or had P value < .1 in the univariate analyses. For the predictors of non-albicans versus albicans infection, the following variables were entered in the model: KAMC versus KFMC, medical versus nonmedical admission, Candida score, APACHE II score, SOFA score on diagnosis day, insulin-treated diabetes, hemodialysis, history of recent surgery, prior antibacterial and antifungal therapy, and recent neutropenia. The hospital mortality rates were compared in certain subgroups, which were selected based on clinical relevance. For the higher versus lower age, APACHE II score, and SOFA score, categorization was based on the median values. For the predictors of hospital mortality, the following variables were entered in the model: KAMC versus KFMC, invasive candidiasis leading/contributing to ICU admission versus occurring during critical illness, Candida score, age, APACHE II score, SOFA on diagnosis day, empirical antifungal therapy versus treatment, and renal replacement therapy after invasive candidiasis diagnosis. The results were presented as odds ratio (OR) with 95% confidence interval (CI). A P < .05 was considered statistically significant. Data were analyzed using SPSS version 15.0 (SPSS Inc, Chicago, Illinois).
Candida score, more insulin-treated diabetics, and more patients with prior recent antibacterial and antifungal treatment.

On multivariable logistic regression analysis, only candidemia was independently associated with non-albicans infection (OR: 6.74; 95% CI: 2.41-18.91).

Table 2 also describes the susceptibility of Candida to antifungal agents. Resistance to fluconazole was present in 31 (27.9%) of 111 patients (5/30 [16.7%] albicans, 11/19 [57.9%] parapsilosis, 8/24 [33.3%] glabrata, and 3/3 [100%] krusei), resistance to voriconazole in 9/99 (8.1%; 4/29 [13.8%] albicans, 2/19 [10.5%] glabrata, 1/21 [4.8%] tropicalis, 1/19 [5.3%] parapsilosis, and 3/3 [100%] krusei), resistance to caspofungin in 3/102 (2.9%; 1/28 [3.6%] albicans, 1/22 [4.5%] glabrata and one-fourth [25%] dubliniensis), and resistance to amphotericin B in 3/96 (3.1%; 2/28 [7.1%] albicans and ½ [50%] lusitaniae). There was no difference in fluconazole resistance between KAMC and KFMC (29.0% and 22.2%, respectively; \( P = .35 \)). All fluconazole-resistant Candida parapsilosis (n = 11) occurred at KAMC.

Management of Invasive Candidiasis

Table 3 describes certain management elements of invasive candidiasis. Antifungal therapy was empirical in 42.9%
(46% for candidemia cases) with caspofungin being the most commonly used agent. When caspofungin was used as empirical therapy, it was appropriate in 34 (97.1%) of 35 patients. When fluconazole was used, it was appropriate in 2 (50%) of 4 patients. Combination antifungal therapy was used in only 1 patient. In patients with candidemia, antifungal therapy was started —1 hour (median, 25th and 75th percentiles = −35 and 13 hours) before culture result was known (59.6% of therapy was initiated after knowing the culture result).

Antifungal agents were changed in 34 patients: amphotericin B in 4 to caspofungin (n = 3) and fluconazole (n = 1); caspofungin in 19 to anidulafungin (n = 4), fluconazole (n = 11), and voriconazole (n = 1); anidulafungin in 2 to fluconazole (n = 2); and fluconazole in 9 to anidulafungin.

### Table 2. Antifungal Susceptibility and Minimal Inhibitory Concentrations for Isolated *Candida*

|                      | All Patients, N = 162 | Albicans, a n = 62 | Non-albicans, a n = 91 | P Value |
|----------------------|-----------------------|--------------------|------------------------|---------|
| Susceptibility to antifungal agents, n (%) |                        |                    |                        |         |
| Amphotericin B       | 93/96 (96.9)           | 26/28 (92.9)       | 67/68 (98.5)           | .20     |
| Caspofungin          | 99/102 (97.0)          | 27/28 (96.4)       | 72/74 (95.9)           | 1.0     |
| Anidulafungin        | 4/4 (100)              | 1/1 (100)          | 3/3 (100)              | -       |
| 5-Flucytosine        | 85/104 (81.7)          | 24/30 (80.0)       | 61/73 (83.6)           | .67     |
| Fluconazole          | 80/111 (72.1)          | 25/30 (83.3)       | 55/81 (67.9)           | .15     |
| Itraconazole         | 60/93 (64.5)           | 21/26 (80.8)       | 39/67 (58.2)           | .04     |
| Voriconazole         | 91/99 (91.9)           | 25/29 (86.2)       | 66/70 (94.3)           | .23     |
| Minimal inhibitory concentration, median (25th and 75th percentiles) |                        |                    |                        |         |
| Amphotericin B       | 0.5 (0.41 and 1.00)    | 0.50 (0.25 and 1.00) | 0.50 (0.47 and 1.00) | .83 b   |
| Caspofungin          | 0.06 (0.03 and 0.50)   | 0.03 (0.03 and 0.11) | 0.12 (0.053 and 0.50) | .04 b   |
| Anidulafungin        | Not available          | Not available      | Not available          |         |
| 5-Flucytosine        | 0.06 (.006 and 0.153)  | 0.09 (0.06 and 0.12) | 0.06 (0.06 and 0.25) | .94 b   |
| Fluconazole          | 16.00 (1.00 and 80.00) | 0.75 (0.25 and 97.25) | 28.00 (7.00 and 80.00) | .099 b  |
| Itraconazole         | 0.25 (0.12 and 0.75)   | 0.06 (0.04 and 12.02) | 0.50 (0.25 and 0.75) | .045 b  |
| Voriconazole         | 0.25 (0.08 and 1.00)   | 0.06 (0.01 and 6.03) | 0.50 (0.25 and 1.00) | .047 b  |

a 9 patients had *Candida* species not identified.

b Mann-Whitney U test.

### Table 3. Management of Invasive Candidiasis.

|                      | All Patients, N = 162 | Albicans, a n = 62 | Non-albicans, a n = 91 | P Value |
|----------------------|-----------------------|--------------------|------------------------|---------|
| First antifungal agent, n (%) |                        |                    |                        |         |
| Empirical            | 62/152 (40.8)          | 21/56 (37.5)       | 40/88 (45.5)           | .35     |
| Therapeutic          | 90/152 (59.2)          | 35/56 (62.5)       | 48/88 (54.5)           |         |
| Amphotericin B       | 7/148 (4.7)            | 1/52 (1.9)         | 5/88 (5.7)             | .06     |
| Caspofungin          | 103/148 (69.6)         | 30/52 (57.7)       | 66/88 (75.0)           |         |
| Anidulafungin        | 18/148 (12.2)          | 10/52 (19.2)       | 8/88 (9.1)             |         |
| Fluconazole          | 19/148 (12.8)          | 11/52 (21.2)       | 8/88 (9.1)             |         |
| Voriconazole         | 1/148 (0.7)            | 0/52 (0)           | 1/88 (1.1)             |         |
| Timing of antifungal therapy (hours), b median (25th and 75th percentiles) | 1.0 (−35.0 and 13.0) | 3.5 (−29.8 and 11.0) | 1.0 (−43.0 and 15.5) | .57 c   |
| Initiation interval of antifungal therapy, b N (%) |                        |                    |                        |         |
| >24 hour before culture result | 28/99 (28.3)          | 6/24 (25.0)        | 22/74 (28.6)           | .31     |
| 0-24 hours before culture result | 12/99 (12.1)          | 3/24 (12.5)        | 9/74 (12.2)            |         |
| 0-24 hours after culture result | 36/99 (36.4)          | 12/24 (50.0)       | 23/74 (35.7)           |         |
| >24 hour after culture result | 23/99 (23.2)          | 3/24 (12.5)        | 20/74 (23.5)           |         |
| First antifungal changed during therapy course | 34/148 (23.0)         | 14/53 (26.4)       | 20/88 (22.7)           | .62     |
| Antifungal therapy clinical effectiveness, d n (%) | 76/108 (70.4)         | 12/18 (66.7)       | 39/56 (69.6)           | .81     |
| Other management interventions, N (%) |                        |                    |                        |         |
| Vasopressors         | 76/107 (71.0)          | 44/62 (71.0)       | 67/90 (74.4)           | .64     |
| Central venous catheter removed/changed | 28/111 (25.2)         | 12/46 (26.1)       | 16/60 (26.7)           | .95     |
| Arterial line removed | 12/111 (10.8)          | 8/46 (17.4)        | 2/60 (3.3)             | .02     |
| Urinary catheter removed/changed | 23/111 (20.7)         | 9/46 (19.6)        | 14/60 (23.3)           | .64     |

a Nine patients had *Candida* species not identified.

b For patients with candidemia.

c Mann-Whitney U test.

d Antifungal therapy was considered completely effective when all symptoms and radiologic and nonradiologic signs caused by invasive candidiasis disappeared.
Table 4. Outcomes of Invasive Candidiasis.

| Outcome                                      | All Patients, N = 162 | Albicans, a n = 62 | Non-albicans, a n = 91 | P Value |
|----------------------------------------------|-----------------------|--------------------|------------------------|---------|
| Hospital mortality, n (%)                    | 95 (58.6)             | 38 (61.3)          | 50 (54.9)              | .44     |
| ICU mortality, n (%)                         | 83 (51.2)             | 32 (51.6)          | 44 (48.4)              | .69     |
| 28-Day mortality, n (%)                     | 92 (57.1)             | 33 (54.1)          | 52 (57.1)              | .71     |
| New RRT after invasive candidiasis, n (%)   | 60 (37.5)             | 19/62 (30.6)       | 39/89 (43.8)           | .10     |
| No code                                      | 52/160 (32.5)         | 17/61 (27.9)       | 31/90 (34.4)           | .40     |
| Mechanical ventilation duration (days), mean (SD) | 25.5 (27.9)         | 22.4 (24.4)        | 27.6 (30.4)            | .39     |
| ICU LOS (days), mean (SD)                   | 42.4 (54.2)           | 40.2 (61.4)        | 43.8 (50.9)            | .69     |
| Hospital LOS (days), mean (SD)              | 88.8 (87.2)           | 86.2 (90.8)        | 92.1 (88.0)            | .67     |

Abbreviations: RRT, renal replacement therapy; ICU, intensive care unit; LOS, length of stay; SD, standard deviation.

*aNine patients had candida species not identified.

Figure 2. Serial Sequential Organ Failure Assessment Scores in survivors and nonsurvivors of patients with invasive candidiasis; P values were > .05 at all points.

Outcomes

Table 4 describes the various outcomes of our cohort. Invasive candidiasis was associated with high hospital mortality (58.6%), prolonged stay on mechanical ventilation, and in the ICU and hospital. Figure 2 shows the progression of SOFA score, which did not differ between survivors and nonsurvivors. The mortality rates according to the Candida species are described in Figure 3A for all patients with invasive candidiasis and in Figure 3B for patients with candidemia.

Table 5 shows the hospital mortality in selected subgroups. The hospital mortality was higher in KAMC compared with KFMC, when invasive candidiasis led/contributed to ICU admission compared when it developed during critical illness, in patients with Candida score ≥2 compared with <2 (Candida score was 1.74 ± 1.23 in survivors and 2.14 ± 1.10 in nonsurvivors; P = .03).

On multivariable logistic regression analysis, the predictors of mortality were renal replacement therapy after invasive candidiasis diagnosis (OR: 5.42; 95% CI: 2.16-13.56) and invasive candidiasis leading/contributing to ICU admission versus occurring during critical illness (OR: 2.87; 95% CI: 1.22-6.74).

Discussion

In this study, we found that invasive candidiasis was mostly due to non-albicans species and was associated with high mortality; there was no significant outcome difference between albicans and non-albicans infections; invasive candidiasis leading/contributing to ICU admission versus occurring during critical illness and requirement for renal replacement therapy were predictors of hospital mortality; and resistance to amphotericin B and echinocandins was rare.

It is estimated that 15% of health-care-associated infections are caused by fungi, and Candida species account for 70% to 90% of all invasive infections. Candida is responsible for 8% to 10% of bloodstream infections in the United States and is ranked seventh in both a large prevalence survey of health-care-associated infections from 183 geographically diverse acute-care hospitals in the United States and a multicenter surveillance study in 16 Brazilian hospitals. While in Europe, Candida species account for 2% to 3% of bloodstream infections and are ranked sixth to tenth among health-care-associated infections. At least 15 distinct Candida species that produce disease in humans, but >90% of invasive infections are caused by 5 common pathogens: Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis, and Candida krusei. Candida albicans was previously the dominant species in invasive candidiasis, accounting for 65% to 70% of the total number of Candida isolates; however, in recent years, non-albicans species has been responsible for about 50% of cases in some centers. Additionally, several studies have reported increasing significant variation in the distribution of albicans and non-albicans causing invasive candidiasis in ICUs between health-care facilities. In the Prospective Antifungal Therapy Alliance registry (United States and Canada), non-albicans species accounted for >50% of all cases of invasive candidiasis in 15 (62.5%) of the 24
Historical data indicated that factors associated with increased non-albicans risk were major postoperative cases, gastrointestinal procedure, enteric bacteremia, hemodialysis days, total parenteral nutrition, and number of red blood cell transfusions. Other studies found that cancer, chemotherapy, traumatic brain injury, bacterial sepsis, and previous use of fluconazole may increase the risk of these infections. We found a significant variation in the distribution of albicans and non-albicans in the 2 participating hospitals. This may be related to differences in patient populations and antifungal practices. Additionally, we found that the only independent predictor of non-albicans infection was the presence of candidemia.

Non-albicans species have reduced susceptibilities or even intrinsic resistance to azoles and sometimes echinocandins. Pfaffer et al tested 197 619 clinical Candida isolates from 41 countries (1997-2007) and found that 90.2% of Candida isolates were susceptible to fluconazole; however, 13 of the 31 species exhibited <75% susceptibility. Further, an increase in fluconazole resistance for Candida parapsilosis, Candida guilliermondii, Candida lusitaniae, Candida sake, and Candida pelliculosa was observed over time. Recent data indicated that globally the resistance to fluconazole for the most common non-albicans were 1.2% to 5.2% for Candida parapsilosis, 5.1% to 15% for Candida glabrata, and 2.3% to 24.2% for C tropicalis. In the current study, we observed higher fluconazole resistance (16.7% for C albicans, 57.9% for Candida parapsilosis, and 33.3% for Candida glabrata). Fluconazole resistance has been increasing over time. The high prevalence of fluconazole-resistant Candida parapsilosis at KAMC may be related to antifungal treatment practices and may represent an ongoing outbreak.

Invasive candidiasis is associated with high mortality rate. In an Australian nationwide study of mortality determinants in non-neutropenic ICU patients, the overall
mortality was 52% with a median time to death of 7 days after candidemia. A systematic review of 7 matched cohort and case-control studies found that the mortality attributed to candidemia ranged from 5% to 71%. Factors that influence outcomes may include the virulence of the infecting organism, severity of the underlying illness, and the appropriateness and timing of antifungal treatment. One study found that host factors independently associated with mortality were older age, ICU admission diagnosis other than polytrauma, and mechanical ventilation at time of candidemia. We did not find significant difference in mortality between albicans and non-albicans infections. Candida parapsilosis has been associated with lower mortality rate in other studies. This was not observed in our study, possibly because of high rate of antifungal resistance. In the current study, invasive candidiasis leading/contributing to ICU admission versus occurring during critical illness was an independent predictor of mortality. This may suggest that the underlying illness is an important mortality determinant. The Candida score, which was suggested to guide empirical antifungal therapy, was higher in nonsurvivors but was not an independent predictor of mortality.

Table 5. Hospital Mortality in Subgroups of Patients.

| Subgroup                                           | Mortality, n/N (%) | Relative risk (95% confidence interval) | P Value |
|----------------------------------------------------|--------------------|----------------------------------------|---------|
| Definite invasive candidiasis                      | 68/119 (57.1)      | 0.840 (0.493-1.432)                     | .52     |
| Possible/probable invasive candidiasis             | 27/43 (62.8)       | Reference                               |         |
| Invasive candidiasis led/contributed to ICU admission| 41/57 (71.9)      | 1.383 (1.088-1.759)                     | .01     |
| Invasive candidiasis occurred during ICU stay       | 48/95 (50.5)       | Reference                               |         |
| Candidemia                                          | 32/54 (59.3)       | 1.013 (0.812-1.263)                     | .91     |
| Invasive candidiasis without candidemia            | 63/108 (58.3)      | Reference                               |         |
| Albicans                                           | 38/62 (61.3)       | 1.110 (0.856-1.440)                     | .44     |
| Non-albicans                                        | 50/91 (54.9)       | Reference                               |         |
| KAMC                                                | 76/120 (63.3)      | 1.716 (1.019-2.890)                     | .04     |
| KFMC                                                | 19/42 (45.2)       | Reference                               |         |
| Age < 62 years                                      | 46/79 (58.2)       | 0.984 (0.725-1.336)                     | .92     |
| Age ≥ 62 years                                      | 49/83 (59.0)       | Reference                               |         |
| Medical                                             | 78/136 (57.4)      | 0.751 (0.356-1.581)                     | .45     |
| Trauma/postoperative                               | 17/26 (65.4)       | Reference                               |         |
| Diabetes                                            | 61/107 (57.0)      | 0.876 (0.561-1.367)                     | .56     |
| No diabetes                                         | 34/55 (61.8)       | Reference                               |         |
| APACHE II score on ICU admission < 24              | 44/73 (60.3)       | 1.053 (0.771-1.437)                     | .75     |
| APACHE II score on ICU admission ≥ 24              | 45/78 (57.7)       | Reference                               |         |
| SOFA on invasive candidiasis diagnosis day < 12     | 29/53 (54.7)       | 1.059 (0.742-1.511)                     | .75     |
| SOFA on invasive candidiasis diagnosis day ≥ 12     | 30/58 (51.7)       | Reference                               |         |
| Candida score < 2                                   | 15/34 (44.1)       | 0.844 (0.705-1.010)                     | .049    |
| Candida score ≥ 2                                   | 78/124 (62.9)      | Reference                               |         |
| Empirical antifungal agents                         | 39/62 (62.9)       | 1.171 (0.902-1.521)                     | .24     |
| Therapeutic antifungal agents                       | 42/90 (53.3)       | Reference                               |         |
| >24 hours before culture result                     | 19/32 (59.4)       | 1.200 (0.753-1.912)                     | .88     |
| 0-24 hours before culture result                    | 7/14 (50.0)        | 1.000 (0.696-1.438)                     |         |
| 0-24 hours after culture result                     | 22/41 (53.7)       | 1.083 (0.659-1.780)                     |         |
| >24 hours after culture result                      | 17/34 (50.0)       | Reference                               |         |
| Echinocandin (caspofungin/anidulafungin)            | 68/121 (56.2)      | 0.942 (0.404-2.198)                     | .89     |
| Fluconazole                                         | 11/19 (57.9)       | Reference                               |         |
| Vasopressors                                        | 70/118 (59.3)      | 1.111 (0.664-1.857)                     | .69     |
| No vasopressors                                     | 24/43 (55.8)       | Reference                               |         |
| Mechanical ventilation                              | 74/125 (59.2)      | 1.080 (0.611-1.911)                     | .79     |
| No mechanical ventilation                          | 21/37 (56.8)       | Reference                               |         |
| Central venous catheter removed/changed            | 14/23 (60.9)       | 1.103 (0.822-1.480)                     | .52     |
| Central catheter not removed/changed                | 28/53 (52.8)       | Reference                               |         |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; KAMC, King Abdulaziz Medical City; KFMC, King Fahd Medical City; SOFA, Sequential Organ Failure Assessment.

aAnalysis restricted for candidemia.
et al also demonstrated that delayed administration of antifungal treatment >12 hours after a positive blood culture was an independent mortality predictor (adjusted OR: 2.09; 95% CI: 1.53-2.84).\cite{47} Another study showed a significant mortality benefit to receiving antifungal treatment within 72 hours of a positive blood culture (30-day mortality for early treatment: 27% vs 40%; \( P = .004 \); hazard ratio: 1.41; 95% CI: 1.01-1.98).\cite{48}

However, the Australian Candidemia Study group found that antifungal therapy, but not the timing or choice of antifungal agent, was significantly associated with survival on multivariable logistic regression analysis.\cite{45} A recent observational study found that both hospital mortality and ICU mortality were significantly lower in patients treated with an echinocandin compared with fluconazole, voriconazole, or itraconazole.\cite{49}

In our study, the mortality associated with invasive candidiasis was high (59%). Reasons could be delay in antifungal therapy and inadequate source control as we observed that empirical therapy was provided in 40.8% of our patients, and the central venous catheter was removed in 30% of candidemia cases. Catheter removal may have an additive beneficial effect to adequate empirical therapy in candidemia.\cite{50} On the other hand, invasive candidiasis may be a sign of severe illness and treatment may not change illness course in many patients. Nevertheless, earlier appropriate antifungal therapy and removal of contaminated central venous catheters or drainage of infected material are advocated.\cite{33}

The study should be interpreted taking into accounts its strengths and limitations. The strength included the prospective and wide range of data collection, the adjudication of infection by 2 intensivists, and the availability of susceptibility data on majority of patients. The limitations include that it was performed at only 2 centers in 1 city. We used the definitions created by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) for invasive fungal diseases, which were made for research purposes and apply to immunocompromised patients but not necessarily to critically ill patients. Moreover, the lack of susceptibility data on some patients limited our analysis for the association of resistance on outcome.

In conclusion, *Candida non-albicans* was responsible for most cases of invasive candidiasis but with significant variation between the 2 hospitals where the study was conducted. Hence, hospital epidemiologic data are important in management. Fluconazole resistance was common (28%), but resistance to amphotericin B and caspofungin was rare. Antifungal therapy was initiated after culture results in >50% of cases suggesting low clinical suspicion. Invasive candidiasis was associated with high mortality, which may reflect the severity of underlying illness.

**Authors’ Note**

Ethics approval was obtained from the institutional review boards of King Abdullah International Medical Research Center and King Fahad Medical City (Protocol RC11/096). Informed consents were obtained from enrolled patients. The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Hasan M. Al-Dorzi made substantial contributions to conception and design, acquisition, analysis, and interpretation of data; drafted the manuscript, and revised it critically for important intellectual content. Hussam Sakkijha made substantial contributions to acquisition and interpretation of data and revised the manuscript for important intellectual content. Raymond Khan made substantial contributions to design, acquisition, and interpretation of data and contributed to manuscript drafting and revised it critically for important intellectual content. Tarek Al disobah made substantial contributions to design, acquisition, and interpretation of data and revised the manuscript critically for important intellectual content. Aron Toledo made substantial contributions to acquisition of data and revised the manuscript for important intellectual content. Sameera M. Al Johani made substantial contributions to acquisition and interpretation of data and contributed to manuscript drafting and revised it critically for important intellectual content. Yaseen M. Arabi made substantial contributions to design and interpretation of data and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

**Acknowledgments**

The authors thank Albandari Almutairi, Sherif Khalil, and Fakhar Siddiqui (MSD Scientific Office-Saudi Arabia) for coordinating and supporting the study.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was funded by MSD as an investigator-initiated study (MIISP-40089).

**ORCID iD**

Hasan M. Al-Dorzi, MD https://orcid.org/0000-0002-3772-8949

**References**

1. Lavreidere M, Labbe AC, Restierv C, et al. Susceptibility patterns of Candida species recovered from Canadian intensive care units. *J Crit Care*. 2007;22(3):245-250.
2. van de Veerdonk FL, Kullberg BJ, Netea MG. Pathogenesis of invasive candidiasis. *Curr Opin Crit Care*. 2010;16(5):453-459.
3. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302(21):2323-2329.
4. Macphail GL, Taylor GD, Buchanan-Chell M, Ross C, Wilson S, Kureishi A. Epidemiology, treatment and outcome of candidemia: a five-year review at three Canadian hospitals. *Mycoses*. 2002;45(5-6):141-145.
5. Pfaller M, Diekema D, Gibbs D, et al. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: a 10.5-year analysis of susceptibilities of Candida species to fluconazole and voriconazole as determined by CLSI standardized disk diffusion. *J Clin Microbiol*. 2010;48(4):1366-1377.
6. Kaaniche FM, Allela R, Cherif S, ben Algia N. Invasive candidiasis in critically ill patients. *Trend Anaesth Crit Care*. 2016;11:1-5.

7. Sanglard D, Odds FC. Resistance of Candida species to antifungal agents: molecular mechanisms and clinical consequences. *Lancet Infect Dis*. 2002;2(2):73-85.

8. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of America. *Clin Infect Dis*. 2015;62(4):e1-e50.

9. Eggimann P, Bille J, Marchetti O. Diagnosis of invasive candidiasis in critically ill patients: the NEMIS prospective multicenter study. *Clin Infect Dis*. 2009;48(12):1624-1633.

10. Rentz AM, Halpern MT, Bowden R. The impact of candidemia on length of hospital stay, outcome, and overall cost of illness. *Clin Infect Dis*. 1998;27(4):781-788.

11. Blumberg HM, Jarvis WR, Soucie JM, et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The national epidemiology of mycosis survey. *Clin Infect Dis*. 2001;33(2):177-186.

12. Al-Hedaithy SS. The yeast species causing fungemia at a university hospital in Riyadh, Saudi Arabia, during a 10-year period. *Mycoses*. 2003;46(8):293-298.

13. Osoba AO, Al-Mowallad AW, McAlear DE, Hussein BA. Candidemia and the susceptibility pattern of Candida isolates in blood. *Saudi Med J*. 2003;24(10):1060-1063.

14. Al-Jasser AM, Elkhizzi NA. Distribution of Candida species among bloodstream isolates. *Saudi Med J*. 2004;25(5):566-569.

15. Al-Tawfiq JA. Distribution and epidemiology of Candida species causing fungemia at a Saudi Arabian hospital, 1996-2004. *Int J Infect Dis*. 2007;11(3):239-244.

16. Leroy O, Gangneux JP, Montravers P, et al. Epidemiology, management and historical trends in the epidemiology of candidemia in critically ill patients: an analysis of five multicenter studies sequentially conducted over a 9-year period. *Inten Care Med*. 2005;31(10):1804-1810.

17. Al-Hedaithy SS. The yeast species causing fungemia at a university hospital in Riyadh, Saudi Arabia, during a 10-year period. *Mycoses*. 2003;46(8):293-298.

18. Osoba AO, Al-Mowallad AW, McAlear DE, Hussein BA. Candidemia and the susceptibility pattern of Candida isolates in blood. *Saudi Med J*. 2003;24(10):1060-1063.

19. Al-Tawfiq JA. Distribution and epidemiology of Candida species causing fungemia at a Saudi Arabian hospital, 1996-2004. *Int J Infect Dis*. 2007;11(3):239-244.

20. Omran AS, Makkawy EA, Baig K, et al. Ten-year review of invasive Candida infections in a tertiary care center in Saudi Arabia. *Saudi Med J*. 2014;35(8):821-826.

21. Arabi Y, Alshimemeri A, Taher S. Weekend and weeknight admissions have the same outcome of weekday admissions to an intensive care unit with onsite intensivist coverage. *Crit Care Med*. 2006;34(3):605-611.

22. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008;46(12):1813-1821.

23. Leon C, Ruiz-Santana S, Saavedra P, et al. Usefulness of the “Candida score” for discriminating between Candida colonization and invasive candidiasis in non-neutropenic critically ill patients: a prospective multicenter study. *Crit Med*. 2009;37(5):1624-1633.

24. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ ACCP/ATS/SIS international sepsis definitions conference. *Intensive Care Med*. 2003;29(4):530-538.

25. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care–associated infections. *PloS One*. 2015;10(8):e0146909.

26. Calandra T, Roberts JA, Antonelli M, Bassetti M, Vincent JL. Diagnosis and management of invasive candidiasis in the ICU: an updated approach to an old enemy. *Crit Care*. 2016;20(1):125.

27. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of America. *Crit Care Med*. 2016;40(10):1489-1498.

28. Lorhotaly O, Renaudet C, Sibton K, et al. Worrisome trends in incidence and mortality of candidemia in intensive care units (Paris area, 2002-2010). *Inten Care Med*. 2014;40(9):1303-1312.

29. Pfifer MA, Andes DR, Diekema DJ, et al. Epidemiology and outcomes of invasive candidiasis due to non-albicans species of Candida in 2,496 patients: data from the Prospective Antifungal Therapy (PATH) registry 2004–2008. *PloS One*. 2014;9(7):e101510.
37. Chow JK, Golan Y, Ruthazer R, et al. Risk factors for albicans and non-albicans candidemia in the intensive care unit. Crit care Med. 2008;36(7):1993-1998.
38. Shigemura K, Osawa K, Jikimoto T, et al. Comparison of the clinical risk factors between candida albicans and candida non-albicans species for bloodstream infection. J Antibi (Tokyo). 2014;67(4):311-314.
39. Wu JQ, Zhu LP, Ou XT, et al. Epidemiology and risk factors for non-Candida albicans candidemia in non-neutropenic patients at a Chinese teaching hospital. Med Mycol. 2011;49(5):552-555.
40. Wang L, Tong Z, Wang Z, et al. Single-center retrospective study of the incidence of, and risk factors for, non-C. albicans invasive candidiasis in hospitalized patients in China. Med mycol. 2014;52(2):115-122.
41. Arendrup MC. Update on antifungal resistance in aspergillus and candida. Clin Microbiol Infect. 2014;20(suppl 6):42-48.
42. Chapman B, Slavin M, Marriott D, et al. Changing epidemiology of candidaemia in Australia. J Antimicrob Chemother. 2017;72(4):1270.
43. Whaley SG, Berkow EL, Rybak JM, Nishimoto AT, Barker KS, Rogers PD. Azole antifungal resistance in candida albicans and emerging Non-albicans candida species. Front Microbiol. 2016;7:2173.
44. Tan TY, Hsu LY, Alejandria MM, et al. Antifungal susceptibility of invasive Candida bloodstream isolates from the Asia-Pacific region. Med Mycol. 2016;54(5):471-477.
45. Marriott DJ, Playford EG, Chen S, et al. Determinants of mortality in non-neutropenic ICU patients with candidaemia. Crit Care. 2009;13(4):R115.
46. Parkins MD, Sabuda DM, Elsayed S, Laupland KB. Adequacy of empirical antifungal therapy and effect on outcome among patients with invasive Candida species infections. Antimicrob chemother. 2007;60(3):613-618.
47. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of Candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob agents chemother. 2005;49(9):3640-3645.
48. Grim SA, Berger K, Teng C, et al. Timing of susceptibility-based antifungal drug administration in patients with Candida bloodstream infection: correlation with outcomes. J Antimicrob chemother. 2012;67(3):707-714.
49. Cui N, Wang H, Qiu H, Li R, Liu D. Impact of initial empirical antifungal agents on the outcome of critically ill patients with invasive candidiasis: analysis of the China-scan study. Int J Antimicrob Agents. 2017;50(1):74-80.
50. Garnacho-Montero J, Díaz-Martín A, García-Cabrera E, de Pipaón MRP, Hernández-Caballero C, Lepe-Jiménez JA. Impact on hospital mortality of catheter removal and adequate antifungal therapy in Candida spp. bloodstream infections. Antimicrob Chemother. 2013;68(1):206-213.