Ten-year review of invasive Candida infections in a tertiary care center in Saudi Arabia


ABSTRACT

Objectives: To review the epidemiology of invasive Candida infections in a single center in Saudi Arabia over a subsequent 10-year period.

Methods: This retrospective study was carried out in a single center in Saudi Arabia over a 10-year period. Records of all patients with invasive Candida infections (ICI) over the period from January 2003 to December 2012 were reviewed. Mann-Whitney U test was used for comparison of Candida albicans (C. albicans) versus non-albicans Candida species, and fluconazole resistance versus fluconazole susceptible in relation to crude mortality at 30 days and 90 days.

Results: Eight hundred positive sterile site cultures, associated with 652 ICI were identified. Median age was 52 years and 53% of patients were males. Candida albicans were the most common species (38.7%), followed by Candida tropicalis (18.9%), and Candida glabrata (16.3%). The proportion of ICI caused by C. albicans remained stable over time (p=0.07), but C. glabrata increased significantly (p<0.001). The median rate of ICI per 1,000 hospital discharges per year was 1.65, with a significant trend towards higher rates over time (p=0.01). Most isolates were susceptible to fluconazole, voriconazole, and amphotericin B. Only 66.7% of Candida krusei were susceptible to caspofungin. Overall 30-day crude mortality was 40.6%. There was no significant difference in crude mortality in association with C. albicans compared with non-albicans species, nor in association with fluconazole resistance.

Conclusion: The rate of ICI increased significantly in the proportion of ICI caused by C. glabrata. Most isolates remain susceptible to caspofungin, voriconazole, and amphotericin B. The crude mortality remains high.


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Candida species are important causes of severe infections, especially in higher risk groups such as immune compromised patients and those admitted to the intensive care units. In addition to causing considerable mortality and morbidity, invasive Candida infections have resulted in prolonged hospital stays and excessive healthcare costs. The epidemiology of invasive Candida infections has changed considerably over time across many parts of the world with non-albicans Candida species becoming more prevalent and increasing resistance to commonly used antifungal agents. Most Candida treatment guidelines generally recommend early empiric antifungal therapy for patients suspected or known to have invasive Candida infection, pending confirmation of the species, and their antimicrobial susceptibilities. Delayed appropriate antifungal therapy is an important contributor to the high morbidity and mortality associated with invasive Candida infections. To avoid such delays, empiric antifungal therapy should be guided by the known local epidemiology, the prevailing Candida species, and antifungal susceptibilities patterns. Prince Sultan Military Medical City is a large tertiary center in Riyadh, Saudi Arabia, with an average of approximately 40,000 discharges per year. Clinical services include subspecialized surgery, hemato-oncology, hematopoietic stem cell, and solid organ transplantation. There are more than 100 adult and 100 neonatal and pediatric intensive care beds. Candida blood stream infections for the 6-year period that extended from 1996-2002 were previously reported. This is a follow-up study aiming to review the epidemiology of invasive Candida infections in the same institution over the subsequent 10-year period. We describe the species distribution, clinical outcome, and in-hospital mortality along with the associated anti-fungal susceptibility patterns. The findings will inform policy development and clinical decision making at the local, national, and regional levels.

Methods. We undertook a retrospective review of microbiological and clinical records for the period from January 2003 to December 2012 and retrieved details of all Candida species isolated from cultures of sterile site samples (namely, blood, cerebrospinal fluid, other body fluid, and tissue biopsies). Candida species identification was based on a combination of colonial morphology, germ tube, growth on CHROMagar (Saudi Prepared Media Laboratory, Riyadh, KSA) and API 20 C AUX (BioMérieux, Marcy-L’Etoile, France). Minimum inhibitory concentrations were determined using Etest (BioMérieux, Marcy-L’Etoile, France) and Sensititre YeastOne (Trek Diagnostic, West Sussex, UK) and interpreted according to the clinical break points and epidemiological cut-off values recommended by Clinical Laboratory Standards Institute (CLSI). The data collated included sample types, Candida species isolated, and antifungal susceptibility results where available. Positive cultures from the same patient dated within 14 days of one another were considered as single episodes. Rates of invasive Candida infection were calculated per 1,000 discharges over the study period. Crude mortality was calculated at 30 and 90 days from date of the first culture from which Candida was isolated.

The study was approved by the institution’s Research Committee.

Statistical analysis. Mann-Whitney U test was used for comparison of Candida albicans (C. albicans) versus non-albicans Candida species, and fluconazole resistant versus fluconazole susceptible in relation to crude mortality at 30 days and 90 days. Univariate and regression analyses were used to identify the association of age and fluconazole resistance with crude-mortality. Regression analysis was also used to assess changes in proportions and rates over time. Normality of the distribution was confirmed using Shapiro-Wilk test and graphical methods to confirm its linearity. A p-value less than 0.05 was considered significant. Statistical analyses were performed using Microsoft Excel (Microsoft Inc., Redmond, USA) and Statistical Package for Social Science for Windows, Version 21.0 (IBM, Armonk, NY, USA).

Results. A total of 800 positive cultures associated with 652 episodes of invasive Candida infection were identified. Median patient age was 52 years (range one month to 107 years). Male patients constituted 53.8% versus 46.2% females (p=0.49). Isolates from blood cultures (82.1%) and tissue cultures (15.2%) predominated. The most common Candida species isolated was C. albicans (38.7%), followed by Candida tropicalis (18.9%), Candida glabrata (C. glabrata) (16.3%) and Candida parapsilosis (12.6%) (Table 1). The proportion of invasive Candida infections caused by C. albicans remained stable over the study period.
Invasive Candida infections ... Omrani et al

(r^2=0.35, p=0.07). However, there was a significant trend towards increasing *C. glabrata* over time (r^2=0.78, p<0.001). The median rate of invasive Candida infection per 1,000 hospital discharges per year was 1.65 (interquartile range [IQR] 1.11-2.05). The rate of invasive Candida infections per 1,000 discharges per year increased significantly over the study years (r^2 = 0.56, p=0.01) (Figure 1). A total of 709 isolates were tested for susceptibility to fluconazole. Overall, 89.9% of *C. albicans* isolates, 93.8% of *C. tropicalis* isolates, and 98.8% of *C. parapsilosis* isolates were susceptible. The proportion of isolates susceptible to fluconazole remained generally stable over the study years (r^2=0.41, p=0.06) (Table 2). The majority of tested isolates were susceptible to voriconazole and amphotericin B. However, only 89.3% of *C. parapsilosis* and 66.7% of *C. krusei* were susceptible to caspofungin (Table 3). The overall 30-day crude mortality was 40.6% (median 39.1% per year, IQR 36.3-47.5%), while 90-day crude mortality was 51.8% (median 48.5% per year, IQR 45.0-59.0%) (Figure 1). The highest crude mortality at 30 days was associated with *C. guilliermondii* followed by *C. tropicalis* and *C. krusei*. On the other hand, crude mortality at 90 days was highest in association with *C. krusei*, followed by *C. guilliermondii* and *C. tropicalis* (Figure 2). There was no statistically significant

Table 1 - Candida species causing invasive infection by year isolated.

<table>
<thead>
<tr>
<th>Year/species</th>
<th>Candida albicans</th>
<th>Candida tropicalis</th>
<th>Candida glabrata</th>
<th>Candida parapsilosis</th>
<th>Candida guilliermondii</th>
<th>Candida krusei</th>
<th>Candida species (unspecified)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>23 (60.5)</td>
<td>10 (26.3)</td>
<td>1 (2.6)</td>
<td>3 (7.9)</td>
<td>1 (2.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>38 (100)</td>
</tr>
<tr>
<td>2004</td>
<td>7 (41.2)</td>
<td>4 (23.5)</td>
<td>1 (5.9)</td>
<td>1 (5.9)</td>
<td>3 (17.6)</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>2005</td>
<td>15 (36.6)</td>
<td>5 (12.2)</td>
<td>2 (4.9)</td>
<td>6 (14.6)</td>
<td>13 (31.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>41 (100)</td>
</tr>
<tr>
<td>2006</td>
<td>23 (50.0)</td>
<td>5 (10.9)</td>
<td>9 (19.6)</td>
<td>3 (6.5)</td>
<td>3 (6.5)</td>
<td>1 (2.2)</td>
<td>2 (4.3)</td>
<td>46 (100)</td>
</tr>
<tr>
<td>2007</td>
<td>27 (38.0)</td>
<td>16 (22.5)</td>
<td>7 (9.9)</td>
<td>14 (19.7)</td>
<td>4 (5.6)</td>
<td>1 (1.4)</td>
<td>2 (2.8)</td>
<td>71 (100)</td>
</tr>
<tr>
<td>2008</td>
<td>29 (35.4)</td>
<td>26 (31.7)</td>
<td>13 (15.9)</td>
<td>4 (4.9)</td>
<td>4 (4.9)</td>
<td>3 (3.7)</td>
<td>3 (3.7)</td>
<td>82 (100)</td>
</tr>
<tr>
<td>2009</td>
<td>27 (33.8)</td>
<td>16 (20.0)</td>
<td>16 (20.0)</td>
<td>12 (15.0)</td>
<td>4 (5.0)</td>
<td>0 (0.0)</td>
<td>5 (6.3)</td>
<td>80 (100)</td>
</tr>
<tr>
<td>2010</td>
<td>38 (35.2)</td>
<td>19 (17.6)</td>
<td>19 (17.6)</td>
<td>19 (17.6)</td>
<td>7 (6.5)</td>
<td>2 (1.9)</td>
<td>4 (3.7)</td>
<td>108 (100)</td>
</tr>
<tr>
<td>2011</td>
<td>31 (33.3)</td>
<td>12 (12.9)</td>
<td>20 (21.5)</td>
<td>14 (15.1)</td>
<td>6 (6.5)</td>
<td>2 (2.2)</td>
<td>8 (8.6)</td>
<td>93 (100)</td>
</tr>
<tr>
<td>2012</td>
<td>32 (42.1)</td>
<td>10 (13.2)</td>
<td>18 (23.7)</td>
<td>6 (7.9)</td>
<td>9 (11.8)</td>
<td>0 (0.0)</td>
<td>1 (1.3)</td>
<td>76 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>252 (38.7)</td>
<td>123 (18.9)</td>
<td>106 (16.3)</td>
<td>82 (12.6)</td>
<td>54 (8.3)</td>
<td>9 (1.4)</td>
<td>26 (4.0)</td>
<td>652 (100)</td>
</tr>
</tbody>
</table>

Data are expressed as number and percentage (%)

Figure 1 - Rate of invasive Candida infection per 1,000 hospital discharges (primary Y-axis) and crude mortality at 30 and 90 days from first positive culture by year of study (secondary Y-axis) by year of study (X-axis).
Invasive Candida infections ... Omrani et al

Table 2 - Fluconazole susceptibility for 688 sterile site Candida isolates by species and year tested.

<table>
<thead>
<tr>
<th>Year</th>
<th>Candida albicans</th>
<th>Candida tropicalis</th>
<th>Candida glabrata</th>
<th>Candida parapsilosis</th>
<th>Candida guilliermondii</th>
<th>Candida krusei</th>
<th>Candida species (unspecified)</th>
<th>Total tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>87.5 (8)</td>
<td>100.0 (4)</td>
<td>0.0 (1)</td>
<td>100.0 (1)</td>
<td>33.3 (3)</td>
<td>0.0 (0)</td>
<td>50.0 (2)</td>
<td>19</td>
</tr>
<tr>
<td>2005</td>
<td>75.0 (16)</td>
<td>100.0 (7)</td>
<td>50.0 (2)</td>
<td>100.0 (7)</td>
<td>58.3 (12)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>44</td>
</tr>
<tr>
<td>2006</td>
<td>55.6 (27)</td>
<td>60.0 (5)</td>
<td>75.0 (12)</td>
<td>100.0 (3)</td>
<td>66.7 (3)</td>
<td>0.0 (2)</td>
<td>100.0 (2)</td>
<td>54</td>
</tr>
<tr>
<td>2007</td>
<td>86.5 (37)</td>
<td>90.0 (20)</td>
<td>83.3 (6)</td>
<td>94.4 (18)</td>
<td>60.0 (5)</td>
<td>0.0 (1)</td>
<td>100.0 (2)</td>
<td>89</td>
</tr>
<tr>
<td>2008</td>
<td>97.1 (34)</td>
<td>90.6 (32)</td>
<td>85.7 (14)</td>
<td>100.0 (5)</td>
<td>60.0 (5)</td>
<td>0.0 (4)</td>
<td>100.0 (4)</td>
<td>98</td>
</tr>
<tr>
<td>2009</td>
<td>93.3 (30)</td>
<td>94.1 (17)</td>
<td>100.0 (16)</td>
<td>100.0 (14)</td>
<td>100.0 (4)</td>
<td>0.0 (0)</td>
<td>100.0 (5)</td>
<td>86</td>
</tr>
<tr>
<td>2010</td>
<td>97.7 (43)</td>
<td>100.0 (20)</td>
<td>95.7 (23)</td>
<td>100.0 (23)</td>
<td>100.0 (8)</td>
<td>0.0 (3)</td>
<td>100.0 (4)</td>
<td>124</td>
</tr>
<tr>
<td>2011</td>
<td>100.0 (34)</td>
<td>100.0 (14)</td>
<td>95.0 (20)</td>
<td>100.0 (15)</td>
<td>100.0 (6)</td>
<td>0.0 (3)</td>
<td>100.0 (8)</td>
<td>100</td>
</tr>
<tr>
<td>2012</td>
<td>100.0 (29)</td>
<td>100.0 (10)</td>
<td>100.0 (17)</td>
<td>100.0 (9)</td>
<td>100.0 (7)</td>
<td>0.0 (0)</td>
<td>50.0 (2)</td>
<td>74</td>
</tr>
<tr>
<td>Total</td>
<td>89.9 (258)</td>
<td>93.8 (129)</td>
<td>91.0 (111)</td>
<td>98.9 (95)</td>
<td>77.4 (53)</td>
<td>0.0 (13)</td>
<td>93.1 (29)</td>
<td>688</td>
</tr>
</tbody>
</table>

Data are presented as percentage susceptible and (number tested).

Figure 2 - Crude mortality at 30 and 90 days from first positive culture by Candida species. C. albicans - Candida albicans, C. tropicalis - Candida tropicalis, C. glabrata - Candida glabrata, C. parapsilosis - Candida parapsilosis, C. guilliermondii - Candida guilliermondii, C. krusei - Candida krusei

The difference between invasive Candida infections caused by C. albicans compared with infections caused by non-albicans species neither in terms of 30-day crude mortality (40.1% versus 41%, p=0.74), nor 90-day crude mortality (51.6% versus 52%, p=0.75). Similarly, crude mortality was not significantly different in patients with infections caused by fluconazole resistant Candida strains compared with those caused by fluconazole susceptible strains (p=0.16 for 30-day mortality; p=0.08 for 90-day mortality). There was however a significant association between the patient’s age and mortality at 30 days (p<0.001) and at 90 days (p<0.001).

Discussion. Our results show that the rate of invasive Candida infections in our institution increased significantly over the years from 2003-2012, with an overall rate of 1.62 per 1,000 discharges. Depending on type of institution and the patient population of interest, previous studies have reported rates ranging from 0.53 to 9.6 episodes of invasive Candida infections per 1,000 discharges.24-28 Out of 652 episodes of invasive Candida infection, C. albicans continued to be the predominant single causative species (38.7%). However, non-albicans Candida species caused almost two-thirds of those infections (62.3%). In the 6-years that preceded the period covered in this report, C. albicans constituted just over half of all Candida blood stream infections (50.7%).18 A similar shift towards less C. albicans and more non-albicans Candida species has been reported from many parts of the world, including the Middle
Invasive Candida infections ... Omrani et al

Table 3 - Voriconazole, caspofungin, and amphotericin B susceptibility for sterile site Candida isolates by species.

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>Candida albicans</th>
<th>Candida tropicalis</th>
<th>Candida glabrata</th>
<th>Candida parapsilosis</th>
<th>Candida guilliermondii</th>
<th>Candida krusei</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole susceptible</td>
<td>99 (98)</td>
<td>98.4 (64)</td>
<td>100 (40)</td>
<td>100 (25)</td>
<td>100 (17)</td>
<td>100 (6)</td>
<td>100 (11)</td>
<td>99.2 (261)</td>
</tr>
<tr>
<td>Caspofungin susceptible</td>
<td>100 (110)</td>
<td>100 (66)</td>
<td>100 (47)</td>
<td>89.3 (28)</td>
<td>100 (18)</td>
<td>66.7 (6)</td>
<td>93.8 (16)</td>
<td>97.9 (291)</td>
</tr>
<tr>
<td>Amphotericin B susceptible</td>
<td>100 (227)</td>
<td>100 (121)</td>
<td>99 (103)</td>
<td>95.1 (82)</td>
<td>100 (50)</td>
<td>100 (14)</td>
<td>95.5 (22)</td>
<td>99.0 (619)</td>
</tr>
</tbody>
</table>

Data are presented as percentage susceptible and (number tested).

References


East and North Africa. Moreover, although C. krusei remained relatively uncommon in our study (1.4%), the proportion of invasive Candida infections caused by C. glabrata increased from 2.6% in 2003 to 23.7% in 2012. With their relatively higher rate of resistance to azole antifungals, the rise of C. glabrata infections is a cause for considerable concern. 26,27,32-38

More than 90% of C. albicans, C. parapsilosis, and C. tropicalis isolates in our study were susceptible to fluconazole and caspofungin. Moreover, the vast majority of C. tropicalis isolates in our study were susceptible to caspofungin, Amphotericin B and non-albicans Candida species. Moreover, fluconazole resistance was compared with infections caused by non-albicans species, especially C. glabrata, C. parapsilosis, and C. tropicalis. In our study, all-cause mortality did not differ significantly in association with invasive C. albicans infections in comparison with infections caused by non-albicans Candida species. Moreover, fluconazole resistance was not associated with increased mortality. The reasons for this are not certain, but may be partly explained by differences in empiric antifungal prescribing practices.

In conclusion, the rate of invasive Candida infections in our center increased significantly over the 10-year period between 2003 and 2012. The proportion of infections caused by non-albicans species, especially C. glabrata, increased significantly in comparison with a previous report from the same institution. Most C. krusei isolates remain susceptible to caspofungin, voriconazole, and amphotericin B. All-cause mortality is high in association with both infections caused by C. albicans and non-albicans Candida species.