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

Ali S. Omrani, FRCP FRCPath, *Eyad A. Makkawy,* MD, *Kamran Baig,* MPH, *Abdullah A. Baredhwan,* MD, *Souad A. Almuthree,* MD, *Noura A. Elkhizzi,* KSU Path, *Ali M. Albarrak,* FRCPC.

ABSTRACT

الأهداف: أجريت هذه الدراسة لمراجعة أنماط إلتهابات الكانديدا على مدى 10 سنوات بأحد المراكز الطبية المرجعية بالمملكة العربية السعودية.

الطريقة: أجريت هذه الدراسة بأثر رجعي في أحد المراكز في المملكة العربية السعودية على مدى 10 سنوات .وقد استخدم اختبار Mann-Whitney U للمقارنة بين كانديدا ألبيكانز (*C. albicans*) *Candida albicans* مقابل أنواع كانديدا الغير ألبيكانز ومقاومة فلوكونازول مقابل فلوكونازول وكانت الوفيات من 30 يوماً إلى90 يوماً.

النتائج: وجدنا 800 مزرعة إيجابية مستخلصة من 652 حالة التهاب كانديدا غير سطحية. كان متوسط أعمار المرضى 52 عاماً و 53% منهم ذكور. كانت فصيلة كانديدا ألبيكانز المسئولة عن 38.7% من الحالات، كانديدا تروبيكالاس 18.9% وكانديدا جلابراتا 16.3%. نسبة الإصابات بفطريات كانديدا جلابراتا زادت بصورة ذات أهمية إحصائية خلال سنوات الدراسة، بينما نسبة كانديدا ألبيكانز بقيت متقاربة. هذا وكان معدل حالات إلتهابات الكانديدا 1.65 لكل 1,000 حالة منومة بالسنة. غالبية الكانديدا بالدراسة كانت ذات إستجابة لمضادات الفطريات مثل فلوكونازول وفوريكونازول وأمفوتيريسين، بينما كانت 66.7% فقط من كانديدا كروزيياي ذات إستجابة لكاسبوفانجين. نسبة الحالات المؤدية إلى الوفاة بلغت 40.6% خلال 30 يوماً من التشخيص، وهذه لم تختلف بصورة مهمة إحصائياً مع أنواع معينة من الكانديدا دون أخرى.

الخاتمة: معدلات الإصابات بالكانديدا مرتفعة نسبياً بمركز الدراسة، مع تزايد نسبة كانديدا جلابراتا وارتفاع معدل الحالات المؤدية إلى الوفاة.

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 (C. 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.

Saudi Med J 2014; Vol. 35 (8): 821-826

From the Division of Infectious Diseases (Omrani, Makkawy, Baredhwan, Almuthree, AlBarrak), the Division of Medical Microbiology (Elkhizzi), Department of Medicine, and the Department of Infection Prevention and Control (Baig), Prince Sultan Military Medical City, Riyadh, Kingdom of Saudi Arabia.

Received 5th May 2014. Accepted 17th June 2014.

Address correspondence and reprint request to: Dr. Ali S. Omrani, Division of Infectious Diseases, Department of Medicine, Prince Sultan Military Medical City, Riyadh, Kingdom of Saudi Arabia. Tel. +966 (11) 4777714 Ext. 25681. Fax. +966 (11) 4756711. E-mail: asomrani@gmail.com

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.[1-4] In addition to causing considerable mortality and morbidity, invasive Candida infections have resulted in prolonged hospital stays and excessive healthcare costs.[2] 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.[1,5,6] 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.[7-12] Delayed appropriate antifungal therapy is an important contributor to the high morbidity and mortality associated with invasive Candida infections.[13-17] To avoid such delays, empiric antifungal therapy should be guided by the known local epidemiology, the prevailing Candida species, and antifungal susceptibilities patterns.[7-10] 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 sub-specialized 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.[18] 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).[19-23] 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

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company. Dr. Ali AlBarrak is a member of the Editorial Team, and was therefore excluded from any final editorial decisions regarding this paper.

(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 the 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.

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

Data are expressed as number and percentage (%)

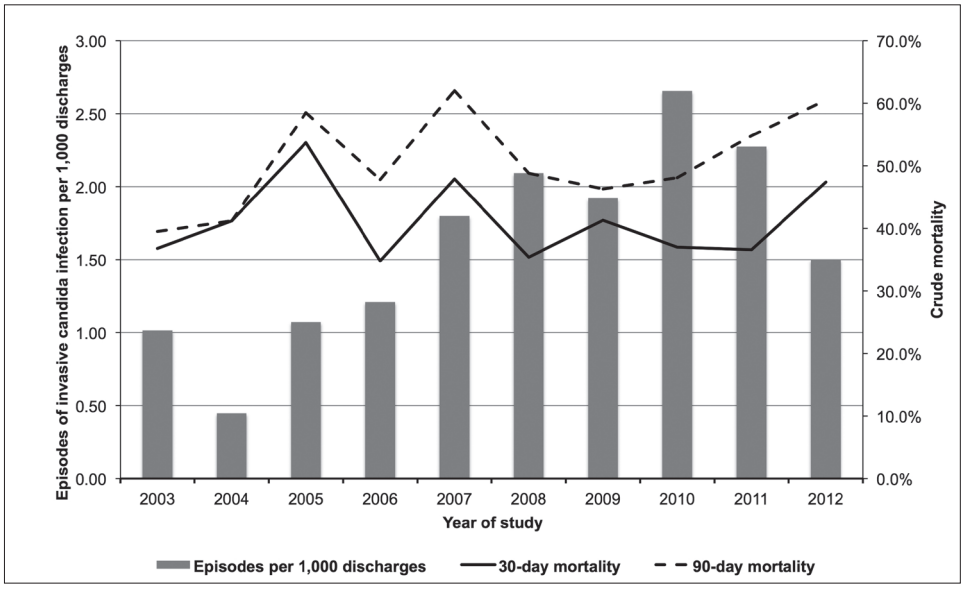
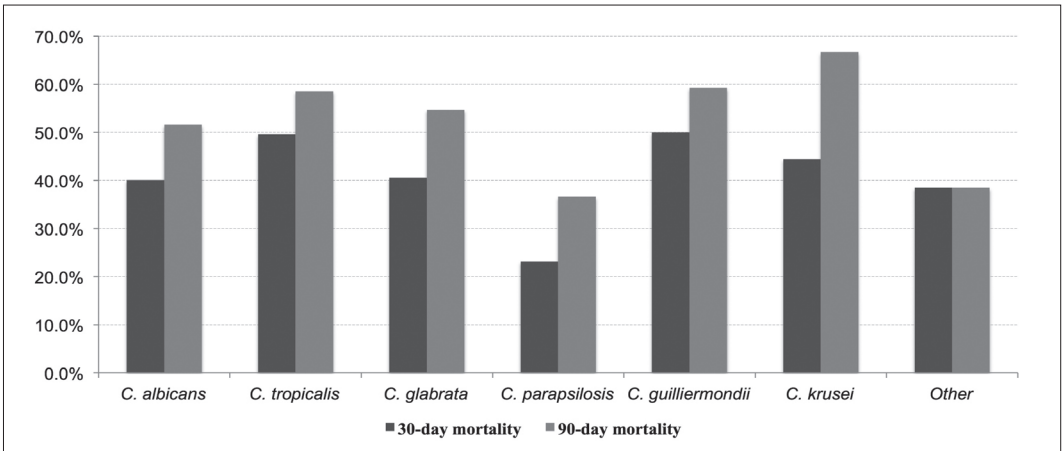


Figure 1 - Rate of invasive Candida infection per 1,000 hospital discharges (primary Y-axis) and crude mortality at 30 and 90 days from first positive culture by year of study (secondary Y-axis) by year of study (X-axis).

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

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

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



	C. albicans	*C. tropicalis*	*C. glabrata*	*C. parapsilosis*	*C. guilliermondii*	*C. krusei*	Other
30-day mortality	101/252	61/123	43/106	19/82	27/54	4/9	10/26
90-day mortality	130/252	72/123	58/106	30/82	32/54	6/9	10/26

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*

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

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

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

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

East and North Africa.[1,3,26,27,29-33] 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 Candida isolates were susceptible to voriconazole and amphotericin B, while 33.3% of *C. krusei* isolates were resistant to caspofungin (**Table 3**). This pattern is generally predictable and is of major influence on recommendations for empiric antifungal therapy ahead of the availability of antifungal susceptibility testing results.[7,8,39]

Approximately two-fifths (40.6%) of patients died of any cause within 30-days of isolation of Candida species from a sterile site culture. Invasive Candida infections are commonly associated with such high rates of crude mortality.[2,24,27,29,30,37,40] A few previous studies have reported higher rates of mortality in associated with non-albicans Candida species, especially *C. krusei*, *C. glabrata* and *C. tropicalis*.[3,35,37,40,41] 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.[18] 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.

References

1. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. ***Clin Microbiol Rev*** 2007; 20: 133-163.
2. Morgan J, Meltzer MI, Plikaytis BD, Sofair AN, Huie-White S, Wilcox S, et al. Excess mortality, hospital stay, and cost due to candidemia: a case-control study using data from population-based candidemia surveillance. ***Infect Control Hosp Epidemiol*** 2005; 26: 540-547.
3. Horn DL, Neofytos D, Anaissie EJ, Fishman JA, Steinbach WJ, Olyaei AJ, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. ***Clin Infect Dis*** 2009; 48: 1695-1703.
4. Eggimann P, Garbino J, Pittet D. Epidemiology of Candida species infections in critically ill non-immunosuppressed patients. ***Lancet Infect Dis*** 2003; 3: 685-702.
5. Marr KA. Invasive Candida infections: the changing epidemiology. ***Oncology (Williston Park)*** 2004; 18 (14 Suppl 13): 9-14.
6. Zirkel J, Klinker H, Kuhn A, Abele-Horn M, Tappe D, Turnwald D, et al. Epidemiology of Candida blood stream infections in patients with hematological malignancies or solid tumors. ***Med Mycol*** 2012; 50: 50-55.
7. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. ***Clin Infect Dis*** 2009; 48: 503-535.
8. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. ***Clin Microbiol Infect*** 2012; 18 Suppl 7: 19-37.
9. Ullmann AJ, Akova M, Herbrecht R, Viscoli C, Arendrup MC, Arikan-Akdagli S, et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). ***Clin Microbiol Infect*** 2012; 18 Suppl 7: 53-67.
10. Bow EJ, Evans G, Fuller J, Laverdière M, Rotstein C, Rennie R, et al. Canadian clinical practice guidelines for invasive candidiasis in adults. ***Can J Infect Dis Med Microbiol*** 2010; 21: e122-e150.
11. Hope WW, Castagnola E, Groll AH, Roilides E, Akova M, Arendrup MC, et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: prevention and management of invasive infections in neonates and children caused by *Candida spp*. ***Clin Microbiol Infect*** 2012; 18 Suppl 7: 38-52.
12. Alothman AF, Al-Musawi T, Al-Abdely HM, Salman JA, Almaslamani M, Yared N, et al. Clinical practice guidelines for the management of invasive Candida infections in adults in the Middle East region: Expert panel recommendations. ***J Infect Public Health*** 2014; 7: 6-19.

13. Gudlaugsson O, Gillespie S, Lee K, Vande Berg J, Hu J, Messer S, et al. Attributable mortality of nosocomial candidemia, revisited. ***Clin Infect Dis*** 2003; 37: 1172-1177.
14. Garey KW, Rege M, Pai MP, Mingo DE, Suda KJ, Turpin RS, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. ***Clin Infect Dis*** 2006; 43: 25-31.
15. Fraser A, Paul M, Almanasreh N, Tacconelli E, Frank U, Cauda R, et al. Benefit of appropriate empirical antibiotic treatment: thirty-day mortality and duration of hospital stay. ***Am J Med*** 2006; 119: 970-976.
16. 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: 3640-3645.
17. Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to Candida infection: importance of empiric therapy and source control. ***Clin Infect Dis*** 2012; 54: 1739-1746.
18. Al-Jasser AM, Elkhizzi NA. Distribution of Candida species among bloodstream isolates. ***Saudi Med J*** 2004; 25: 566-569.
19. Xue G, Xu W, Yu W, Fang Q. N-ethylpyridinium bis(2-thioxo-1,3-dithiole-4,5-dithiolato) nickelate. ***Acta Crystallogr C*** 2003; 59 (Pt 1): m27-m29.
20. Clinical and Laboratory Standards Institute. Method for antifungal disk diffusion susceptibility testing of yeasts; Approved guideline. CLSI document M44-A. Wayne (PA): Clinical and Laboratory Standards Institute; 2004.
21. Clinical and Laboratory Standards Institute. Zone diameter interpretive standards, corresponding minimal inhibitory concentration (MIC) interpretive breakpoints, and quality control limits for antifungal disk diffusion susceptibility testing of yeasts; Informational supplement, CLSI document M44-S2. 2nd ed. Wayne (PA): Clinical and Laboratory Standards Institute; 2008.
22. Clinical and Laboratory Standards Institute. Method for antifungal disk diffusion susceptibility testing of yeasts; Approved guideline. CLSI document M44-A2. 2nd ed. Wayne (PA): Clinical and Laboratory Standards Institute; 2009.
23. Clinical and Laboratory Standards Institute. Clinical and Laboratory Standards Institute. Zone diameter interpretive standards, corresponding minimal inhibitory concentration (MIC) interpretive breakpoints, and quality control limits for antifungal disk diffusion susceptibility testing of yeasts; Informational supplement, CLSI document M44-S3. 3rd ed. Wayne (PA): Clinical and Laboratory Standards Institute; 2009.
24. Al-Tawfiq JA. Distribution and epidemiology of Candida species causing fungemia at a Saudi Arabian hospital, 1996-2004. ***Int J Infect Dis*** 2007; 11: 239-244.
25. Almirante B, Rodríguez D, Park BJ, Cuenca-Estrella M, Planes AM, Almela M, et al. Epidemiology and predictors of mortality in cases of Candida bloodstream infection: results from population-based surveillance, barcelona, Spain, from 2002 to 2003. ***J Clin Microbiol*** 2005; 43: 1829-1835.
26. Hii IM, Chang HL, Lin LC, Lee YL, Liu YM, Liu CE, et al. Changing epidemiology of candidemia in a medical center in middle Taiwan. ***J Microbiol Immunol Infect*** 2013: 7: pii: S1684-1182(13)00162-X.
27. Sampaio Camargo TZ, Marra AR, Silva CV, Cardoso MF, Martino MD, Camargo LF, et al. Secular trends of candidemia in a tertiary care hospital. ***Am J Infect Control*** 2010; 38: 546-551.
28. Yap HY, Kwok KM, Gomersall CD, Fung SC, Lam TC, Leung PN, et al. Epidemiology and outcome of Candida bloodstream infection in an intensive care unit in Hong Kong. ***Hong Kong Med J*** 2009; 15: 255-261.
29. Al Thaqafi AH, Farahat FM, Al Harbi MI, Al Amri AF, Perfect JR. Predictors and outcomes of Candida bloodstream infection: eight-year surveillance, western Saudi Arabia. ***Int J Infect Dis*** 2014; 21: 5-9.
30. Ellis M, Hedstrom U, Jumaa P, Bener A. Epidemiology, presentation, management and outcome of candidemia in a tertiary care teaching hospital in the United Arab Emirates, 1995-2001. ***Medical Mycology*** 2003; 41: 521-528.
31. Mokaddas EM, Al-Sweih NA, Khan ZU. Species distribution and antifungal susceptibility of Candida bloodstream isolates in Kuwait: a 10-year study. ***J Med Microbiol*** 2007; 56 (Pt 2): 255-259.
32. Chen PY, Chuang YC, Wang JT, Sheng WH, Yu CJ, Chu CC, et al. Comparison of epidemiology and treatment outcome of patients with candidemia at a teaching hospital in Northern Taiwan, in 2002 and 2010. ***J Microbiol Immunol Infect*** 2014; 47: 95-103.
33. Falagas ME, Roussos N, Vardakas KZ. Relative frequency of albicans and the various non-albicans Candida spp among candidemia isolates from inpatients in various parts of the world: a systematic review. ***Int J Infect Dis*** 2010; 14: e954-e966.
34. Ha YE, Peck KR, Joo EJ, Kim SW, Jung SI, Chang HH, et al. Impact of first-line antifungal agents on the outcomes and costs of candidemia. ***Antimicrob Agents Chemother*** 2012; 56: 3950-3956.
35. Hachem R, Hanna H, Kontoyiannis D, Jiang Y, Raad I. The changing epidemiology of invasive candidiasis: *Candida glabrata* and *Candida krusei* as the leading causes of candidemia in hematologic malignancy. ***Cancer*** 2008; 112: 2493-2499.
36. Lyon GM, Karatela S, Sunay S, Adiri Y; Candida Surveillance Study Investigators. Antifungal susceptibility testing of Candida isolates from the Candida surveillance study. ***J Clin Microbiol*** 2010; 48: 1270-1275.
37. Pemán J, Cantón E, Gobernado M. Spanish ECMM Working Group on Candidaemia. Epidemiology and antifungal susceptibility of Candida species isolated from blood: results of a 2-year multicentre study in Spain. ***Eur J Clin Microbiol Infect Dis*** 2005; 24: 23-30.
38. Silva S, Negri M, Henriques M, Oliveira R, Williams DW, Azeredo J. *Candida glabrata, Candida parapsilosis,* and *Candida tropicalis*: biology, epidemiology, pathogenicity and antifungal resistance. ***FEMS Microbiol Rev*** 2012; 36: 288-305.
39. Orasch C, Marchetti O, Garbino J, Schrenzel J, Zimmerli S, Mühlethaler K, et al. Candida species distribution and antifungal susceptibility testing according to EUCAST and new vs. old clsi clinical breakpoints: a six-year prospective candidemia survey from the fungal infection network of Switzerland (FUNGINOS). ***Clin Microbiol Infect*** 2013: 4: [Epub ahead of print]
40. Ortega M, Marco F, Soriano A, Almela M, Martínez JA, López J, et al. Candida species bloodstream infection: epidemiology and outcome in a single institution from 1991 to 2008. ***J Hosp Infect*** 2011; 77: 157-161.
41. Andes DR, Safdar N, Baddley JW, Playford G, Reboli AC, Rex JH, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. ***Clin Infect Dis*** 2012; 54: 1110-1122.