Journal of Infection and Public Health (2014) 7, 6—19

http://www.elsevier.com/locate/jiph

Clinical practice guidelines for the management of invasive *Candida* infections in adults in the Middle East region: Expert panel recommendations

Adel F. Alothman[a,*], Tariq Al-Musawi[b], Hail M. Al-Abdely[c], Jameela Al Salman[d], Muna Almaslamani[e], Nadine Yared[f], Adeel A. Butt[g], Nirvana Raghubir[h], Waleed El Morsi[h], Abdulhakeem O. Al Thaqafi[i]

[a] *King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia*
[b] *Saad Specialist Hospital, Al-Khobar, Saudi Arabia*
[c] *King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia*
[d] *Salmaniya Medical Complex, Manama, Bahrain*
[e] *Hamad Medical Corporation (HMC), Weill Cornell Medical College, Qatar, State of Qatar*
[f] *Lebanese University, Faculty of Medical Sciences, Beirut, Lebanon*
[g] *Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates*
[h] *Pfizer Inc., Dubai, United Arab Emirates*
[i] *King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia*

Received 7 June 2013; received in revised form 5 August 2013; accepted 12 August 2013

KEYWORDS
Candida;
Treatment;
Guidelines;
Candidiasis;
Middle East

Abstract Invasive *Candida* infections contribute to significant morbidity and mortality in patients with healthcare-associated infections. They represent a major burden on the public health system, and are challenging to diagnose and treat.

A multidisciplinary expert panel critically reviewed available evidence to provide consensus recommendations for the management of invasive *Candida* infections in the Middle East.

Abbreviations: ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmB-d, AmB deoxycholate; AMMI, Association of Medical Microbiology and Infectious Disease; BSI, blood stream infection; CAGTA, *C. albicans* germ-tube antibodies; ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; ECIL4, European Council on Infections in Leukaemia; EORTC/MSG, 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; ICU, intensive care unit; IDSA, Infectious Disease Society of America; L-AmB, liposomal AmB; LFAmB, lipid formulation AmB.

* Corresponding author at: Head of Infectious Diseases Division, Department of Medicine, King Abdulaziz Medical City, P.O. Box 22490, Riyadh 11426, Saudi Arabia. Tel.: +966 1 8011725; fax: +966 1 8014229.

E-mail addresses: othmanaf@hotmail.com (A.F. Alothman), dr_tmusawi@hotmail.com (T. Al-Musawi), habdely@gmail.com (H.M. Al-Abdely), jalsalman@hotmail.com (J.A. Salman), malmaslamani@hmc.org.qa (M. Almaslamani), nay04@mail.aub.edu (N. Yared), aabutt@skmc.ae (A.A. Butt), nirvana.raghubir@pfizer.com (N. Raghubir), waleed.elmorsi@pfizer.com (W.E. Morsi), thaqafiao1@ngha.med.sa (A.O. Al Thaqafi).

1876-0341/$ — see front matter
http://dx.doi.org/10.1016/j.jiph.2013.08.002

Based on diagnosis, recommendations were provided for the management of *Candida* infections in non-neutropenic and neutropenic patients. Polyenes (amphotericin B-deoxycholate [AmB-d] and lipid formulations amphotericin B [LFAmB]), triazoles (fluconazole, itraconazole and voriconazole), echinocandins (caspofungin, anidulafungin, and micafungin) and flucytosine are the recommended categories of antifungal agents for treatment of *Candida* infections. Echinocandins are preferred for treatment of proven and suspected *Candida* infections, especially in critically ill patients or those with previous exposure to azoles. Recommendations were also provided for infections caused by specific *Candida* species as well as management of different disease conditions.

The experts highlighted that the guidelines should be used along with clinical judgment. Given the paucity of published data from the region, research in the form of randomized clinical trials should be given priority.

Contents

Introduction

Candida species are one of the most common fungal pathogens seen in nosocomial settings, causing invasive infections mainly in neutropenic and severely ill non-neutropenic patients. *Candida* species are responsible for approximately 15% of all hospital-acquired infections, more than 72% of all nosocomial fungal infections, and 8—15% of all nosocomial blood stream infections (BSIs) with 25—50% of nosocomial candidemia occurring in intensive care units (ICUs) [1—3]. The most frequently associated risk factors with invasive candidiasis include prolonged use of broad-spectrum antibacterial therapy, length of ICU stay, use of central venous catheters, receipt of parenteral nutrition, neutropenia, use of immunosuppressive agents, implantable prosthetic devices and renal replacement therapy by patients in ICUs [4].

Invasive candidiasis is associated with high mortality, with crude mortality estimated to be as high as 47%, and attributable mortality to be in the range of 15—20% [4]. The burden of *Candida* infections on healthcare services is substantial. According to a study by Morgan et al. *Candida* infections significantly increased the total hospital charges and cost of hospitalization ($6,000—$29,000 and $3,000—$22,000, respectively), and length of stay (3—13 days) [5]. Regional data on cost associated with invasive candidiasis is lacking although it is estimated to be similar to the data obtained from other regions of the world.

The management of invasive candidiasis, from prevention to early diagnosis, and the selection of appropriate treatment, is a challenge for clinicians. Additional challenges which are specific to the Middle East region include the limited number of publications on fungal infections and restricted modalities for diagnosis. Regional guidelines that take local settings into account are essential to improve management of invasive *Candida* infections in the Middle East region.

The objective of this article is to publish clinical practice guidelines on the diagnosis and treatment of invasive *Candida* infections in the Middle East region, based on the consensus recommendations of an expert panel that met in Dubai on June 15th 2012. This is the first time that treatment guidelines for invasive *Candida* infections have been developed for the region, and they aim to equip healthcare practitioners in the Middle East for better management of invasive *Candida* infections.

Methods

Expert panel

A panel of experts met on 15th June 2012 in Dubai to reach a consensus and develop clear clinical practice guidelines to aid diagnosis and treatment of invasive *Candida* infections in the Middle East. The panel included specialists in infectious diseases and intensivists with expertise in the management of invasive *Candida* infections. The experts were chosen from different countries of the region — four from the Kingdom of Saudi Arabia and one each from Bahrain, Qatar, United Arab Emirates (UAE) and Lebanon.

Evidence evaluation

Recommendations from most recent international guidelines for invasive *Candida* infections were reviewed prior to the expert panel meeting. The panel critically analysed recommendations from these guidelines as well as available published literature on diagnosis and treatment of invasive *Candida* infections.

The main source of evidence was the Infectious Disease Society of America (IDSA) 2009 guidelines [4]. In addition, the panel referred to the Association of Medical Microbiology and Infectious Disease (AMMI) Canada Guidelines 2010 [6], the meeting report from the 21st European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) and the 27th International Congress of Chemotherapy providing the first European Society of Clinical Microbiology and Infectious Diseases guidelines for the diagnosis and management of *Candida* infections [7], the European Council on Infections in Leukaemia (ECIL4) 2011 update [8], and the Australian and New Zealand guidelines [9].

The validity, clinical relevance and applicability of the evidence for invasive *Candida* infections in Middle East were discussed. After considering the evidence, the panel achieved a consensus on a number of recommendations that are supported by best scientific evidence.

Levels of recommendation

The panel reviewed several grading systems for recommendations and agreed on a three-tier grading system: Grade A supports a strong recommendation based on evidence from at least one randomized controlled clinical trial to Grade C for which there are limited data to support a recommendation (Table 1).

Table 1 Grading system.

Grade	Definition
A	Strongly recommended based on evidence from ≥1 properly randomized, controlled trial
B	Recommended, based on evidence from ≥1 well-designed clinical trial; from cohort or case-controlled analytic studies, from multiple case series
C	Recommendation based on limited data from few retrospective case series, case reports, preclinical studies and expert opinion

Guideline development

The discussions and consensus statements were recorded at the meeting and written up as a full manuscript draft by a professional medical writer. The panel reviewed, edited and provided comments on the outline and manuscript drafts until a final version was reached that was approved by all members.

Epidemiology of invasive *Candida* infections in the Middle East region

Incidence

There has been an increase in the global incidence of *Candida* infections in the past decade. A large survey of bloodstream infections in US hospitals revealed that *Candida* spp. were the fourth most common cause of pathogen involved in sepsis with an incidence of 4.6 cases per 10,000 admissions [10]. A prospective hospital-based population study performed by the European Confederation of Medical Mycology in seven European countries reported that the rate of candidemia ranges from 2.0 to 3.8 cases of candidemia per 10,000 admissions and 0.30—0.41 case per 10,000 patient hospital days [11].

The epidemiology of candidemia and invasive *Candida* infections in the Middle East region has not been studied as extensively as in the Western countries. Al-Tawfiq et al. reported that the annual incidence of candidemia in Saudi Arabia ranged between 0.2 and 0.76 cases/1000 hospital discharges with an incidence of 0.45—1.6 per 10,000 patient days per year [12]. In UAE, the incidence of candidemia was reported to be 0.77/1000 discharges [13].

Mortality

Invasive *Candida* infection was associated with high mortality ranging from 21.5% to 34.7% in a European study [14] and 19—24% in a US study [5]. In Saudi Arabia, the mortality ranged from 43% to 71% [12,15]. According to a study conducted in UAE, the crude mortality was 50% and mortality attributable to candidemia was 30% [13].

Species distribution

Globally, *Candida albicans* is the most frequently reported species isolated from patients with invasive candidiasis, accounting for 63.8% of isolates [16]. The situation in the Middle East seems to be similar. In most studies from this region, more than 50% of the species isolated were *C. albicans*, followed by *Candida tropicalis*, *Candida parapsilosis* and *Candida glabrata* (Table 2). Epidemiological studies in Europe and the USA suggest an increasing emergence of non-albicans *Candida* species, in particular *C. glabrata*. However, the distribution in the Middle East varies from the Western countries with less incidence of *C. glabrata* in our region. This may change with time and surveillance studies should therefore be conducted periodically.

More isolates of *Candida* are susceptible to fluconazole and voriconazole in the Middle East region (0.6% and 0.3% resistant, respectively) compared with North America (5.1% and 3.6% resistant respectively), probably due to less exposure of the isolates in this region to antifungal agents [16]. In Saudi Arabia, less than 5% of *C. albicans* were resistant to amphotericin B, in comparison with >35% of strains that were resistant to fluconazole [15].

Risk factors

Risk factors for *Candida* infections have not been extensively studied in the Middle East region. The main risk factor for invasive *Candida* infections reported in Saudi Arabia is the use of central venous catheters with 83—87% of candidemia occurring in patients with central venous catheters [12,15]. Other predisposing factors included stays in ICU (77%), use of broad-spectrum antibiotic therapy (74—96%), complicated abdominal surgeries (22%), total parenteral nutrition (52%), neutropenia (9%), acute renal failure (24%), malignancy (26%) and burns (15%) [12,15].

Table 2 Distribution of *Candida* species isolated from patients with invasive candidiasis in the Middle East region.

	Multi-centre study ($N = 8259$ over 10.5 years) [16]	Saudi Arabia ($N = 98$ over 8 years) [12]	Saudi Arabia ($N = 189$ over 10 years) [50]	Saudi Arabia ($N = 31$ over 2 years) [15]	Saudi Arabia ($N = 32$ over 5 years) [51]	UAE ($N = 60$ over 6 years) [13]	Kuwait ($N = 136$ over 5 years) [52]
Candida albicans	67.0%	53%	50.3%	71%	19%	45%	34%
Candida glabrata	8.8%	7%	7.4%	3%	3%	5%	2.8%
Candida tropicalis	6.6%	19%	27%	13%	25%	15%	10.6%
Candida parapsilosis	6.0%	16%	7.9%	13%	44%	5%	31.9%
Candida krusei	2.4%	—	3.2%	—	6%		7.0%

Table 3 Definition of invasive fungal infection.[a]

Category	Definition
Proven	Proof of invasive fungal disease by demonstration of fungal elements in diseased tissue of most conditions
Probable	Host factor, clinical features and mycological evidence are present
Possible	Host factor and clinical features without mycological evidence

[a] de Pauw et al. [19].

Diagnosis of invasive *Candida* infections

Early diagnosis and treatment are associated with a better prognosis [17]. Detection of *Candida* by culture from blood or sterile body sites remains the gold standard method for diagnosis in spite of its poor sensitivity. New microbiological non-culture-based assays have been developed in the last few years, including detection of (1,3)-b-D-glucan antigen, *C. albicans* germ-tube antibodies (CAGTA) and fungal DNA by polymerase chain reaction (PCR) [18].

The expert panel agreed that the most recent 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) should be used as the gold standard in the region. The definitions provide three categories for diagnosis of invasive *Candida* infection: proven, probable and possible (Table 3) [19].

According to the EORTC/MSG Consensus Group, a ''proven'' invasive fungal infection is defined as a positive fungal culture or histological analysis of a tissue specimen taken from a disease site, or the identification or appearance of fungal or hyphal elements in a biopsy from a sterile site. ''Probable'' and ''possible'' invasive fungal infections are further defined on the basis of specific host factors (e.g. neutropenia, transplantation, immunosuppressive therapy), clinical signs and symptoms of fungal infection, and mycological evidence that encompasses culture and microscopic analysis but also indirect tests, such as antigen detection.

It is to be noted that the recommended mycological criteria include standardized and validated tests. Since none of the techniques have been clinically validated and have no standard methodology yet, molecular methods for detection, such as PCR,

were not included in the definitions. The expert panel agreed that the germ-tube test could be used in conjunction with gold standard recommendations outlined above, and should not be used in place of the recommended guidelines.

According to the expert panel, the guidelines for diagnosis should be applied wherever possible, utilizing regional expert advice and resources where appropriate. The panel acknowledged that many centres in the Middle East region do not have internal accredited pathology laboratories for diagnosing fungal infections. However, the group agreed that every effort should be made to diagnose infections to the species level and that a local reference laboratory should be utilized if resources are not available in the local hospital.

Consensus recommendations for treatment of *Candida* infections

The major classes of therapeutic agents for treatment of candidiasis include: polyenes, triazoles, echinocandins and flucytosine. The available evidence for these agents is briefly discussed below.

Amphotericin B (AmB): Amphotericin B deoxycholate (AmB-d) was the standard drug for the treatment of candidiasis for a long time. However, the clinical efficacy was limited due to infusion-related acute reactions and significant nephrotoxicity. Various lipid-based derivatives known as Lipid Formulation AmB (LFAmB), including liposomal amphotericin B (L-AmB) and amphotericin B lipid complex (ABLC), were developed to improve the tolerability profile of AmB-d. These are associated with less toxicity, but are considerably more expensive than AmB-d. Amphotericin B colloidal dispersion (ABCD) is not used frequently because it has a high rate of infusion-related reactions [20—22].

Azoles: Fluconazole, itraconazole, voriconazole and posaconazole exhibit similar activity against most *Candida* species [4]. Each of the azoles has less activity against *C. glabrata* and *C. krusei*. Clinical efficacy of the azoles has been demonstrated in various comparative randomized trials with AmB-d [23—26]. Evidence suggests that voriconazole and fluconazole had similar, but not superior, efficacy to AmB-d but significantly reduced nephrotoxicity [23,24]. A meta-analysis of trials comparing fluconazole with AmB-d found no significant differences in efficacy between these two agents across a range of clinical and microbiological outcomes [24]. Voriconazole was shown to be as effective with fewer side effects as AmB induction therapy, followed by fluconazole in non-neutropenic patients with candidemia [23].

Limited data exist for itraconazole in the treatment of invasive candidiasis. Evidence suggests the use of itraconazole in patients with mucosal candidiasis, especially if treatment with fluconazole fails [27]. Posaconazole does not have an indication for primary candidiasis therapy.

Echinocandins: Echinocandins (caspofungin, anidulafungin and micafungin) are used extensively for treatment of candidemia and invasive candidiasis due to their broad-spectrum activity against *Candida* species, and each has demonstrated success in approximately 75% of patients in randomized clinical trials [4]. Numerous randomized trials have compared the efficacy of echinocandins to either an amphotericin B formulation or fluconazole among patients (the majority of whom were non-neutropenic patients) with invasive candidiasis [28—31]. In one randomized trial, caspofungin demonstrated equivalent efficacy compared to amphotericin B [28]. In another randomized multinational non-inferiority trial comparing micafungin to liposomal amphotericin, the success rates for clinical and microbiologic cure were similar [31]. A recent comparative trial demonstrated that anidulafungin was superior to fluconazole in both *C. albican*s and non-albicans *Candida* infections, favouring the use of echinocandins in severely ill patients [30]. A recent review of pooled data from most large randomized clinical trials on candidemia has concluded a better outcome for patients that were treated with echinocandins [32].

Limited efficacy data exists for use of echinocandins in neutropenic patients; data are mainly derived from small subset analyses of randomized trials and open-label studies [28,29,33,34]. These studies have demonstrated that echinocandins have similar or better response rates compared to the formulations of amphotericin B. Dosage adjustment for renal insufficiency or dialysis is not required for any of the echinocandins. Caspofungin is the only echinocandin for which dosage reduction is recommended for patients with moderate to severe hepatic dysfunction.

Based on the diagnosis, the expert panel provided recommendations for management of *Candida* infections in non-neutropenic and neutropenic patients. Recommendations for specific species and disease conditions are also summarized.

Table 4 Summary of recommendations for proven invasive *Candida* infections.

Condition	Primary	Alternative
Proven *Candida* infection		
Non-neutropenic patients	Micafungin (A) Anidulafungin (A) Caspofungin (A)	LFAmB (A) Voriconazole (A) Fluconazole (A) AmB-d (A)
Neutropenic patients	Micafungin (B) Caspofungin (B) Anidulafungin (B)	LFAmB (B) Voriconazole (B) AmB-d (B) Fluconazole (B)[a]
Suspected *Candida* infection		
Non-neutropenic patients	Micafungin (C) Anidulafungin (C) Caspofungin (C)	LFAmB (B) Voriconazole (B) Fluconazole (B)[a] AmB-d (B)
Neutropenic patients	Caspofungin (A) LFAmB (A)	Voriconazole (B) Itraconazole (B)[a] IV/PO solution AmB-d (B) Fluconazole (B)[a] Micafungin (C) Anidulafungin (C)

AmB-d: amphotericin B-deoxycholate; LFAmB: lipid formulation of amphotericin B.
[a] Use in stable patient with no prior azole use.

Recommendations for treatment of proven *Candida* infections

Non-neutropenic patients (Table 4)

In non-neutropenic patients, an echinocandin (micafungin, anidulafungin, caspofungin) is strongly recommended for first-line treatment for most adult patients (A). As a result of their efficacy, favorable safety profile and very few drug interactions, the echinocandins are favored for initial therapy for patients who have a recent history of exposure to an azole, a moderately severe to severe illness (i.e. are hemodynamically unstable), an allergy or intolerance to azoles or AmB, or a high risk of infection with *C. krusei* or *C. glabrata* (Tables 4 and 5).

Voriconazole and fluconazole are recommended as alternative treatments (A). Based on tolerance and/or availability, the expert panel also recommends LFAmB (which includes ABLC and L-AmB) and AMB-d as alternative therapies (A). The IDSA 2009 guidelines recommend fluconazole in patients who have mild to moderate illness (i.e. are hemodynamically stable), who have no previous exposure to azoles, and who do not belong in a group at high risk of *C. glabrata* infection (e.g. elderly patients, patients with cancer, and patients with diabetes). The expert panel recommend switching from echinocandin to fluconazole for patients with isolates that are likely to be susceptible to flucanazole (e.g. *C. albicans* and *C. parapsilosis*) and are clinically stable. Voriconazole has a very important role in patients who have fluconazole-resistant isolates of *C. krusei, C. guilliermondii* or *C. glabrata* that have documented voriconazole susceptibility and who are ready for transition from an echinocandin or AmB to oral therapy.

According to IDSA 2009 guidelines, although posaconazole shows *in vitro* activity against *Candida* species, there is insufficient clinical data to make an evidence-based recommendation for treatment of candidiasis other than oropharyngeal candidiasis [4]. The expert panel were in concurrence with IDSA 2009 recommendations. The expert panel does not recommend itraconazole in the treatment of invasive candidiasis due to the lack of published clinical data, the potential for unfavourable drug interactions and drug-related adverse events.

Neutropenic patients (Table 4)

The efficacy of antifungal agents has not been evaluated in neutropenic patients by robust randomized clinical trials, and is obtained from small single-arm studies or subset analyses of randomized studies that recruited non-neutropenic patients [4]. In the past, AmB formulation has been used for treatment of candidemia in the neutropenic patient. Newer agents like voriconazole and the echinocandins are being used increasingly in this patient

Table 5 Species-specific recommendations.

Species	Primary therapy	Alternative therapy
Candida glabrata	Echinocandin (B)	LFAmB (C) AmB-d (C)
Candida parapsilosis	Fluconazole (B) LFAmB (B) [in neutropenic patients]	AmB-d (B)
Candida krusei	Echinocandin (B)	LFAmB (B) Voriconazole (B)

AmB-d: amphotericin B-deoxycholate; LFAmB: lipid formulation of amphotericin B.

group, despite limited supporting data [4]. A recent systematic review of 17 randomized controlled treatment trials revealed benefit with non-polyene compounds compared to AmB [35]. The results also demonstrated that echinocandins were associated with the benefit of favourable outcomes with the least side effects and toxicity.

The expert panel recommends all three echinocandins (micafungin, anidulafungin and caspofungin) for first-line treatment in neutropenic patients (B). Voriconazole, LFAmB and AmB-d are recommended as alternative therapies (B). Fluconazole is recommended as an alternative treatment in patients who are stable with no recent azole exposure (B).

Treatment of specific species (Table 5)

C. glabrata: The expert panel recommend using echinocandins in non-nuetropenic and nuetropenic patients (B). It is advisable not to switch to fluconazole or voriconazole without confirmation of isolate susceptibility. Continuation of fluconazole or voriconazole therapy in patients who are stable and have negative culture is reasonable. In neutropenic patients, alternate treatment includes AmB-d orLFAmB, if feasible (C) (Table 5).

C. parapsilosis: Fluconazole (B) is the preferred treatment option in non-neutropenic patients due to the decreased *in vitro* activity of echinocandins against *C. parapsilosis* and reports of echinocandin resistance among selected isolates. In neutropenic patients, LFAmB (B) is also preferred. AmB-d (B) is recommended only if there is no access to fluconazole or LFAmB. If the patient is receiving an echinocandin, is clinically stable, and follow-up culture results are negative, completing therapy with echinocandin is acceptable.

C. krusei: Echinocandins are recommended as a first-line treatment (B). According to IDSA guidelines a short course of intravenous echinocandin therapy (3—5 days) followed by transition to oral fluconazole or voriconazole is a reasonable approach to the treatment of candidemia in a stable patient. However, there are not many clinical data to support this management strategy. In neutropenic patients, alternative treatments are LFAmB (B) and voriconazole (B).

Intravascular catheters

The expert panel strongly recommends that intravascular catheters be removed in non-neutropenic patients when candidemia is recognized (C). Catheter removal is a controversial issue. While studies have demonstrated that catheter removal is associated with shorter duration of candidemia [36] and reduced mortality [36,37], some data suggest that early removal of central venous catheters are not associated with clinical benefit [38].

The expert panel suggests venous catheter removal including the removal of tunneled catheters, if feasible, for neutropenic patients who have persistent candidemia or hemodynamically unstable (B).

Duration of therapy

The duration of therapy in most clinical trials was a minimum of two weeks following negative blood cultures; this strategy was associated with few complications and relapses [25,26,28—30]. Based on this evidence, the expert panel recommends that therapy should be continued for 14 days after resolution of all signs and symptoms of candidemia infection and the clearance of organisms from the bloodstream. For neutropenic patients, resolution of neutropenia should also be considered.

Consensus recommendations for empirical treatment of suspected *Candida* infection (Table 4)

Early identification and treatment of patients at risk of *Candida* infection is critical to successful therapy. It has been increasingly recognized that waiting for cultures to become positive is an unsatisfactory approach in severely ill patients or those at high risk of invasive *Candida* infection, and that risk stratification and early empiric therapy are

required to improve patient outcomes. Evidence suggests that adequate empirical therapy has been associated with reduced mortality and reduced incidence of proven candidiasis [4,39]. However the benefit must be weighed against the risk of toxicity, costs and emergence of resistance [4]. The 2009 IDSA guidelines recommend that empiric antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and who have persistent fevers despite antibacterial therapy.

Non-neutropenic patients

In non-neutropenic patients, all three echinocandins (micafungin, anidulafungin or caspofungin) are recommended as initial therapy (C), especially in patients with moderately severe to severe illness, recent azole exposure or patients who are at high risk of infection due to *C. glabrata* or *C. krusei*. Fluconazole is recommended as an alternative therapy, especially in non-critically ill patients with known azole-susceptible *Candida* species or who have no prior exposure to azoles (B). Other recommended alternate therapies include voriconazole, LFAmB and AmB-d (B).

The panel agreed that in non-neutropenic patients, empirical treatment should be continued for 14 days.

Neutropenic patients

The panel recommends using caspofungin or LFAmB as first-line empiric therapy in neutropenic patients (A). Alternative therapies include voriconazole IV (B), itraconazole [IV/PO solution] (B), and AmB-d [IV] (B). Due to its narrow spectrum, fluconazole (B) can be used as an alternative therapy in patients who are stable with no prior azole use. Micafungin and anidulafungin can be used as alternative therapy, although there are limited data to support their use (C).

The expert panel recommends that antifungal treatment can be stopped upon resolution of all signs and symptoms of candidemia and resolution of neutropenia for at least 48 h.

The expert panel recommends using the doses within the prescribing information unless otherwise stated. Please refer to Table 6 for the recommended dosing of each agent.

Table 6 Dosing recommendations.

Agent	Dose
Micafungin	100 mg daily
Anidulafungin	Loading dose 200 mg, then 100 mg daily
Caspofungin	Loading dose 70 mg, then 50 mg daily
Voriconazole	400 mg [6 mg/kg] every 12 hours for 2 days, then 200 mg [3 mg/kg] every 12 hours
Fluconazole	Loading dose 800 mg [12 mg/kg] then 400 mg [6 mg/kg] daily
LFAmB	3—5 mg/kg daily
AmB-d	0.5—1.0 mg/kg daily

AmB-d: amphotericin B-deoxycholate; LFAmB: lipid formulation of amphotericin B.

Disease specific recommendations (Table 7)

Chronic disseminated candidiasis

Evidence for treatment of chronic disseminated candidiasis has been reported mainly with fluconazole, AmB-d and LFAmB [40—44]. Fluconazole is recommended as first-line treatment in stable patients (B), while LFAmB and AmB-d are preferred in patients who are acutely ill or have refractory disease (B). Alternative therapy can include AmB (B) or an echinocandin (B), followed by fluconazole. The expert panel advises that treatment should be continued for weeks to months until calcification or resolution of hepatic lesions occurs, and should be continued through periods of immunosuppression (e.g. chemotherapy, transplantation) (Table 7).

Osteoarticular *Candida* infections

AmB-d, fluconazole and, more recently, caspofungin have been studied for treatment of osteoarticular *Candida* infections [4]. For osteomyelitis and septic arthritis, the expert panel agreed that fluconazole (C) or LFAmB followed by fluconazole (C) may be used as first-line treatment. Echinocandin (C) or AmB-d (C), followed by fluconazole is recommended as alternative therapy. Surgical debridement is suggested in all cases. For prosthetic joint infections, device removal is recommended in most cases (B). The recommended antifungal therapy includes fluconazole, LFAmB, an echinocandin or AmB-d for at least six weeks (C). The expert panel recommends chronic suppression with fluconazole if the device cannot be removed (C).

CNS candidiasis

Optimal treatment of Central Nervous System (CNS) candidiasis has not been evaluated by randomized controlled trial, with the majority of evidence available for AmB-d [45—48]. The panel prefers LFAmB with or without flucytosine (C) as initial treatment as it is associated with less toxicity compared to AmB-d. Liposomal amphotericin B may achieve better concentrations in the CNS than ABLC [49]. Fluconazole as a step-down therapy

Table 7 Disease-specific guidelines.

Condition	Primary therapy	Alternative therapy
Chronic disseminated candidiasis	• Fluconazole 400 mg (6 mg per kg) daily, for stable patients (B) • LFAmB 3—5 mg per kg daily (B) or AmB-d 0.5—0.7 mg per kg daily, for severely ill patients (B) • AmB for 1—2 weeks, followed by oral fluconazole 400 mg (6 mg/kg) daily (B)	• AmB (B) or an echinocandin[a] (B), followed by fluconzole
Osteoarticular *Candida* infection		
Osteomyelitis	• Fluconazole 400 mg (6 mg per kg) daily for 6—12 months (B) • LFAmB 3—5 mg per kg daily for several weeks, then fluconazole for 6—12 months (C)	• Echinocandin[a] (C) or AmB-d (C) 0.5—1 mg/kg daily for several weeks then fluconazole for 6—12 months
Septic arthritis	• Fluconazole 400 mg (6 mg per kg) daily for at least six weeks (B) • LFAmB 3—5 mg per kg daily for several weeks, then fluconazole to completion (B)	• Echinocandin[a] (C) or AmB-d (C) 0.5—1 mg/kg daily for several weeks then fluconazole to completion
CNS candidiasis	• LFAmB 3—5 mg per kg, with or without flucytosine 25 mg per kg po, four times daily for several weeks (C)	• Step down to fluconazole 400—800 mg (6—12 mg per kg) daily (C)
Candida endophthlamitis	• AmB-d 0.7—1 mg per kg, with flucytosine 25 mg per kg po, four times daily (C) • Fluconazole 6—12 mg per kg daily (B)	• LFAmB 3—5 mg per kg daily (C) • Voriconazole 6 mg per kg every 12 h for two doses, then 3—4 mg per kg every 12 h (C) • Echinocandin[a] (C)
Cardiovascular system		
Pericarditis/myocarditis/ suppurative thrombophlebitis)	• LFAmB 3—5 mg per kg daily (C) • Fluconazole 400—800 mg (6—12 mg per kg) daily (C)	• Echinocandin[a] (C) • Step down to fluconazole 400—800 mg (6—12 mg per kg) daily (C)
Endocarditis	• Echinocandin[a] (C) • LFAmB 3—5 mg per kg daily, four times daily with or without 5-FC, 25 mg per kg, four times daily (C)	• Step down to fluconazole 400—800 mg (6—12 mg per kg) daily (C)
Candiduria		
Asymptomatic cystitis	• Therapy not usually indicated, unless patient is at high risk (e.g. neutropenic adults) or is undergoing urologic procedures (C) • Elimination of predisposing factors recommended	—
Symptomatic cystitis	• Fluconazole, 200 mg (3 mg per kg) daily for 2 weeks (C)	• AmB-d 0.3—0.6 mg per kg for 1—7 days (C) • Flucytosine, 25 mg per kg four times daily for 7—10 days (C)

Table 7 (*Continued*)

Condition	Primary therapy	Alternative therapy
Pyelonephritis	• AmB-d, 0.5—0.7 mg per kg daily, with or without flucytosine, 25 mg per kg four times daily (C)	• AmB-d, 0.5—0.7 mg per kg daily, with or without flucytosine, 25 mg per kg po four times daily (C) • Flucytosine alone for 2 weeks (C)
Urinary fungus balls	• Surgical removal • Fluconazole, 200—400 mg (3—6 mg per kg) daily (C) • AmB-d, 0.5—0.7 mg per kg daily, with or without flucytosine, 25 mg per kg po four times daily (C)	

[a] Dosing of echinocandin in adults is as follows: anidulafungin 200 mg loading dose, then 100 mg daily; caspofungin 70 mg loading dose, then 50 mg daily; and micafungin 100 mg daily.

(C) is suggested following response to LFAmB with or without flucytosine. Therapy should be continued for weeks to months until resolution of symptoms and CSF abnormalities, and clearance on imaging. Removal of infected ventricular devices is recommended by the experts (B).

Candida endophthlamitis

There is limited evidence for management of *Candida* endophthlamitis, with no controlled trials of treatment regimens. AmB-d with flucytosine (B) can be used as first-line treatments for advancing lesions or lesions threatening the macula, whereas fluconazole (B) can be used in less severe cases. LFAmB (C), voriconazole (C) or an echinocandin (C) can be used as an alternative treatment for those who are not responding to primary therapy with AmB-d or fluconazole. The recommended duration of therapy is at least 4—6 weeks and is determined by repeated examinations to verify resolution. For patients with severe endophthalmitis and vitreitis, the expert panel strongly recommends surgical intervention with partial vitrectomy and intravitreal antifungal therapy with AmB-d (B).

Cardiovascular system

- Pericarditis, myocarditis and suppurative thrombophlebitis: LFAmB (C), AmB-d or fluconazole (C) in combination with either a pericardial window or pericardiectomy can be used as first-line therapy. Recommended alternative therapies include an echinocandin (C) and step-down therapy to fluconazole in stable patients (C). Duration of therapy is often several months.

  For suppurative thrombophlebitis, surgical incision and drainage or resection of the vein is recommended, if feasible; treatment should be continued for at least two weeks after resolution of candidemia. Treatment should be discontinued upon resolution of the thrombus and if clinical and culture data are encouraging.
- Endocarditis: Echinocandin (micafungin, anidulafungin and caspofungin) (C) or LFAmB with or without flycytosine (C) could be used as first-line therapies. Step down to fluconazole could be used as an alternative in patients who are clinically stable with negative blood culture. Valve replacement is strongly recommended. Following surgery, treatment should be continued for at least 6 weeks and should be continued for a longer duration in patients with perivalvular abscesses and other complications. In patients who are unable to undergo surgical removal of the valve, chronic suppression with fluconazole is recommended; lifelong suppressive therapy is recommended for prosthetic valve endocarditis if the valve cannot be replaced.

Candiduria

For asymptomatic candiduria, therapy is not usually indicated unless the patient is at high risk (e.g. neutropenic) or is undergoing urologic procedures. The panel recommends elimination of predisposing factors which often results in resolution of candiduria. For patients undergoing urologic procedures, fluconazole or AmB-d is recommended for several days before and after the procedure (C).

- For symptomatic candiduria, fluconazole is recommended for 2 weeks. Alternate therapies include AmB-d or oral flucytosine. AmB-d bladder irrigation is recommended only for patients with refractory fluconazole-resistant organisms (e.g. *Candida krusei, C. glabrata*) (C).
- Treatment recommendations for pyelonephritis include fluconazole therapy for two weeks;

AmB-d with or without flucytosine or flucytosine alone is recommended alternatives (C).

- For urinary fungus balls, the panel strongly recommends surgical removal. Primary therapy includes fluconazole and AmB-d with or without flucytosine. Local irrigation with AmB-d may be a useful adjunct to systemic antifungal therapy. Treatment duration should be until resolution of symptoms and negative urine cultures (C).

Monitoring performance

The expert panel agrees with the performance measures recommended by IDSA 2009 guidelines [4] and advise the following:

1. Delay in initiation of antifungal therapy has been associated with increased mortality. The expert panel therefore recommends commencement of antifungal therapy within 24 h following a positive blood culture. The clearance of *Candida* from the bloodstream should be confirmed with follow-up blood cultures which must be performed daily or every other day until demonstration of negative culture for yeast.
2. The expert panel suggests conducting dilated ophthalmological evaluation for all patients with candidemia to look for evidence of *Candida* endophthalmitis. This is done when candidemia appears to be controlled and upon resolution of neutropenia in neutropenic patients.

Limitations and future direction

This article outlines the recommendations for management of *Candida* infections in the Middle East region. However, there are several limitations to optimal management of invasive *Candida* infections in the region. The most important limitation is the paucity of regional data regarding epidemiology, diagnosis, prophylaxis, empiric and pre-emptive treatment strategies. Priority should be given towards research of these topics in initiate improve management of *Candida* infections in the region.

The panel acknowledged that not all hospitals in the Middle East have their own accredited pathology laboratories. However, efforts should be made to send samples to reference laboratories within the region. Efforts should also be made to enable *Candida* speciation and susceptibility testing at the local laboratories; germ-tube testing should be carried out in all cases. In addition to the above limitations, access to treatments and reimbursement remains a challenge in this region.

The recommendations provided in this article are aimed to assist the clinicians to better manage invasive *Candida* infections and should be used along with clinical judgement. The expert panel hopes this will help in reducing mortality rates from invasive *Candida* infections in the region.

Funding

No funding sources.

Competing interests

The authors who contributed to this article have disclosed the following industry relationships: Dr. Adel Alothman reports receiving honoraria for lectures from Pfizer, MSD and Alhikma Companies. Dr. Tariq Al Musawi reports receiving honoraria for lectures from Pfizer, GSK, Astra Zeneca and MSD. Dr. Hail M. Al-Abdely, Dr. Muna Almaslamani and Dr. Jameela Al Salman have nothing to declare. Dr. Nadine Yared reports receiving honoraria for lectures from Pfizer and MSD. Dr. Adeel A. Butt reports receiving investigator initiated research support from Pfizer and Merck to his institution. Dr. Abdulhakeem Althaqafi reports receiving honoraria for lectures and payment for board membership from Pfizer and MSD, and research grant from Sanofi-Pasture. Dr. Nirvana Raghubir and Dr. Waleed El Morsi are employed by Pfizer.

All authors received honoraria and support to travel to the meeting at which these guidelines were discussed (funded by Pfizer).

Ethical approval

Not required.

Author contributions

All authors contributed extensively to the work presented in this manuscript. Dr. Alothman led the development of the manuscript. All authors participated in the review, contributed to the content and approved all sections of the manuscript.

Acknowledgement

Medical writing support in the development of this manuscript was provided by Dwiti Narayanan from Choice Healthcare Solutions and funded by Pfizer.

References

[1] McNeil MM, Nash SL, Hajjeh RA, Phelan MA, Conn LA, Plikaytis BD, Warnock DW. Trends in mortality due to invasive mycotic diseases in the United States, 1980—1997. Clin Infect Dis 2001;33:641—7.
[2] Fridkin SK, Jarvis WR. Epidemiology of nosocomial fungal infections. Clin Microbiol Rev 1996;9:499—511.
[3] Rangel-Frausto MS, Wiblin T, Blumberg HM, Saiman L, Patterson J, Rinaldi M, et al. National epidemiology of mycoses survey (NEMIS): variations in rates of bloodstream infections due to Candida species in seven surgical intensive care units and six neonatal intensive care units. Clin Infect Dis 1999;29:253—8.
[4] Pappas PG, Kauffman CA, Andes D, Benjamin Jr DK, Calandra TF, Edwards Jr JE, 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—35.
[5] 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—7.
[6] Bow EJ, Evans G, Fuller J, Laverdiere 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—50.
[7] Pagano L, Lumb J. Update on invasive fungal disease. Future Microbiol 2011;6:985—9.
[8] Raoul H, Ursula F, Bertrand G, Patricia R, Anne T, Catherine C. Antifungal therapy in leukemia patients; 2011.
[9] Thursky KA, Playford EG, Seymour JF, Sorrell TC, Ellis DH, Guy SD, et al. Recommendations for the treatment of established fungal infections. Intern Med J 2008;38:496—520.
[10] Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309—17.
[11] Tortorano AM, Kibbler C, Peman J, Bernhardt H, Klingspor L, Grillot R. Candidaemia in Europe: epidemiology and resistance. Int J Antimicrob Agents 2006;27:359—66.
[12] 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—44.
[13] 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. Med Mycol 2003;41:521—8.
[14] Hassan I, Powell G, Sidhu M, Hart WM, Denning DW. Excess mortality, length of stay and cost attributable to candidaemia. J Infect 2009;59:360—5.
[15] Akbar DH, Tahawi AT. Candidemia at a University Hospital: epidemiology, risk factors and predictors of mortality. Ann Saudi Med 2001;21:178—82.
[16] Pfaller MA, Diekema DJ, Gibbs DL, Newell VA, Ellis D, Tullio V, et al. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997—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;48:1366—77.
[17] Ruhnke M, Rickerts V, Cornely OA, Buchheidt D, Glockner A, Heinz W, et al. Diagnosis and therapy of Candida infections: joint recommendations of the German Speaking Mycological Society and the Paul-Ehrlich-Society for Chemotherapy. Mycoses 2011;54:279—310.
[18] Peman J, Zaragoza R. Current diagnostic approaches to invasive candidiasis in critical care settings. Mycoses 2010;53:424—33.
[19] de Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, 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;46:1813—21.
[20] Deray G. Amphotericin B nephrotoxicity. J Antimicrob Chemother 2002;49(Suppl. 1):37—41.
[21] Walsh TJ, Hiemenz JW, Seibel NL, Perfect JR, Horwith G, Lee L, et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin Infect Dis 1998;26:1383—96.
[22] Wingard JR. Lipid formulations of amphotericins: are you a lumper or a splitter? Clin Infect Dis 2002;35:891—5.
[23] Kullberg BJ, Sobel JD, Ruhnke M, Pappas PG, Viscoli C, Rex JH, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet 2005;366:1435—42.
[24] Kontoyiannis DP, Bodey GP, Mantzoros CS. Fluconazole vs. amphotericin B for the management of candidaemia in adults: a meta-analysis. Mycoses 2001;44:125—35.
[25] Rex JH, Bennett JE, Sugar AM, Pappas PG, van der Horst CM, Edwards JE, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. Candidemia Study Group and the National Institute. N Engl J Med 1994;331:1325—30.
[26] Rex JH, Pappas PG, Karchmer AW, Sobel J, Edwards JE, Hadley S, et al. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. Clin Infect Dis 2003;36:1221—8.
[27] Eichel M, Just-Nubling G, Helm EB, Stille W. Itraconazole suspension in the treatment of HIV-infected patients with fluconazole-resistant oropharyngeal candidiasis and esophagitis. Mycoses 1996;39(Suppl. 1):102—6.
[28] Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002;347:2020—9.
[29] Kuse ER, Chetchotisakd P, da Cunha CA, Ruhnke M, Barrios C, Raghunadharao D, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet 2007;369:1519—27.
[30] Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007;356:2472—82.
[31] Shorr AF, Wu C, Kothari S. Outcomes with micafungin in patients with candidaemia or invasive candidiasis due to *Candida glabrata* and Candida krusei. J Antimicrob Chemother 2011;66:375—80.
[32] 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—22.
[33] Pappas PG, Rotstein CM, Betts RF, Nucci M, Talwar D, de Waele JJ, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis 2007;45:883—93.
[34] Betts R, Glasmacher A, Maertens J, Maschmeyer G, Vazquez JA, Teppler H, et al. Efficacy of caspofungin against invasive Candida or invasive Aspergillus infections in neutropenic patients. Cancer 2006;106:466—73.
[35] Kanji JN, Laverdiere M, Rotstein C, Walsh TJ, Shah PS, Haider S. Treatment of invasive Candidiasis in neutropenic patients: systematic review of randomized controlled treatment trials. Leuk Lymphoma 2013;24(7):1479—87.
[36] Nguyen MH, Peacock Jr JE, Tanner DC, Morris AJ, Nguyen ML, Snydman DR, et al. Therapeutic approaches in patients with candidemia. Evaluation in a multicenter, prospective, observational study. Arch Intern Med 1995;155: 2429—35.
[37] Luzzati R, Amalfitano G, Lazzarini L, Soldani F, Bellino S, Solbiati M, et al. Nosocomial candidemia in non-neutropenic patients at an Italian tertiary care hospital. Eur J Clin Microbiol Infect Dis 2000;19:602—7.
[38] Nucci M, Anaissie E, Betts RF, Dupont BF, Wu C, Buell DN, et al. Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. Clin Infect Dis 2010;51:295—303.
[39] Guery BP, Arendrup MC, Auzinger G, Azoulay E, Borges Sa M, Johnson EM, et al. Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part II Treatment. Intens Care Med 2009;35:206—14.
[40] Thaler M, Pastakia B, Shawker TH, O'Leary T, Pizzo PA. Hepatic candidiasis in cancer patients: the evolving picture of the syndrome. Ann Intern Med 1988;108:88—100.
[41] Walsh TJ, Whitcomb PO, Revankar SG, Pizzo PA. Successful treatment of hepatosplenic candidiasis through repeated cycles of chemotherapy and neutropenia. Cancer 1995;76:2357—62.
[42] Gokhale PC, Barapatre RJ, Advani SH, Kshirsagar NA, Pandya SK. Successful treatment of disseminated candidiasis resistant to amphotericin B by liposomal amphotericin B: a case report. J Cancer Res Clin Oncol 1993;119:569—71.
[43] Anaissie E, Bodey GP, Kantarjian H, David C, Barnett K, Bow E, et al. Fluconazole therapy for chronic disseminated candidiasis in patients with leukemia and prior amphotericin B therapy. Am J Med 1991;91:142—50.
[44] Kauffman CA, Bradley SF, Ross SC, Weber DR. Hepatosplenic candidiasis: successful treatment with fluconazole. Am J Med 1991;91:137—41.
[45] Sanchez-Portocarrero J, Perez-Cecilia E, Corral O, Romero-Vivas J, Picazo JJ. The central nervous system and infection by Candida species. Diagn Microbiol Infect Dis 2000;37:169—79.
[46] Nguyen MH, Yu VL. Meningitis caused by Candida species: an emerging problem in neurosurgical patients. Clin Infect Dis 1995;21:323—7.
[47] Voice RA, Bradley SF, Sangeorzan JA, Kauffman CA. Chronic candidal meningitis: an uncommon manifestation of candidiasis. Clin Infect Dis 1994;19:60—6.
[48] Geers TA, Gordon SM. Clinical significance of Candida species isolated from cerebrospinal fluid following neurosurgery. Clin Infect Dis 1999;28:1139—47.
[49] Groll AH, Giri N, Petraitis V, Petraitiene R, Candelario M, Bacher JS, et al. Comparative efficacy and distribution of lipid formulations of amphotericin B in experimental *Candida albicans* infection of the central nervous system. J Infect Dis 2000;182:274—82.
[50] Al-Hedaithy SS. The yeast species causing fungemia at a university hospital in Riyadh, Saudi Arabia, during a 10-year period. Mycoses 2003;46:293—8.
[51] Bukharie HA. Nosocomial candidemia in a tertiary care hospital in Saudi Arabia. Mycopathologia 2002;153:195—8.
[52] Khan ZU, Chugh TD. Invasive fungal infections in Kuwait: a retrospective study. Indian J Chest Dis Allied Sci 2000;42:279—87.