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REVIEW

# Invasive candidiasis in critical care setting, updated recommendations from "Invasive Fungal Infections-Clinical Forum", Iran

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## Abstract

Invasive candidiasis (IC) bears a high risk of morbidity and mortality in the intensive care units (ICU). With the current advances in critical care and the use of wide-spectrum antibiotics, invasive fungal infections (IFIs) and IC in particular, have turned into a growing concern in the ICU. Further to blood cultures, some auxil-

iary laboratory tests and biomarkers are developed to enable an earlier detection of infection, however these test are neither consistently available nor validated in our setting. On the other hand, patients' clinical status and local epidemiology data may justify the empiric antifungal approach using the proper antifungal option. The clinical approach to the management of IC in febrile, non-neutropenic critically ill patients has been defined in available international guidelines; nevertheless such recommendations need to be customized when applied to our local practice. Over the past three years, Iranian experts from intensive care and infectious diseases disciplines have tried to draw a consensus on the management of IFI with a particular focus on IC in the ICU. The established IFI-clinical forum (IFI-CF), comprising the scientific leaders in the field, has recently come up with and updated recommendation on the same (June 2014). The purpose of this review is to put together literature insights and Iranian experts' opinion at the IFI-CF, to propose an updated practical overview on recommended approaches for the management of IC in the ICU.



**Key words:** Invasive candidiasis; Intensive care unit; IFI-clinical forum; Recommendations; Iran

**Core tip:** The present consensus statement has attempted to summarize the practical highlights regarding the management of Invasive Candidiasis (IC) in critical care setting. This easy-to-follow clinical pathway is expected to be not only of interest but also of clinical use for those who deal with the management of invasive fungal infections in hospital setting and especially the intensive care units. The focus of this paper is the concept of timely management of IC in critically ill patients.

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## INTRODUCTION

Despite the remarkable progress in the diagnostic and therapeutic approaches, infections continue to be a critical challenge in the intensive care units (ICUs) worldwide[1]. The use of wide-spectrum antibiotics, advanced care in the ICU and improved knowledge on fungal infections have potentially led to an increased incidence of invasive fungal infections (IFIs) especially in critically ill and immunosuppressed patients[2-4]. IFIs are shown to be often hard to diagnose and treat in critical care setting[4]. Timely management of IFIs based on risk stratification and empirical approach is shown to be of meaningful clinical benefit, meanwhile dependence on the culture results and relying on fungal biomarkers may delay clinical decisions and lead to potential complications, morbidity and mortality in such patients[5,6]. There are risk prediction models which suggest empirical approach for patients who are supposed to significantly benefit from empirical antifungal therapy[7,8]. Despite the validated clinical impact of applying IFIs' predictive tools such as Candida Score[9,10], many clinicians seem not to be consistently using them in routine practice[11]. This report is based on the communicated insights and position statements within the IFI-clinical forum comprising an Iranian panel of intensive care experts. The present article summarizes a literature review on the role of IFIs in mortality and morbidity in critical care setting, experts' panel inputs as well as updates on the local consensus and international guidelines with regard to the management of invasive candidiasis (IC) in ICU patients.

## THE UNMET NEED WHICH PROMPTED AN "IFI-CLINICAL FORUM" ESTABLISHMENT

In compliance with the international guidelines on the management of IC in ICU, a group of Iranian experts in the fields of intensive care and infectious disease consolidated a consensus as a simple algorithmic approach in the management of IC in critical care setting in 2013[12]. This was primarily rooting in an earlier local consensus on the same, published in 2011; while the first report was predominantly based upon the infectious disease experts' opinion[13]. Pursuant to the above publications, an IFI-Clinical Forum (IFI-CF) comprising Iranian critical care experts and infectious disease specialists was established in 2014. The IFI-CF was formed to pursue clinical research, idea exchange and regular updates and recommendations with regard to optimal management of IFIs. The forum attempts to improve the current situation in the diagnosis and management of IC in critical care units by means of continued education, research and promoting evidence-based practice.

To reach the above, field experts from different universities across Iran attended a round table discussion on 26-27 June 2014. Discussions in this clinical forum revolved around updated epidemiologic insights on IC in ICU, the related diagnostic challenges, therapeutic approaches and proper antifungal options in ICU-admitted patients afflicted with IC.

The meeting objectives, established as part of the planning process, were used to guide development of meeting content and activities. Following two days of scientific debates, reviewing evidence and case discussions, the panel could unanimously draw an updated recommendation for the management of IC in the ICU. This meeting and similar future ones will hopefully allow opti-

mizing models of patient care with regard to IFIs in ICU through an inter-professional influence.

Materializing the above perspective is believed to depend upon five tenets including: 1-classifying the critically ill patients' risk for IFIs, 2-defining a timely and reasonable approach for treating IFIs in ICU-admitted patients, 3-developing center-based algorithms for diagnosis, treatment and surveillance of ICU patients with high risk of IFIs, as epidemiology may differ center by center, 4-determining advantages and disadvantages of antifungal options when used in the ICU and 5-optimizing antifungal treatment paradigm in our local setting for ICU patients who are at increased risk or clinical suspicion for IFIs.

## LITERATURE REVIEW, PARTICIPANTS AND GROUP CONSENSUS

A systematic literature search in PubMed, Scopus, Cochrane and Google Scholar databases (1990-2014) was conducted using the combination of our keywords including invasive fungal infections, ICU, diagnosis, treatment approach, antifungal therapy and recommendations. Following the cross-check, documents describing the significance of IFIs in ICU and recommendations for diagnosis and treatment approaches were isolated for review and discussions. Most recent guidelines[12,14-17] and relevant papers were circulated among all IFI-CF attendees one month prior to the meeting.

The IFI-CF delegates discussed the available evidence, shortcomings and clinical challenges in the management of IFIs and particularly IC in ICU-admitted patients. Each delegate was invited based on his/her expertise in the management of IC and other fungal infections in critical care setting. All experts actively participated during the plenary talks, problem-based round table discussions and case studies over a 2-d interactive discussion forum. Through a point-to-point systematic approach and discussions on key issues such as: 1-local epidemiology of IFIs, 2-preferred diagnostic and therapeutic approaches, 3-implication of risk prediction tools and 4-optimized antifungal therapy, the available evidence as well as participants' inputs/responses were compiled to draw a clinical pathway.

## EPIDEMIOLOGIC INSIGHTS ON INVASIVE CANDIDIASIS; A GLOBAL AND LOCAL PROBLEM ON THE RISE

The current advances in critical care and the advent of broad-spectrum antibiotics not only have resulted in patients' longer survival but also in increasing the incidence of opportunistic infections such as IFIs over the past decade[18]. Currently, IFIs constitute a clinical issue on the rise in the ICUs both in the developing and developed world[19,20]. Predisposing factors such as patients' complicated medical or surgical status, invasive bedside procedure and wide administration of antibiotics have contributed to increased rate of IFIs, mainly IC and invasive aspergillosis (IA), in the ICU[21-23]. *Candidemia* is thus far known to be the most prevalent fungal infection afflicting ICU patients[23]. According to an elegant survey which was carried out in over 1000 ICUs in more than 70 countries, almost one fifth of the isolated pathogens in ICU patients were found to be fungi[24]. Based on the same report, *Candida* species (spp.) were almost 10 times more isolated than aspergillosis and known to be linked with a high mortality and increased hospital length of stay (LoS) as well as medical care cost[24]. Since most of the diagnostic tests lack proper specificity and the culture result normally requires a long time, diagnosis of IFIs and IC in particular remains a challenge. Cumulating evidence suggest that institution of appropriate antifungal therapy upon initial clinical suspicion of IFIs is crucial for a positive outcome[8].

The increasing risk of IFIs in ICU, as well as the criticality of the timely decision making on treatment with the most proper options, have turned IFIs' management to a difficult task for intensivists. While the incidence of IFIs in immunocompromised hosts such as transplanted patients, those with hematologic malignancies or human immunodeficiency virus is significant, this report focuses on IFIs in non-neutropenic critically ill ICU-admitted patients. *Candida* spp. are considered the fourth most common blood stream infection (BSI) isolated from ICU-admitted patients in the West[25]. Where *Candida albicans* (*C. albicans*) has long been regarded as the most prevalent candida type, the relatively recent emergence of non-albicans species such as fluconazole-resistant *Candida krusei* (*C. krusei*) and *Candida glabrata* (*C. glabrata*) has turned into a challenge[20,25]. Recent data suggests an increased incidence of non-albicans *Candida* species. As such, *C. glabrata* and *Candida parapsilosis* (*C. parapsilosis*) are now ranked as second in the Northern Europe and the United States[26,27], and in Latin America and Southern Europe[28,29], respectively. Some predisposing factors including central venous catheters (CVC), total parenteral nutrition (TPN), and prior azole exposure are proposed to result in the emergence of non-albicans *Candida* species. Previous exposure to azole is particularly linked to isolation of *C. krusei* and *C. glabrata*[30].

Based on our practice, the incidence of *Candidemia*, and other fungal infections in Iran seem to be on a steep rise. A local epidemiological survey on IFIs in ICU and transplant wards in Iran suggested *C. albicans*, *Penicillium* spp., *Aspergillus niger*, and *Cladosporium spp.* as the most dominant isolates[31]. According to this report, environmental fungal contamination was found to be more prominent in ICU and the length of hospital stay in critical care setting was strongly associated with the colonization of fungi.

Another local epidemiology research on IFIs in pediatric patients with advanced kidney disease undergoing peritoneal dialysis and adults with kidney transplantation showed the significant impact of *Candidemia* on mortality and morbidity[32]. Furthermore, based on a

multi-center analysis on the prevalence of deep-seated mycosis in immunocompromised hosts in Tehran, Iran, *Candida* spp. were isolated in almost 70% of IFIs cases[33]. Of note, non-albicans spp. comprised almost one third of the *Candida* infections suggesting a possible clinical challenge with fluconazole-resistant *Candida* species[31-34]. The current state of our local epidemiologic insights on IFIs are in line with those of international reports[19,20,35-37]. Further research is needed to draw a clearer map about the incidence of IC and IA and the related subspecies in ICUs of different hospitals, cities and provinces all around Iran. There is an urgent need for institutions to set tight nosocomial IFIs surveillance and protective measures including hand hygiene and aseptic techniques especially upon bedside intensive care interventions.

## DIAGNOSTIC CHALLENGES OF INVASIVE CANDIDIASIS IN THE INTENSIVE CARE UNIT

The diagnosis of IC can be either definitive or probable. The definitive diagnosis is based upon identification of *Candida* in the blood or its histological characterization in tissue[12]. However, in almost half of the instances, specimen may reveal false-negative results and the tissue may not be available in critical care setting. Moreover, awaiting culture results requires much time and defers the clinical decision making. Further to culture and tissue examination, some auxiliary testing methods and biomarkers such as 1-3 beta-D-Glucan (BDG) and pan-fungal polymerase chain reaction (PCR) may suggest probable IC when positive[38-40].

The BDG test detects beta-D-glucan which is an important constituent of the cell wall of pathogenic fungi. This test may however be a subject to a notable false-positive results in patients who receive albumin, immunoglobulins and beta lactams as well as those who are on hemodialysis with cellulose membrane[39]. Furthermore, the test is incapable to differentiate between *Candida* and *Aspergillus*, and remains inconclusive for *Zygomycetes* and *Cryptococcal* infection[39,41]. To indicate the probability of invasive candidiasis based on such a test, a single positive test lacks enough sensitivity thus serial measurements may be required. PCR which detects fungal nucleic acid is found to have a high sensitivity and specificity[42]. Although it is shown to be a highly promising tool in the diagnosis of IFIs, it is neither available nor validated in many settings and its exact use in clinic is questionable[38,43].

Given the time-consuming nature of all the aforementioned laboratory tests, and considering the critical time span for initialization of the therapy, the diagnosis of IC in ICU remains a challenge. Over the past decade some risk prediction models have put forward a pathway to identify patients at increased risk for IFIs. Evidence has suggested clinical benefits of empirical antifungal therapy in non-neutropenic critically-ill patients who remain febrile despite adequate antibiotic therapy and are characterized as high risk[7,8,11].

## RISK STRATIFICATION TOOLS AND PREDICTIVE MODELS; PATH TO A TIMELY APPROACH

Prompt diagnosis and management of IC should be sought as it leads to a significant decline in human and cost burden in the ICU[26,27]. Potential risk factors for IC are compiled into risk prediction models. The proper use of these models in clinical practice would help clinicians identify the high-risk patients who significantly benefit from timely treatment against IC[10,11,44]. Meanwhile, the positive auxiliary tests such as BDG and/or PCR may further add to the accuracy of the risk prediction tools for IC[43,45,46]. Some of these validated tools include the Candida Score[9,47] and Ostrosky-Zeichner[23] model. Calculating the candida score assists a risk-factor-based prediction of IC depending on the presence or absence of four independent risk factors in febrile non-neutropenic critically-ill patients. These risk factors are severe sepsis (2 points), TPN (1 point), multifocal colonization (1 point), and surgery (1 point). The candida score of $\geqslant 3$ is shown to predict IC with a sensitivity and a specificity of 81% and 74%, respectively[9]. These "risk factors" which are proposed as Candida Prediction Rules have been reported in many other studies[47-53]. In addition to Leon's Candida Score[47] and the Ostrosky-Zeichner[23] model, other models such as Agvald-Ohman *et al*[48], Pittet *et al*[49], Hermsen *et al*[51], Paphitou *et al*[52], and Dupont *et al*[53] tried to establish similar frameworks putting together risk factors which contribute to IC while assigning separate relative risk scores for each variable. There is a visible overlap in considered risk factors among these models. Several differences in these studies make it difficult to draw a generally applicable conclusion. Figure 1 summarizes these risk prediction models with risk factors in common amongst them. According to these models, the most commonly considered risk factors such as TPN, use of wide-spectrum antibiotics, CVC, recent gastrointestinal (GI) surgery, use of steroids, dialysis and sepsis are regarded as the most significant contributors to IC in critical care units. Although fungal colonization is known to be linked with the development of *Candidemia*, based on more recent investigations, only a small proportion of colonized patients (3%-25%) are found to develop invasive candidiasis[48,54].

Some of the important differences in IC risk prediction models which are outlined in Figure 1 include the heterogeneity in the examined populations, non-similarity in the underlying disease severity, incidence of IC in centers where the investigations were carried out and the study end-points. It should be noted that most models were defined in surgical ICU populations[23,48,49,51-53].

Intra-abdominal infections secondary to intestinal perforations and anastomotic leakage are also among the risk factors in patients who tend to mostly benefit from

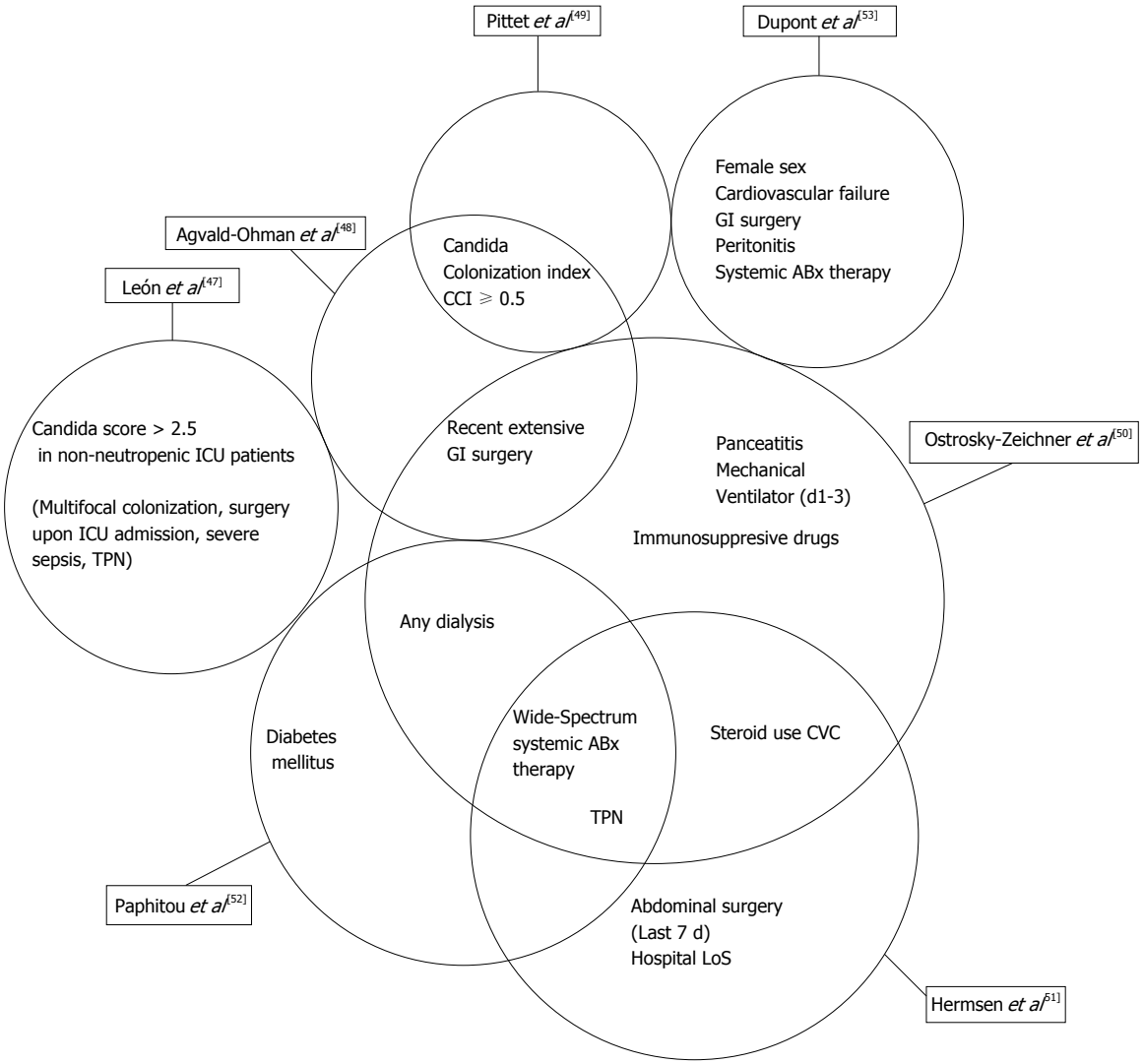


**Figure 1 Risk prediction models for invasive candidiasis in critically ill patients with overlapping contributing factors.** Factors which are common in several risk-prediction models appear to bear a higher relative risk for IC. Given the heterogeneity in study designs and populations, these models can hardly be merged to represent a single paradigm, however their common contributing factors appear to be of higher predictive value for IC prediction. So far, the most widely applied predictive tool for IC is the Leon's Candida Score followed by the Ostrosky-Zeichner's model. ABx: Antibiotic; CCI: Candida colonization index; CVC: Central venous catheter; GI: Gastrointestinal; ICU: Intensive care unit; TPN: Total parenteral nutrition; LoS: Length of stay.

timely antifungal therapy for IC[23]. Fluconazole (FCZ) has been the most abundant antifungal regimen used to treat IC. However the critical concern is the imprudent and wide usage of FCZ which has resulted in an increased resistance and the shift to non-albicans species[55]. Considering the emergence of different *Candida* species rather than *C. albicans*, a more justified approach should be sought to: 1-ensure the timely treatment of IC and 2-cover fluconazole-resistant *Candida* species.

## APPROACH TO INVASIVE CANDIDIASIS IN INTENSIVE CARE UNIT

Treatment approaches towards IC in the ICU comprise prophylaxis, empirical-, preemptive- and targeted-therapy[56].

Prophylaxis, which is done to prevent IFIs development, is characterized as the use of antifungals in high-risk subjects in whom no sign or symptom of infection is so far documented. While FCZ is the main regimen used for this purpose, echinocandins (ECH) have recently been field tested with successful results[57].

On the other hand, initiation of antifungal agents in the presence of multiple risk factors and positive biomarkers such as BDG or PCR or other paraclinical findings is referred to as the pre-emptive treatment[56].

The time of treatment initiation is a key factor for the favorable outcome of IC[56,58]. According to several investigations[58-60], delayed antimicrobial therapy for more than 24 to 48 h negatively affects mortality. As such, in critically-ill or hemodynamically-unstable patients, late antifungal therapy may potentially predict death. Therefore, upon clinical suspicion for *Candidemia*, blood cultures need to be obtained and the treatment should to be administered without proof of IC based on the culture result[17]. This is generally referred to as the empirical approach. Prolonged length of stay in the ICU, surgery,

**Table 1 Recommended treatment options for invasive candidiasis in adult non-neutropenic critically-ill patients based on the current international and local practice guidelines/consensus statements**

| Guideline | First choice | First alternative | Second alternative |
|---|---|---|---|
| ECCMID[15] | ECH | VCZ, L-AMB | FCZ |
| European experts opinion[16] | FCZ (stable patients and susceptible isolates)<br>ECH (severe sepsis, micafungin last choice) | L-AmB | |
| IDSA[14] | FCZ (stable patients, azole naive)<br>ECH (critically ill, Severe sepsis, recent azole exposure) | AmB or L-AmB | VCZ |
| Canadian practice guideline for invasive candidiasis in adults[17] | FCZ (stable patients, azole naïve)<br>ECH (stable or unstable patients, recent azole exposure, avoid in *C. parapsilosis*) | AmB or L-AmB | |
| Consensus statement from the Iranian panel of experts[12] | FCZ (stable, No prior azole exposure, when hospital epidemiology indicates low incidence of NAC Spp.)<br>ECH (hemodynamic instability, Fluconazole resistance) | VCZ, AmB or L-AmB (if available), considering the tolerability and cost *vs* utility | |

ECCMID: European Congress of Clinical Microbiology and Infectious Diseases; ECH: Echinocandins; VCZ: Voriconazole; AmB: Amphotericin B; L-AmB: Liposomal Amphotericin B; FCZ: Fluconazole; IDSA: Infectious Disease Society of America; NAC: Non-albicans *Candida*.

multi-focal *Candida* colonization, sepsis, the use of TPN and/or wide-spectrum antibiotics are the key risk factors which warrant the empirical use of antifungals[14,56]. These are the risk factors considered in the "Candida Score"[47].

According to the latest international guidelines[14-17], the appropriate empirical antifungal choice greatly depends upon the local resistance patterns, likelihood of the presence of non-albicans species, hemodynamic status and criticality of the illness, prior exposure to azoles, pharmacodynamics and pharmacokinetics as well as the potential adverse effects of the selected antifungal, and last but not least, availability and cost of the treatment.

Based on the current guidelines, FCZ, ECH, amphotericin B (AmB) or its lipid formulations [Liposomal Amphotericin B (L-AmB)] and voriconazole (VCZ) are the recommended options while the first two are considered as the preferred choices in many instances. When the patient is hemodynamically unstable or has a prior exposure to FCZ with a high probability of non-albicans *candida* isolation (*i.e.,* or *C. glabrata* or *C. krusei*), echinochandins (*e.g.,* Caspofungin) are the preferred options[14,16]. AmB or L-AmB remain as alternative choices[14,17]. According to the Infectious Disease Society of America guideline, echinocandins should be taken as the first option in hemodynamically-unstable critically-ill patients[14]. Moreover, the most recent Canadian guideline contains similar recommendations about the critically-ill[17]. Caspofungin (CFG) is the only available echinocandin in our practice. De-escalation from CFG to FCZ is warranted in case of favorable clinical response and sterilization of blood cultures[12]. Based on the same guidelines, FCZ is suggested in hemodynamically stable cases without FCZ exposure over the last 30 d[14,15], meanwhile CFG is an equally suggested alternative[14,16,17]. Identification of local and general resistance patterns in our ICUs at different provinces would assist Iranian physicians to take more evidence-based decisions in their daily practice of IFIs management especially in the vulnerable critically-ill patients. In case of catheter-related BSI, an antifungal choice with activity against biofilm (*e.g.,* CFG or AmB) should be considered. CVCs should be removed at earliest. Generally, when the treatment is started, serial blood cultures should be taken to ensure blood sterilization. Treatment duration is 14 d after the negative blood culture[14,17].

Recommendations from the current international guidelines are summarized in Table 1. Table 2 demonstrates the dosing recommendations for the preferred options.

## THE PANEL'S POSITION ON THE MANAGEMENT OF IC IN CRITICALLY-ILL PATIENTS

The current consensus roots in the earlier position statement from the Iranian experts in IFI-CF[12]. This report is considered as an updated recommendation for local practitioners who are involved in the management of IC critically-ill patients. Considering the limitations such as lack of availability or validity of fungal biomarker tests, narrow antifungal options and cost utility issue in our local practice, a customized format of international guidelines clinical pathway was drawn and agreed by the experts' panel. There is less focus on fungal biomarkers in this algorithm compared to the earlier consensus from the Iranian experts. Furthermore; prophylaxis, empirical, pre-emptive and targeted approaches are separately highlighted. The suggested clinical pathway is illustrated in Figure 2.

Some other issues including the importance of catheter removal, fundoscopic examination, frequency of blood cultures after the initiation of antifungal therapy, the possibility to draw a pathway for the patients without clinical response, and the subtype-specific antifungal therapy were also addressed by the panel. Below are some recommendations with regard to the above issues: (1) With respect to the clinical manifestations of suspected IFIs in the ICU and routine clinical evaluations, fundoscopic examination needs to be done by an intensivist. However, this examination has a low negative predictive value against IFIs and treatment should be based on a wider risk stratification and assessment; (2) In case of a documented IFI, catheter removal becomes mandatory

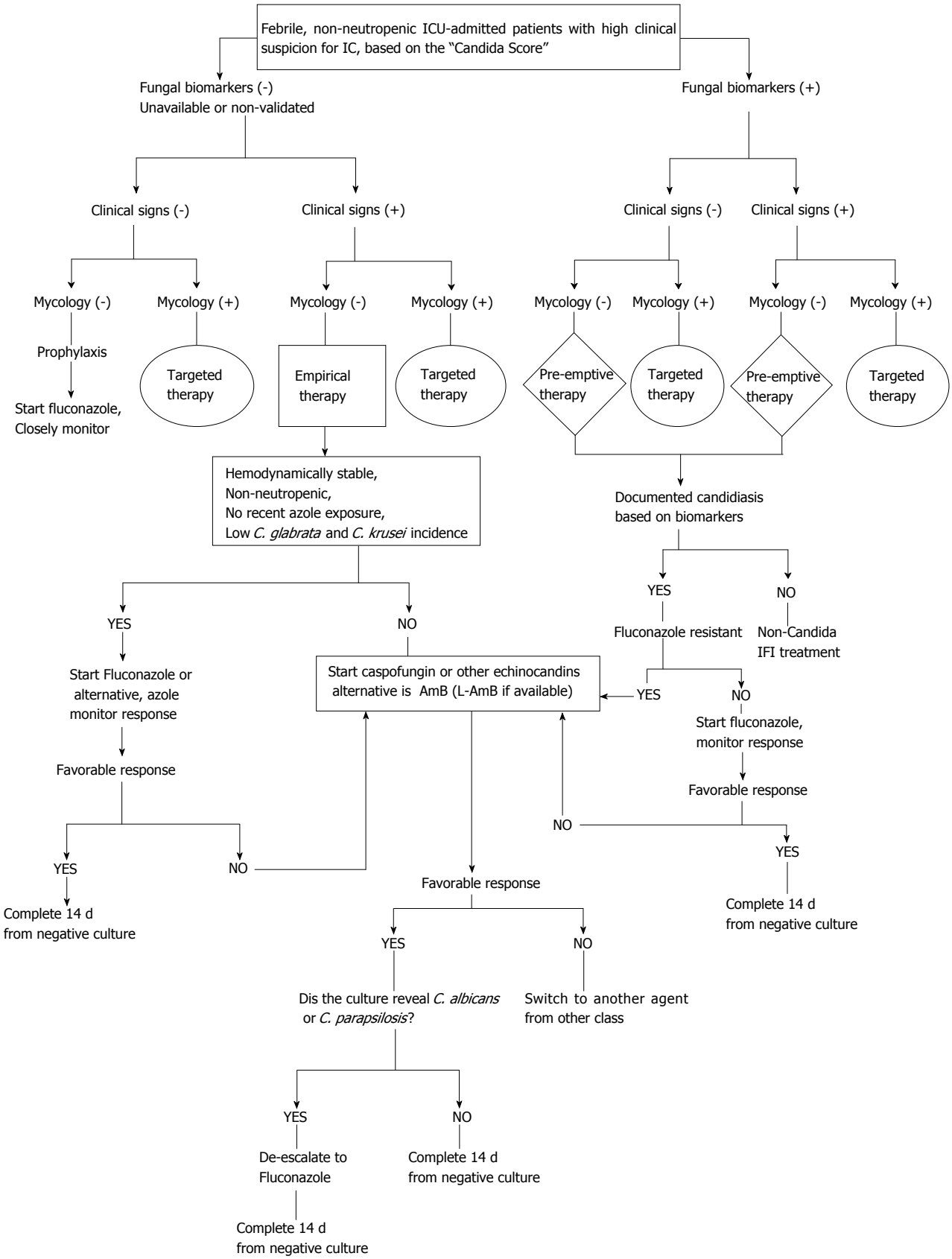


**Figure 2 Management of invasive candidiasis in critical care setting.** An updated consensus from the Iranian experts at invasive fungal infection-clinical forum. For justification and referencing see "diagnostic challenges of invasive candidiasis in the intensive care unit" and "approach to invasive candidiasis in intensive care unit" in the present report. IC: Invasive candidiasis; ICU: Invasive fungal infection; AmB: Amphotericin B; L-AmB: Liposomal Amphotericin B; IFIs: Invasive fungal infections.

**Table 2 Recommended therapy with proper dosing in invasive candidiasis based on the current practice guidelines and consensus statements[12,14-16]**

| Recommended treatment | *Candidemia* (non-neutropenic patients, moderate to severe illness) | *Candidemia* (neutropenic patients) | Candida glabrata | Candida parapsilosis | Solid organ transplant recipients (prophylaxis) | ICU prophylaxis (high risk patients only) |
|---|---|---|---|---|---|---|
| Caspofungin | 70 mg *iv* loading dose, then 50 mg/d per *iv* | 70 mg *iv* loading dose, then 50 mg/d per *iv* | 70 mg *iv* loading dose, then 50 mg/d per *iv* | | | |
| Micafungin | 100 mg/d per *iv* | 100 mg/d per *iv* | 100 mg/d per *iv* | | | |
| Anidulafungin | 200 mg/*iv* loading dose; then 100 mg/d per *iv* | 200 mg/*iv* loading dose; then 100 mg/d per *iv* | 200 mg/*iv* loading dose; then 100 mg/d per *iv* | | | |
| Fluconazole | | | | 800 mg *iv* loading, then 400 mg/d per *iv* or PO | 200-400 mg/d *iv* or PO for 7-14 d | 400 mg/d per *iv* or PO |
| (Alternative regimen) Fluconazole | 800 mg *iv* loading, then 400 mg/d per *iv* or PO | 800 mg *iv* loading, then 400 mg/d per *iv* or PO | | | | |
| (Alternative regimen) Voriconazole if mold coverage is desired | | 6 mg/kg per *iv* q12h for 2 doses; then 4 mg/kg *iv* q12h or 200 mg PO q12h | | | | |
| (Alternative regimen) Fluconazole or Voriconazole | | | With susceptibility testing | | | |
| (Alternative regimen) Echinocandins | | | | If already responding to therapy | | |
| (Alternative regimen) Liposomal Amphotericin B | | | | | 1-2 mg/kg *iv*/d for 7-14 d | |

ICU: Intensive care unit; PO: Per Os (Oral administration); *iv*: Intravenous.

since eradicating the infection without removing the device looks unlikely. The challenge will arise in the context of suspected IFIs in the presence of permanent catheters, pace makers, implantable cardioverter defibrillator or cardiac resynchronization therapy, *etc*. where some expert recommend a "device salvage trial" for successful outcome. Taken together, the general recommendation is to remove catheters the soonest possible; (3) The duration of antifungal therapy depends mainly on both response to treatment and status of blood culture at the beginning of IFI therapy. Normally, 72 to 96 h of treatment duration is adopted with a repeated blood culture after IFI therapy was started. The treatment will usually be stopped after 14 d since the first negative blood culture. If the therapy was started empirically (no positive blood culture), the duration of therapy is 14 d provided the patient's condition is improving on treatment. Repeated blood culture will prove whether the fungal infection is resolved; (4) Drawing a clinical pathway for non-responding patients may be difficult but still possible. Lack of response may be due to an alternative diagnosis, either non-fungal or additional microbial infections which have not been properly covered in the current therapy. Either way, a review has to be done to detect the possible source of infection and necessary investigations including standard blood cultures, non-culture based assessments, if available, and possible imaging studies such as high-resolution computed tomography and advanced ultrasound should be considered to diagnose a possibly-disseminated IFIs or resistant organisms not fully sensitive to the current therapy. In challenging, non-responding IFI cases, the treatment should be adjusted with the possibility of combination antifungal therapy. Finally, lack of response may be due to inappropriate source control including devices, foreign bodies, and surgically-accessible factors like collections which require appropriate interventions. One should always bear in mind that the lack of response may be due to non-infectious causes which also need to be well-explored; and (5) Based on the risk and severity assessment, empirical approach allows the timely management of IFIs. According to the evidence highlighted in this report, moderate- to high-risk patients for severe infections require echinocandins. Streamlining depends on response and the culture results. Meanwhile, mild infections in stable patients can still be treated with FCZ. Suspected *Aspergillus* requires VCZ, whereas the emerging and rare fungal infections would still require AmB. Furthermore, the possibility of combination antifungal therapy should be considered.

## CONCLUSION

IC is a serious clinical condition with a notable risk of death in critically-ill patients when not treated properly. Increased awareness and practical insights through share of experience as well as adherence to international and local guidelines are key elements of success in the management of IC in the ICU.

According to the panel's opinion, LoS in the ICU and total days on mechanical ventilation, the presence of CVC/TPN, dialysis catheters, use of broad spectrum antibiotics, sepsis, presence of GI surgery, burn and high Acute Physiology and Chronic Health Evaluation II Score (> 16)[61] were considered as main risk factors justifying the empirical antifungal therapy against IC in febrile, non-neutropenic critically-ill patients admitted to the ICU.

The entire panel admitted that lack of experience and insufficient awareness is the main cause for delayed initiation of antifungal therapy in critically-ill patients. Meanwhile half of the participants believed that the paucity of diagnostic tools and inconsistent availability of the therapeutic options are crucial obstacles in parallel. All experts agreed that holding well-planned educational programs and fostering scientific activities within our IFI-CF will be a road to increase awareness and better practice with regard to the management of IFIs in critical care setting.

Upon conclusion, experts at the IFI-CF decided to continue holding regular meetings at institutional level in order to educate junior ICU staff and increase their awareness on the management of IC in the ICU.

The IFI-CF became determined to conduct biannual meetings to share experience and update local guidelines on IFIs management as required. In addition, utilizing the already established consensus, the experts agreed to pursue preparing printed protocols in each ICU in order to make it easier for the juniors to follow and implement.

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## REFERENCES

1 **Traynor K**. ICU infection-prevention efforts could be better, study finds. *Am J Health Syst Pharm* 2014; **71**: 444, 446 [PMID: 24589533 DOI: 10.2146/news140022]

2 **Hung CY**, Kao KC, Wang PN, Hu HC, Hsieh MJ, Fu JY, Chang CH, Li LF, Huang CC, Tsai YH, Yang CT. Invasive fungal infection among hematopoietic stem cell transplantation patients with mechanical ventilation in the intensive care unit. *BMC Infect Dis* 2012; **12**: 44 [PMID: 22339791 DOI: 10.1186/1471-2334-12-44]

3 **Martino R**, Lopez R, Sureda A, Brunet S, Domingo-Albós A. Risk of reactivation of a recent invasive fungal infection in patients with hematological malignancies undergoing further intensive chemo-radiotherapy. A single-center experience and review of the literature. *Haematologica* 1997; **82**: 297-304 [PMID: 9234575]

4 **Yu Y**, Du L, Yuan T, Zheng J, Chen A, Chen L, Shi L. Risk factors and clinical analysis for invasive fungal infection in neonatal intensive care unit patients. *Am J Perinatol* 2013; **30**: 589-594 [PMID: 23277386 DOI: 10.1055/s-0032-1329688]

5 **Ostrosky-Zeichner L**. Systemic antifungal therapy in patients without documented invasive fungal infection: a peek into the world of empirical antifungal therapy*. *Crit Care Med* 2012; **40**: 997-998 [PMID: 22343851 DOI: 10.1097/CCM.0b013e31823e9514]

6 **Zaragoza R**, Pemán J, Salavert M, Viudes A, Solé A, Jarque I, Monte E, Romá E, Cantón E. Multidisciplinary approach to the treatment of invasive fungal infections in adult patients. Prophylaxis, empirical, preemptive or targeted therapy, which is the best in the different hosts? *Ther Clin Risk Manag* 2008; **4**: 1261-1280 [PMID: 19337433 DOI: 10.2147/TCRM.S3994]

7 **Huibregtse JM**, Engelke DR, Thiele DJ. Copper-induced binding of cellular factors to yeast metallothionein upstream activation sequences. *Proc Natl Acad Sci USA* 1989; **86**: 65-69 [PMID: 2643107]

8 **Harrison D**, Muskett H, Harvey S, Grieve R, Shahin J, Patel K, Sadique Z, Allen E, Dybowski R, Jit M, Edgeworth J, Kibbler C, Barnes R, Soni N, Rowan K. Development and validation of a risk model for identification of non-neutropenic, critically ill adult patients at high risk of invasive Candida infection: the Fungal Infection Risk Evaluation (FIRE) Study. *Health Technol Assess* 2013; **17**: 1-156 [PMID: 23369845 DOI: 10.3310/hta17030]

9 **Paramythiotou E**, Frantzeskaki F, Flevari A, Armaganidis A, Dimopoulos G. Invasive fungal infections in the ICU: how to approach, how to treat. *Molecules* 2014; **19**: 1085-1119 [PMID: 24445340 DOI: 10.3390/molecules19011085]

10 **Leroy G**, Lambiotte F, Thévenin D, Lemaire C, Parmentier E, Devos P, Leroy O. Evaluation of "Candida score" in critically ill patients: a prospective, multicenter, observational, cohort study. *Ann Intensive Care* 2011; **1**: 50 [PMID: 22128895 DOI: 10.1186/2110-5820-1-50]

11 **Bruyère R**, Quenot JP, Prin S, Dalle F, Vigneron C, Aho S, Leon C, Charles PE. Empirical antifungal therapy with an echinocandin in critically-ill patients: prospective evaluation of a pragmatic Candida score-based strategy in one medical ICU. *BMC Infect Dis* 2014; **14**: 385 [PMID: 25015848 DOI: 10.1186/1471-2334-14-385]

12 **Ahmadi A**, Ardehali SH, Beigmohammadi MT, Hajiabdolbaghi M, Hashemian SM, Kouchek M, Majidpour A, Mokhtari M, Moghaddam OM, Najafi A, Nejat R, Niakan M, Lotfi AH, Amirsavadkouhi A, Shirazian F, Tabarsi P, Taher MT, Torabi-Nami M. Invasive candidiasis in intensive care unit; consensus statement from an Iranian panel of experts, July 2013. *JRSM Open* 2014; **5**: 2042533313517689 [PMID: 25057376 DOI: 10.1177/2042533313517689]

13 **Mardani M**, Tabarsi P, Yadegarinia D, Talebi Taher M, Najafi N, Hajabdolbaghi M, Rasoolinejad M, Badiei P, Janbakhsh A, Salehi H, Khorvash F, Aghazadeh K, Mansouri D, Namazi NMK. Treatment of invasive fungal infection: Recommendations from scientific leaders' meeting on November 3rd, 2011 tehran-iran. *Iran J Clin Infect Dis* 2011; **6**: 179-181

14 **Pappas PG**, Kauffman CA, Andes D, Benjamin DK, Calandra TF, Edwards JE, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **48**: 503-535 [PMID: 19191635 DOI: 10.1086/596757]

15 **Cornely OA**, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, Meersseman W, Akova M, Arendrup MC, Arikan-Akdagli S, Bille J, Castagnola E, Cuenca-Estrella M, Donnelly JP, Groll AH, Herbrecht R, Hope WW, Jensen HE, Lass-Flörl C, Petrikkos G, Richardson MD, Roilides E, Verweij PE, Viscoli C, Ullmann AJ. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect* 2012; **18** Suppl 7: 19-37 [PMID: 23137135 DOI: 10.1111/1469-0691.12039]

16 **Kullberg BJ**, Verweij PE, Akova M, Arendrup MC, Bille J, Calandra T, Cuenca-Estrella M, Herbrecht R, Jacobs F, Kalin M, Kibbler CC, Lortholary O, Martino P, Meis JF,

Muñoz P, Odds FC, De Pauw BE, Rex JH, Roilides E, Rogers TR, Ruhnke M, Ullmann AJ, Uzun Ö, Vandewoude K, Vincent JL, Donnelly JP. European expert opinion on the management of invasive candidiasis in adults. *Clin Microbiol Infect* 2011; **17** Suppl 5: 1-12 [PMID: 21884296 DOI: 10.1111/j.1469-0691.2011.03615.x]

17 **Bow EJ**, Evans G, Fuller J, Laverdière M, Rotstein C, Rennie R, Shafran SD, Sheppard D, Carle S, Phillips P, Vinh DC. Canadian clinical practice guidelines for invasive candidiasis in adults. *Can J Infect Dis Med Microbiol* 2010; **21**: e122-e150 [PMID: 22132006]

18 **Gonçalves-Pereira J**, Pereira JM, Ribeiro O, Baptista JP, Froes F, Paiva JA. Impact of infection on admission and of the process of care on mortality of patients admitted to the Intensive Care Unit: the INFAUCI study. *Clin Microbiol Infect* 2014; Clin Microbiol Infect: [PMID: 24975209 DOI: 10.1111/1469-0691.12738]

19 **Castón-Osorio JJ**, Rivero A, Torre-Cisneros J. Epidemiology of invasive fungal infection. *Int J Antimicrob Agents* 2008; **32** Suppl 2: S103-S109 [PMID: 19013332 DOI: 10.1016/S0924-8579(08)70009-8]

20 **Cuenca-Estrella M**, Bernal-Martinez L, Buitrago MJ, Castelli MV, Gomez-Lopez A, Zaragoza O, Rodriguez-Tudela JL. Update on the epidemiology and diagnosis of invasive fungal infection. *Int J Antimicrob Agents* 2008; **32** Suppl 2: S143-S147 [PMID: 19013339 DOI: 10.1016/S0924-8579(08)70016-5]

21 **Hu R**, Jiang XY, Wu Y. Risk factors for invasive pulmonary fungal infection in patients with hematological malignancies not receiving hematopoietic stem cell transplant. *Neoplasma* 2012; **59**: 669-675 [PMID: 22862167 DOI: 10.4149/neo_2012_085]

22 **Sun YQ**, Xu LP, Liu DH, Zhang XH, Chen YH, Chen H, Ji Y, Wang Y, Han W, Wang JZ, Wang FR, Liu KY, Huang XJ. The incidence and risk factors of invasive fungal infection after haploidentical haematopoietic stem cell transplantation without in vitro T-cell depletion. *Clin Microbiol Infect* 2012; **18**: 997-1003 [PMID: 22085092 DOI: 10.1111/j.1469-0691.2011.03697.x]

23 **Ostrosky-Zeichner L**. Clinical prediction rules for invasive candidiasis in the ICU: ready for prime time? *Crit Care* 2011; **15**: 189 [PMID: 21943066 DOI: 10.1186/cc10422]

24 **Vincent JL**, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; **302**: 2323-2329 [PMID: 19952319 DOI: 10.1001/jama.2009.1754]

25 **Darouiche RO**. Candida in the ICU. *Clin Chest Med* 2009; **30**: 287-293, vi-vii [PMID: 19375635 DOI: 10.1016/j.ccm.2009.02.013]

26 **Gagne JJ**, Goldfarb NI. Candidemia in the in-patient setting: treatment options and economics. *Expert Opin Pharmacother* 2007; **8**: 1643-1650 [PMID: 17685882 DOI: 10.1517/14656566.8.11.1643]

27 **Falagas ME**, Apostolou KE, Pappas VD. Attributable mortality of candidemia: a systematic review of matched cohort and case-control studies. *Eur J Clin Microbiol Infect Dis* 2006; **25**: 419-425 [PMID: 16773391 DOI: 10.1007/s10096-006-0159-2]

28 **Tragiannidis A**, Tsoulas C, Kerl K, Groll AH. Invasive candidiasis: update on current pharmacotherapy options and future perspectives. *Expert Opin Pharmacother* 2013; **14**: 1515-1528 [PMID: 23724798 DOI: 10.1517/14656566.2013.805204]

29 **Leroy O**, Gangneux JP, Montravers P, Mira JP, Gouin F, Sollet JP, Carlet J, Reynes J, Rosenheim M, Regnier B, Lortholary O. Epidemiology, management, and risk factors for death of invasive Candida infections in critical care: a multicenter, prospective, observational study in France (2005-2006). *Crit Care Med* 2009; **37**: 1612-1618 [PMID: 19325476 DOI: 10.1097/CCM.0b013e31819efac0]

30 **Playford EG**, Marriott D, Nguyen Q, Chen S, Ellis D, Slavin M, Sorrell TC. Candidemia in nonneutropenic critically ill patients: risk factors for non-albicans Candida spp. *Crit Care Med* 2008; **36**: 2034-2039 [PMID: 18552700 DOI: 10.1097/CCM.0b013e3181760f42]

31 **Kordbacheh P**, Zaini F, Kamali F, Ansari K, Safara M. Study on the sources of nosocomial fungal infections at intensive care unit and transplant wards at a teaching hospital in tehran. *Iranian J Publ Health* 2005; **34**: 1-8

32 **Hooman N**, Madani A, Sharifian Dorcheh M, Mahdavi A, Derakhshan A, Gheissari A, Esfahani ST, Otukesh H, Mohkam M, Falahzadeh MH, Hosseini Al Hashemi G, Azir A, Merikhi A, Golikhani F, Latif E, Karimi S, Zakavat T, Mohseni P, Ataei N, Nickavar A, Basiratnia M. Fungal peritonitis in Iranian children on continuous ambulatory peritoneal dialysis: a national experience. *Iran J Kidney Dis* 2007; **1**: 29-33 [PMID: 19357441]

33 **Bassiri Jahromi S**, Khaksar AA. Deep-seated fungal infections in immunocompromised patients in iran. *Iran J Allergy Asthma Immunol* 2005; **4**: 27-32 [PMID: 17301420]

34 **Naeini AE**, Sharifi M, Shahidi S, Taheri S, Seirafian S, Taheri D, Tazhibi M, Hejazi SH, Naini PE, Harandi AA. Intestinal fungal and parasitic infections in kidney transplant recipients: a multi-center study. *Saudi J Kidney Dis Transpl* 2012; **23**: 677-683 [PMID: 22805377 DOI: 10.4103/1319-2442.98110]

35 **Pfaller MA**, Andes DR, Diekema DJ, Horn DL, Reboli AC, Rotstein C, Franks B, Azie NE. Epidemiology and outcomes of invasive candidiasis due to non-albicans species of Candida in 2,496 patients: data from the Prospective Antifungal Therapy (PATH) registry 2004-2008. *PLoS One* 2014; **9**: e101510 [PMID: 24991967 DOI: 10.1371/journal.pone.0101510]

36 **Quindós G**. Epidemiology of candidaemia and invasive candidiasis. A changing face. *Rev Iberoam Micol* 2014; **31**: 42-48 [PMID: 24270071 DOI: 10.1016/j.riam.2013.10.001]

37 **Yapar N**. Epidemiology and risk factors for invasive candidiasis. *Ther Clin Risk Manag* 2014; **10**: 95-105 [PMID: 24611015 DOI: 10.2147/TCRM.S40160]

38 **Li Y**, Gao L, Ding Y, Xu Y, Zhou M, Huang W, Jing Y, Li H, Wang L, Yu L. Establishment and application of real-time quantitative PCR for diagnosing invasive aspergillosis via the blood in hematological patients: targeting a specific sequence of Aspergillus 28S-ITS2. *BMC Infect Dis* 2013; **13**: 255 [PMID: 23725402 DOI: 10.1186/1471-2334-13-255]

39 **Georgopapadakou NH**. Update on antifungals targeted to the cell wall: focus on beta-1,3-glucan synthase inhibitors. *Expert Opin Investig Drugs* 2001; **10**: 269-280 [PMID: 11178340 DOI: 10.1517/13543784.10.2.269]

40 **Jaijakul S**, Vazquez JA, Swanson RN, Ostrosky-Zeichner L. (1,3)-β-D-glucan as a prognostic marker of treatment response in invasive candidiasis. *Clin Infect Dis* 2012; **55**: 521-526 [PMID: 22573851 DOI: 10.1093/cid/cis456]

41 **Digby J**, Kalbfleisch J, Glenn A, Larsen A, Browder W, Williams D. Serum glucan levels are not specific for presence of fungal infections in intensive care unit patients. *Clin Diagn Lab Immunol* 2003; **10**: 882-885 [PMID: 12965921]

42 **Pfaller MA**, Diekema DJ, Rinaldi MG, Barnes R, Hu B, Veselov AV, Tiraboschi N, Nagy E, Gibbs DL. Results from the ARTEMIS DISK Global Antifungal Surveillance Study: a 6.5-year analysis of susceptibilities of Candida and other yeast species to fluconazole and voriconazole by standardized disk diffusion testing. *J Clin Microbiol* 2005; **43**: 5848-5859 [PMID: 16333066 DOI: 10.1128/JCM.43.12.5848-5859.2005]

43 **Ahmad S**, Khan Z, Mustafa AS, Khan ZU. Seminested PCR for diagnosis of candidemia: comparison with culture, antigen detection, and biochemical methods for species identification. *J Clin Microbiol* 2002; **40**: 2483-2489 [PMID: 12089267]

44 **Posteraro B**, De Pascale G, Tumbarello M, Torelli R, Pennisi MA, Bello G, Maviglia R, Fadda G, Sanguinetti M, Antonelli M. Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1→3)-β-D-glucan assay, Candida score, and colonization index. *Crit Care* 2011; **15**: R249 [PMID: 22018278 DOI: 10.1186/cc10507]

45 **Goudjil S**, Kongolo G, Dusol L, Imestouren F, Cornu M,

Leke A, Chouaki T. (1-3)-β-D-glucan levels in candidiasis infections in the critically ill neonate. *J Matern Fetal Neonatal Med* 2013; **26**: 44-48 [PMID: 22913303 DOI: 10.3109/14767058.2012.722716]

46 **Tissot F**, Lamoth F, Hauser PM, Orasch C, Flückiger U, Siegemund M, Zimmerli S, Calandra T, Bille J, Eggimann P, Marchetti O. β-glucan antigenemia anticipates diagnosis of blood culture-negative intraabdominal candidiasis. *Am J Respir Crit Care Med* 2013; **188**: 1100-1109 [PMID: 23782027 DOI: 10.1164/rccm.201211-2069OC]

47 **León C**, Ruiz-Santana S, Saavedra P, Galván B, Blanco A, Castro C, Balasini C, Utande-Vázquez A, González de Molina FJ, Blasco-Navalproto MA, López MJ, Charles PE, Martín E, Hernández-Viera MA. Usefulness of the "Candida score" for discriminating between Candida colonization and invasive candidiasis in non-neutropenic critically ill patients: a prospective multicenter study. *Crit Care Med* 2009; **37**: 1624-1633 [PMID: 19325481 DOI: 10.1097/CCM.0b013e31819daa14]

48 **Agvald-Ohman C**, Klingspor L, Hjelmqvist H, Edlund C. Invasive candidiasis in long-term patients at a multidisciplinary intensive care unit: Candida colonization index, risk factors, treatment and outcome. *Scand J Infect Dis* 2008; **40**: 145-153 [PMID: 17852926 DOI: 10.1080/00365540701534509]

49 **Pittet D**, Monod M, Suter PM, Frenk E, Auckenthaler R. Candida colonization and subsequent infections in critically ill surgical patients. *Ann Surg* 1994; **220**: 751-758 [PMID: 7986142]

50 **Ostrosky-Zeichner L**, Sable C, Sobel J, Alexander BD, Donowitz G, Kan V, Kauffman CA, Kett D, Larsen RA, Morrison V, Nucci M, Pappas PG, Bradley ME, Major S, Zimmer L, Wallace D, Dismukes WE, Rex JH. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. *Eur J Clin Microbiol Infect Dis* 2007; **26**: 271-276 [PMID: 17333081 DOI: 10.1007/s10096-007-0270-z]

51 **Hermsen ED**, Zapapas MK, Maiefski M, Rupp ME, Freifeld AG, Kalil AC. Validation and comparison of clinical prediction rules for invasive candidiasis in intensive care unit patients: a matched case-control study. *Crit Care* 2011; **15**: R198 [PMID: 21846332 DOI: 10.1186/cc10366]

52 **Paphitou NI**, Ostrosky-Zeichner L, Rex JH. Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials. *Med Mycol* 2005; **43**: 235-243 [PMID: 16010850]

53 **Dupont H**, Bourichon A, Paugam-Burtz C, Mantz J, Desmonts JM. Can yeast isolation in peritoneal fluid be predicted in intensive care unit patients with peritonitis? *Crit Care Med* 2003; **31**: 752-757 [PMID: 12626979 DOI: 10.1097/01.CCM.0000053525.49267.77]

54 **Blumberg HM**, Jarvis WR, Soucie JM, Edwards JE, Patterson JE, Pfaller MA, Rangel-Frausto MS, Rinaldi MG, Saiman L, Wiblin RT, Wenzel RP. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. *Clin Infect Dis* 2001; **33**: 177-186 [PMID: 11418877 DOI: 10.1086/321811]

55 **Vandijck DM**, Blot SI, Vandekerckhove L, Vogelaers DP. Fluconazole exposure and selection for Candida non-albicans. *Anesth Analg* 2008; **107**: 2091; author reply 2091-2092 [PMID: 19020168 DOI: 10.1213/ane.0b013e3181896c22]

56 **Mikolajewska A**, Schwartz S, Ruhnke M. Antifungal treatment strategies in patients with haematological diseases or cancer: from prophylaxis to empirical, pre-emptive and targeted therapy. *Mycoses* 2012; **55**: 2-16 [PMID: 21554421 DOI: 10.1111/j.1439-0507.2010.01961.x]

57 **Senn L**, Eggimann P, Ksontini R, Pascual A, Demartines N, Bille J, Calandra T, Marchetti O. Caspofungin for prevention of intra-abdominal candidiasis in high-risk surgical patients. *Intensive Care Med* 2009; **35**: 903-908 [PMID: 19172247 DOI: 10.1007/s00134-009-1405-8]

58 **Garey KW**, Rege M, Pai MP, Mingo DE, Suda KJ, Turpin RS, Bearden DT. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis* 2006; **43**: 25-31 [PMID: 16758414 DOI: 10.1086/504810]

59 **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 [PMID: 16127033 DOI: 10.1128/AAC.49.9.3640-3645.2005]

60 **Garrouste-Orgeas M**, Timsit JF, Tafflet M, Misset B, Zahar JR, Soufir L, Lazard T, Jamali S, Mourvillier B, Cohen Y, De Lassence A, Azoulay E, Cheval C, Descorps-Declere A, Adrie C, Costa de Beauregard MA, Carlet J. Excess risk of death from intensive care unit-acquired nosocomial bloodstream infections: a reappraisal. *Clin Infect Dis* 2006; **42**: 1118-1126 [PMID: 16575729 DOI: 10.1086/500318]

61 **Muskett H**, Shahin J, Eyres G, Harvey S, Rowan K, Harrison D. Risk factors for invasive fungal disease in critically ill adult patients: a systematic review. *Crit Care* 2011; **15**: R287 [PMID: 22126425 DOI: 10.1186/cc10574]

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