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REVIEW

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Invasive Candida Infections in the ICU: Diagnosis and Therapy

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Abstract

Invasive fungal infections have become a serious problem in the critically ill. One of the main reasons is the development of an immunocompromised condition. The most frequently found pathogens are Candida species. In order to provide adequate treatment, understanding this potentially life-threatening infection is mandatory. The aim of this summary is to view Candida infections from a different perspective and to give an overview on epidemiology, the range of pathophysiology from colonization to the invasive infections, and its impact on mortality. New therapeutic options will also be discussed and how these relate to current guidelines. Finally, the key issue of the choice of antifungal agents will be evaluated.

Keywords: Candida, invasive Candidiasis, diagnostics, therapeutic algorihms

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Introduction

The incidence of invasive mycoses has increased five fold in the past decade caused by two underlying factors. Firstly, more and more patients with impaired immunity are being treated and secondly, prolonged stay in hospitals facilitates the development of invasive mycoses [1,2]. Although means of diagnosing mycoses has improved, early specific diagnosis still remains a challenge [3]. The high mortality and morbidity related to invasive fungal infections renders early adequate source a pivotal role [4,5]. The problem stems from the fact that clinicians often fail to consider the possible outcomes of these infections, and also that the etiology of the infection is not always adequately established. The aim of this review is to give guidance on how to develop a somewhat different way of thinking about both diagnostics and therapy. Accordingly, a brief review of the decision algorithms necessary to establish diagnosis and starting antifungal therapy will be preented, followed by guidance on choosing appropriate antifungal agents.

Epidemiology, Incidence, Mortality

There are 100,000 known fungus species of which 400 are important from a medical point of view. Less than fifty of the species are human pathogens. Most of the infections are nosocomial and account for approximately 15% of healthcare related infections. Candida species are responsible for the vaste majority of fungal infections (70-90%), followed by the Aspergillus species (10-20%) [6]. EPIC II, (2007) was a one-day, prospective point prevalence study which highlighted Candidae as the third most common pathogen, responsible for 17% of all the infections [7]. A Swiss study confirmed that one-third of candidaemia occurs in intensive care units (ICU) [8]. Candida infections occur five to ten times more often (2-6.7 in 1000 admitted patients) in ICUs than on medical or surgical wards. In the USA it is the third and fourth most common pathogen isolated from blood cultures and accounts for 8-10% of bloodstream infections. In Europe it is the sixth to tenth most commonly identified pathogen and responsible for 2-3% of bloodstream infections [9]. According to current data, mortality rate of invasive Candida infections is considered high. Recent studies indicate it varies between 40-60% [10-12] and within certain conditions mortality can reach 100% [5]. Epidemiology of candidae has changed in the past 20 years. While earlier candida albicans was the dominant pathogen and caused two-thirds of the infections, currently increasing number of non-*albicans* species can be noticed and are responsi-

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ble for almost 50% of the infections. These include *C. glabrata*, *C. krusei*, *C. tropicalis* and *C. parapsilosis* [13]. There are several other factors, which can affect the occurrence of different candida species. While *Candida glabrata* is more common among elderly people, *Candida parapsilosis* is more common in Australia, South-America and Southern Europe than in North-America or Northern Europe [13]. Characteristics of the different Candida species are shown in Table 1 [14].

Pathomechanism of invasive infections, endangered patients and risk factors

Since different candida species are part of the normal skin and mucous membrane flora, including oropharyngs, vagina and colon, colonization can occur already in the newborns during the birth process. Colonization is not harmful among healthy subjects, however candida species can overgrow the normal flora through changes in the microbiom associated with among others, antibiotic therapy, burn injury, neutropenia and diabetes mellitus, and additionaly certain predisposing factors such as weak natural immunity, impaired cellular immunity, diabetes mellitus, and pregnancy. These factors can predispose to an invasive candida infections. Different impacts on deep tissues can lead to micro-invasion due to barrier damage, and a possible source of candidaemia. Although this does not necessarily progress in all cases to severe sepsis or septic shock, it can cause dissemination of the mycoses initiating endophtalmitis, hepatosplenic, CNS, infective endocarditis or abscesses in different organs and tissues, and subsequently the establishment of severe sepsis.

An important clinical issue is to identify which patients are more susceptible to invasive candida infection. The most susceptible patients are those with imparied immunity, but several other medical conditions should be taken into account. These are summarised in Table 2 and 3.

Table 1. Characteristics of common non-albicans species

Species	Characteristics
C. glabrata	Most common in elderly patients Most common in malignancies Geographic variation Associated to the use of specific antibiotics, (piperacillin/tazobactam, vancomycin) Common in patients under TPN and with CVC Isolation system Solid organ transplantation Fluconazole exposure
C. parapsilosis	Nosocomial outbreaks Formation of biofilms in CVC Implanted devices TPN Less susceptible to echinocandins The second most common isolated strain in children
C. tropicalis	Haematological malignancies Neutropenia
C. krusei	Use of piperacillin/tazobactam, vancomycin Innate resistance to fluconazole Haematological malignancies Neutropenia Recent gastrointestinal surgery Fluconazole exposure
C. guiillermondi	Less susceptible to echinocandins Less susceptible to fluconazole Intravascular catheters

The table was imported from Paramythiotou E et al: Invasive Fungal Infections in the ICU: How to Approach, How to Treat [14], CVC = Central venous catheters, TPN = Total Parenteral Nutrition

Table 2. Endangered patients who are more susceptible to Candida infection

Impaired immunity	Other medical conditions
Oncology	Hollow organ perforation
Haemato-oncology	Great abdominal surgery
Febrile neutropenia	Urologic intervention with parallel candiduria
Neutropenia	Polytrauma
HIV, AIDS	Malnutrition
Immunosuppressive therapy	Severe pancreatitis
Burn injury, where more than 50% of body surface is affected	ICU

Table 3. Risk factors in terms of Candida infection

High risk	Non-specific risk
Multiple colonization	Elderly age>65 years
Broad spectrum AB therapy	Diabetes mellitus
TPN	Renal failure
Dialysis	Surgical intervention
APACHE II > 20 points	Foley catheter
CVC	Catheters inserted to vessels
Candiduria> 105cfu/ml	Long ICU stay> 7 days
	Multiple transfusion

CVC = Central venous catheters, TPN = Total Parenteral Nutrition

From colonisation to infection

Candida colonisation and infection are two closely related consecutive events which can occur following illness. On admission to an ICU only 5-15% of the patients were reported to have candida colonisation, however this number increases to 50-80% during their stay in ICU. Only 5-30% of these patients developed an invasive candida infection [16]. Multifocal colonisation is common among ICU patients, mainly among those who have spent more than seven days on the ICU. The most commonly loci are the stomach (45.6%), oropharyngeal samples (34.3%), the trachea (23.4%), perirectal region (21.2%) and the urinary tract (18.7%). Recent studies show that the relative risk of invasive candidiasis was significantly higher in those patients whose faecal samples (7.5% vs. 3.2%, p=0.019) or urine samples (9.2% vs. 5.2%, p=0.032) were positive. Multifocal colonisation was found to be an independent risk factor of invasive candidiasis. Pursuant to these results patients should be screened (faeces, urine, tracheal aspirate) twice a week enabeling the clinicians to identify patients at high risk of invasive candida infection. Samples taken from other locations such as the stomach, skin, or pharynx, should also be taken into account [17,18]. Colonization can be low or high. The latter occurs if at least three samples are positive on two or more consecutive occasions [19].

Invasive candidiasis is a collective term which includes several indicators.

- Primary candidaemia is said to exist if one or more blood cultures taken from peripheral venous boold are positive for the fungus.
- Intra-abdominal candidiasis is said to exist if candida is detected in peritoneal fluid obtained by direct punction or from an intra-operative sample, or from a sample taken through an intra-abdominal drain, inserted within the past 24 hours, or when a direct microscopic examination confirms fungal yarns.
- A mixed form candidiasis can consist of the elements constituting primer and intra-abdominal candidiasis. This group includes one-third of the patients.

Most cases of invasive candidiasis occur between five to twelve days in an ICU. It is essential to differentiate between catheter-related candidaemia and primer or intra-abdominal candidiasis-related candidaemia, since the latter has lower morbidity and mortality. Diagnosis of this can be established if the catheter sample and the peripheral blood sample confirms the same candida species. Rare manifestations of invasive candidiases exist i.e. endophtalmitis, endocarditis, meningitis, pleural, bone and joint or hepatosplenic candidiasis. According to recent knowledge, colonisation of the GI tract (endogene path) has a prominent role in development of primary candidiasis while cases of catheter-related candida infections occur through the exogene path and are in relation with colonisation of the patient's skin and of the healthcare workers' hands [16].

Invasive candidiases can be separated into three groups: proven, probable or possible. Differentiation is based on cultures, biomarkers, clinical picture and the patient's individual risk factors [16,20,21]. Infection is confirmed if proliferous fungal presence is proven from blood or infected tissue samples and microbiologic examination identify candida species in obtained samples. Infection is proven if both histology and microbiology identify proliferous fungal presence from blood or infected tissue samples. Infection is probable if a compromised patient who has been in the ICU for a prolonged period has heavily colonised severe sepsis or septic shock and positive for mannan, 1-3 beta-d-glucan, a known serum biomarker for candidemia. Infection is possible if an endangered patient who has been in an ICU for a prolonged period has heavily colonised severe sepsis or septic shock but negative biomarkers.

Diagnostics

Numerous options are available for diagnosis, however none is perfect in itself. These include different scoring systems to assess risk, and highly sophisticated laboratory measures to identify the pathogen. These must be combined, as systemic candidiasis is often accompanied with no candidemia, thus risk adapted empiric antifungal therapies play a crucial role in treating invasive candidiases [22,23].

Risk scores and prediction rules

Colonisation index

Colonisation and its degree has a crucial role in the development of invasive candida infection. In a study by Pitett et al [19], 29 severely colonised patients were investigated, of whom eleven had documented invasive candidiasis. The colonisation index was 0.47 in patients with no infection and 0.7 in patients with infection

(p<0.01). The cut-off value of colonisation index was defined as >0.5 which predicted the presence of invasivity six days earlier than microbiologic cultures. This was confirmed by several subsequent studies [15,24-26]. The negative predictive value of colonisation index is 100%, its positive predictive value is 66% [27], with a sensitivity of 64% and a specificity of 69.7% [25].

According to this, the dynamics and degree of colonisation can be established through periodical screening of samples taken from the nose, throat, armpit, loin, submammal region, stomach, faeces, trachea aspirate and urine. It is advisable to perform screening among endangered patients or patients with risk factors, once or twice a week. Colonisation index can be calculated from the number of samples taken from non-sterile regions idivided by the total number of samples. If the colonisation index exceeds the cut-off value (>0.5) consideration should be given to commensing empiric antifungal therapy.

Candida score

The "Candida Score" [León et al, 2006] is an upgraded version of the Colonisation Index [28], based on a prospective cohort study enrolling 1699 patients, out of which 97 (6%) had invasive candidiasis. The results of this study indicated that surgery [odd ratio (OR): 2.71; 95% confidence interval (Cl): 1.45-5.06], multifocal colonisation (OR: 3.04; 95% CI: 1.45-6.39) and severe sepsis (OR: 7.68; 95% CI: 4.14-14.22) are predictors of invasive candidiasis. One point was allocated for each of these predictive factors in the candida score (except for severe sepsis, to which 2 points were allocated). A Candida score higher that 2,5 points has a sensitivity of 81%, a specificity of 74%, a negative predictive value of 98% and a positive predictive value of 16% for predicting invasive candidiasis. Its clinical adaptability was confirmed by several studies [25,29,30]. However, there are no prospective clinical studies examining the applicability of Candida Score as a guideline to start empiric antifungal therapy.

Ostrosky-Zeichner formula

This prediction formula was meant to identify patients who require antifungal profilaxis when in an ICU. In a study undertaken in a surgical ICU [31], the incidence of invasive candidiasis was found to be higher among those patients who spent four or more days in the ICU, had diabetes mellitus, required acute haemodialysis, total parenteral nutrition or broad spectrum antibiotic therapy, compared to those who did not belong to any of the aformentioned groups. The incidence of invasive candida infection in the two groups was 16.6% compared to 5.5% (p=0.001). Seventy eight % of these patients who later developed candidaemia or invasive candidiasis were identified by this method. Several further investigations reported similar results (Table 4).

Non-culture-based methods

Culture-based diagnostic methods have a low sensitivity of approximately 50% [34], become positive relatively late [35] and they are inadequate for diagnosing deep-seated candidiasis. Moreover, histopathologic methods, body fluid punctures and tissue biopsies are invasive and often clinically contraindicated, making them unavailable in everyday practice [15]. Therefore it is necessary to develop specific diagnostic methods with high sensitivity, which are applicable for quick recognition of invasive candida infections. These include cellular wall components, antigenes, antibodies and methods to identify circulating fungal DNA.

Table 4. Summary of predictive (Ostrosky-Zeichner) formulas

Population, invasive Candidiasis	Risk-based prediction model	Accuracy of prediction
2890 patients [88 (3%) with proven or probable IC] staying ≥4 days in nine US/Brazilian ICUs	Predictive rule – both systemic antibiotics and central venous catheter (day 1–3 of ICU stay); plus two of total parenteral nutrition (day 1–3 of ICU stay), dialysis (day 1–3 of ICU stay), major surgery (day –7 to 0 of ICU stay), pancreatitis (day –7 to 0 of ICU stay), steroids (day –7 to 3 of ICU stay), other immunosuppressive agents (day –7 to 0 of ICU stay)	Captured 34% of IC Sensitivity=34% Specificity=90% PPV=10% NPV=97%
97 ICU patients [22 (4%) with proven or probable IC] staying ≥4 days in six US ICUs	Predictive rule: all of: mechanical ventilation, broad-spectrum antibiotics and central venous catheter (day 1–3 of ICU stay); plus one of: total parenteral nutrition (day 1–3 of ICU stay), dialysis (day 1–3 of ICU stay), major surgery (day –7 to 0 of ICU stay), pancreatitis (day –7 to 0 of ICU stay), steroids (day –7 to 3), other immunosuppressive agents (day –7 to 0 of ICU stay)	Captured 90% of IC Sensitivity=90% Specificity=48% PPV=6% NPV=99%

ICU: intensive care unit, PPV: positive predictive value, NPV: negative predictive value.

(1,3)-b-D-Glucan

Detection of 1,3-b-D-Glucan (BDG) from the bloodstream was first published by Obayashi et al. in 1995 [36]. Subsequent investigations proved that BDG is an early biomarker of fungal infections [37-39] (except for zygomycetes and cryptococcoses which fungi's cellular walls do not contain BDG). Different multicenter studies have also confirmed that a cut-off value of 80 pg/ml can detect and verify invasive candida infection with good sensitivity and specificity. The test had lower sensitivity and specificity in cases of candida parapsilosis [39]. Nevertheless, it gave positive results ten days before the establishment of a clinical diagnosis of fungal infctions. It seems, that BDG is an adequate indicator of fungal infections hence a reliable biomarker for starting preemptive anti-fungal therapy. Unfortunately the BDG test is relatively costly and needs properly equipped laboratories. The test can give false positive results, mainly in the first three days of being admitted to an ICU, and especially after surgical interventions, immunglobulin therapy, or in cases treated by certain antibiotics for bacterial infections, such as mainly *Streptococcus Pneumoniae*. At the same time, it can cross-react with haemodialysis membranes, gauze albumin or other blood products. The results might also confirm invasive mould fungus infection [40]. Correlation between BDG levels, clinical outcome and treatment response is evidence based [41]. Data about BDG kinetics are lacking, although the results of two studies [30,42] show that decreasing BDG serum levels refer to therapeutic success. If these results are confirmed by further clinical investigations, monitoring BDG levels could be used for assessing antifungal therapy. The test is useful for measuring BDG levels in other body fluids such as cerebro-spinal [43], peritoneal fluid [44], or bronchoalveolar secretions [45]. However validation of these methods will be necessary in the future. 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)], the European Society of Clinical Microbiology and Infectious Diseases (ESCMDI) (candidemia: level evidence II), the Society of Critical Care Medicine (SCCM), European Society of Intensive Care Medicine (ESICM) (IC: Grade 2 B), and the Expert Panel (IAC: BII) all include BDG testing in their recommendations.

Mannan antigene and anti-mannan antibody

Mannan is a polysacharid component of candida cell wall, which circulates in the bloodstream in case of invasive candidiases. Currently latex agglutination and enzyme immunoassay-based methods are in practice for mannan detection [46]. Combined examinations give the best results which means parallel detection of mannan antigene and anti-mannan antibody (Mn-anti-Mn). According to a meta-analisys published in 2010 containing 14 studies - 7 of which included non-neutropenic critically ill patients, the sensitivity of mannan and anti-mannan investigations were 58% and 93% while their specificity were 59% and 83% separately. In cases of Candida albicans, glabrata and tropicalis infections, when these investigations were combined, their sensitivity and specificity improved (83% and 86%) [47]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the Surviving Sepsis Guidelines suggest the performance of a double test with C II evidence in these cases. The cause of the low quality of evidence is that most studies were retrospective and examined heterogeneous patient groups. To clarify the test's role in everyday practice further investigations are necessary, examining homogeneous patient groups, defining the positive and negative predictive values and deciding wether simple or multiple positive results are needed to assert the diagnosis of invasive candida infection.

Detection of candida nucleic acids by PCR

Fungal DNA detection by PCR technics is challenging. Human cell lysis leading to DNA "disengagement" can give false positive results. Exogene contamination from saprophytic or pathogen fungi can also lead to false positive results. Detailed discussion of the difficulties of PCR techniques is beyond the scope of this summary. PCR techniques are capable of early detection of candidaemias and have been widely studied. In a review published by Khot in 2009 [48] the following observations were reported:

- The method is appropriate for early detection of candidaemia.
- PCR is appropriate or detection of organic fragments mainly if it aims a multicopy gene.
- PCR detects non-viable organisms faster than cultures.
- Different platforms, blood samples and target genes are used during the test.

In a later meta-analisys, 4894 patients of 54 studies were examined among who 963 had proven/probable or possible invasive candidiasis. Overall sensitivity and specificity of PCR in detection of invasive candidiasis were 95% and 92% [49].

In those cases when invasive candidiasis was possible, sensitivity of blood cultures and PCR were markedly different, 85% and 38%. PCR is certainly a significantly finer method and detects presence of invasive candidiasis earlier than blood cultures [50].

Direct molecular detection of Candidae from human samples is not a standard method and until it is not valid the place of PCR or other molecular methods in early detection of invasive candidiases remains uncertain.

Culture-based diagnostics

This group includes blood and other culture tests which are considered as the gold standard. Blood culture tests are appropriate and essential microbiologic methods of candidaemia detection. However blood cultures have also several pitfalls. If we assume candidiasis in our patients, a single sample of 40 ml of blood coud be insufficient because the sensitivity of the test is very low. According to the current recommendation 60 ml of blood obtained by peripherial blood punction should be distributed in 3-3 different aerobic and anaerobic containers. This should be repeated daily and the containers should be incubated for a minimum of five days. According to current experience, the sensitivity of blood cultures is around 50-70%. This sensitivity may decrease in patients with neutropenia or during ongoing antifungal therapy [3]. In the case of suspected catheter related infections, samples should also be taken from the catheters to establish a source control. Although blood cultures are an essential part of the diagnostics they cannot be classified as early diagnostic strategies.

In cases of positive culture results for candida species, resistance tests should also be performed, and is important to note that minimal inhibitory concentration (MIC) values can also influence the therapy. The identification of the candida species may take several days after the detection of positive results, however it can be accelerated by some special techniques such as the PNA-FISH (Peptide Nucleic Acid Fluorescence In Situ Hybridization) and MALDI-TOF MS (Matrix Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry). Following blood culture positivity with the PNA-FISH technique, the five most common candida species can be identified in ninty minutes by colour coding, which can also help in choosing the right antifungal agent (*Candida albicans* and *parapsilosis* are coloured in green, *Candida tropicalis* in yellow, *Candida glabrata* and *krusei* in red) [51]. MALDI-TOF MS is a rapid, accurate and low-cost method for identification and characterization of microorganisms. This technology can help to create large spectrum of "fingerprints" which is specific and unique for each micro-organism. The method is perfectly applicable for the identification of the microbes' genus and species levels and also very useful for characterization of fungi [52]. Samples other than blood can also be used for identification of pathogens with MALDI-TOF MS.

Therapeutic strategies in the treatment of invasive Candidiasis

The timing of antifungal therapy in invasive candidiasis is a major factor in terms of outcome. Several studies have proved that a delayed therapy has a negative effect on survival [5, 53-56]. When to commence therapy is closely related to the diagnostic steps and associated possibilities. Four strategies, prophylaxis, pre-emtive, empirical and targeted therapy are outlined.

Prophilaxis

The aim of prophylactic antifungal therapy is preventing infection in those who are at high-risk of developing an invasive candida infection. For prophylactic therapy fluconazole is used in general but recently echinocandins have also been successfully used [57]. Although the use of prophylaxis is well defined among transplanted and haematological patients [3], it is seldom recommended for use in ICU patients [3, 21]. Of course there are certain situations where some groups of patients may benefit from prophylactic treatment [3,58] but further studies are needed to clarify this aspect. The current European recommendations for non-neutropenic patients are summarized in Table 5 [3].

Pre-emptive therapy

According to the ESCMID definition [3], pre-emptive therapy means that there is microbiological evidence of invasive candidasis but the clinical signs of fungal infection are missing. Usually these infections belong to the "possible" or "probable" categories. The microbiological evidence is based on the 1-3 beta-D-glucan biomarker, mannan-antimannan double test or detection of fungal nucleic acid by the PCR test. In addition to the biomarkers, the patients' risk factors also need to be assessed and various score systems must be taken into consideration when starting such therapy. The current European recommendations for pre-emptive antifungal therapy in non-neutropenic patients is given in Table 6 [3].

Table 5 ESCMID recommendation for antifungal prophylaxis in adult non-neutropenic patients [3]

Population	Intention	Intervention	SoR	QoE
Recent abdominal surgery AND recurrent-gastrointestinal perforations or anastomotic leakages	To prevent intra-abdominal Candida infection	Fluconazole 400 mg/day Caspofungin 0/50 mg/day	B C	I II
Critically ill surgical patients with an expected length of ICU stay ‡3 day	To delay the time to fungal infection	Fluconazole 400 mg/day	C	II
Ventilated for 48 h and expected to beventilated for another ‡72 h	To prevent invasive candidiasis/candidaemia	Fluconazole 100 mg/day	C	I
Ventilated, hospitalized for ‡3 day, received antibiotics, CVC, and ‡1 of: parenteral nutrition, dialysis, major surgery, pancreatitis, systemic steroids, immunosuppression	To prevent invasive candidiasis/candidaemia	Caspofungin 50 mg/day	C	II
Surgical ICU patients	To prevent invasive candidiasis/candidaemia	Ketoconazole 200 mg/day	D	I
Critically ill patients with risk factors for invasive candidiasis/candidaemia	To prevent invasive candidiasis/candidaemia	Itraconazole 400 mg/day	D	I
Surgical ICU with catabolism	To prevent invasive candidiasis/candidaemia	Nystatin 4 Mio IU/day	D	I

SoR: Strength of recommendation, QoE: Quality of evidence, ICU: intensive care unit, CVC: central venous catheter, IU: international units.

Empirical therapy

According to the ESCMID definition [3], empirical, fever driven, therapy is when the patient is at-risk of fungal infections with persistent fever but has no microbiological evidence of invasive candidiasis, supported by increased risk scores. Current European recommendations for empirical antifungal therapy in non-neutropenic patients are summarized in Table 6 [3].

Targeted therapy

When the sensitivity to different anticandida agents and the MIC (*minimal inhibitory concentration*) of the Candida species grown from blood culture or other specimen is known, the treatment can be adapted in order to achieve superior results and targeted therapy.

Choice of the antifungal agent and length of therapy

The antifungal agents administered to patients are affected by several factors and circumstances. On the one hand there are a number of national and international guidelines which can help in choosing the appropriate agents. However these guidelines cannot be applied for all clinical scenarios. There are several factors affecting when and what species can be responsible for the invasive candida infection in a particular patient [13,14]. On the other hand, we need to consider local epidemiology and resistance profiles. The antifungal drug's spectrum for drugs are given in Table 7.

In addition we should also be aware on the MIC values (this E-testing can be only carried out in case of

Table 6. ESCMID recommendation for pre-emptive and empirical therapy in adult non-neutropenic patients [3]

Population	Intention	Intervention	SoR	QoE
Adult ICU patients with fever despite broad-spectrum antibiotics and APACHEII >16	To resolve fever	Fluconazole 800 mg/day	D	I
ICU patients persistently febrile, but without-microbiological evidence	To reduce overall mortality	Fluconazole or echinocandin	C	II
ICU patients with candida isolated from respiratory secretions	To cure invasive candidiasis or candidaemia early	Any antifungal	D	II
ICU patients with positive (1,3)-b-D-glucantest	To cure invasive candidiasis or candidaemia early	Any antifungal	C	II
Any patient with Candida isolated from a blood culture	To cure invasive candidiasis	Antifungal treatment	A	II

SoR: Strength of recommendation, QoE: Quality of evidence, APACHE: acute physiology and chronic health evaluation

Table 7. Antifungal activity spectrum and Candida species [59]

Candida spp.	AMB	FLU	ITRA	VOR	POSA	CAS	MIC	ANI
C.albicans	++	++	++	++	++	++	++	++
C.glabrata	+	+/-	+/-	+	+	++	++	++
C.parapsilosis	++	++	++	++	++	+	+	+
C.tropicalis	++	++	++	++	++	++	++	++
C.krusei	+	-	+/-	+	+	++	++	++
C.rugosa	+	+	+	++	++	+	+	+
C.guilliermondii	++	++	++	++	++	+	+	+
C.lusitaniae	++	++	++	++	++	++	++	++
C.inconspicua	++	-	+	+	+	++	++	++
C.norvegensis	++	-	+/-	+/-	+/-	++	++	++

In vitro inherentactivity: ++good activity, +mild activity, +/- slight activity,- no activity. AMB amphotericin B, FLU fluconazole, ITRA itraconazole, VOR voriconazole, POSA posaconazole, CAS caspofungin, MIC micafungin, ANI anidulafungin

fully known species of Candida). The sensibility degree to the antifungal agent, expressed in points, can be interpreted in accordance with the EUCAST (European Committee on Antimicrobial Susceptibility Testing) or CLSI (Clinical and Laboratory Standards Institute) database.

The current European recommendations for antifungal therapy in non-neutropenic adult patients is given in Table 8 [3].

The duration of the therapy is influenced by many factors and current recommendations are mainly based on consensus rather than clear evidence. Basically, in case of a positive blood culture for a candida species, empiric antifungal therapy should be started immediately followed by obtaining daily blood cultures. According to current recommendations, the patient should be treated for a minimum of fourteen additional days after the first negative culture results have been recorded. De-escalation is also possible or a switch to oral therapy after ten days, after taking into account the existing clinical picture [3]. In cases of deep-seated candidiasis, the therapy should be continued for a longer period. In these cases the clinical picture and the source of infection determine the choice of the antifungal agent and the length of therapy. If candidaemia is present, ophthalmological examination and transthoracic or transesophageal echocardiography is mandatory in all cases to exclude intraocular candidiasis and infective endocarditis. The infected intravascular catheters must be removed as soon as possible. If this

Table 8. ESCMID recommendation for antifungal therapy [3]

Intervention	SoR	QoE	Comment
Anidulafungin 200/100 mg	A	I	Consider local epidemiology (Candida parapsilosis, Candida krusei), less drug–drug interactions than caspofungin
Caspofungin 70/50 mg	A	I	Consider local epidemiology (C. parapsilosis)
Micafungin 100 mg	A	I	Consider local epidemiology (C. parapsilosis), less drug–drug interactions than caspofungin,
Amphotericin B liposomal 3 mg/kg	B	I	Similar efficacy as micafungin, higher renal toxicity than micafungin
Voriconazole 6/3 mg/kg/day	B	I	Limited spectrum compared to echinocandins, drug–drug interactions, limitation of IV formulation in renal impairment, consider therapeutic drug monitoring
Fluconazole 400–800 mg	C	I	Limited spectrum, inferiority to anidulafungin (especially in the subgroupwith high APACHE scores), may be better than echinocandins against C. parapsilosis
Amphotericin B lipid complex 5 mg/kg	C	II	-
Amphotericin B deoxycholate 0.7–1.0 mg/kg	D	I	Substantial renal and infusion-related toxicity

SoR: Strength of recommendation, QoE: Quality of evidence

is not possible then echinocandin, liposomal or lipid complex amphotericin-B must be started because they are also able to diffuse into the biofilm [3].

Summary

The increasing number of invasive fungal infections are a real and important problem in critically ill patients. Although significant progress has been made in both the diagnostics and therapy over the last years, invasive fungal infections are still often overlooked. Early diagnosis and antifungal therapy without delay are the only chances that can improve the chances for survival of these patients. According to our present knowledge the preemptive therapy may be the most promising approach. Applying biomarkers and fungal DNA tests can improve diagnostic accuracy and makes early treatment possible. Nevertheless, there are several issues to be solved in the future including both diagnostics, therapy and determination of the length of treatment.

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