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## Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part I. Epidemiology and diagnosis

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**Abstract** *Background:* Invasive candidiasis and candidemia are frequently encountered in the nosocomial setting, particularly in the intensive care unit (ICU). *Objectives and methods:* To review the current management of invasive candidiasis and candidemia in non-neutropenic adult ICU patients based on a review of the literature and a European expert panel discussion. *Results and conclusions:* *Candida albicans* remains the most frequently isolated fungal species followed by *C. glabrata*. The diagnosis of invasive candidiasis involves both clinical and laboratory parameters, but neither of these are specific. One of the main features in diagnosis is the evaluation of risk factor for infection which will identify patients in need of pre-emptive or empiric treatment. Clinical scores were built from those risk

factors. Among laboratory diagnosis, a positive blood culture from a normally sterile site provides positive evidence. Surrogate markers have also been proposed like 1,3  $\beta$ -D glucan level, mannans, or PCR testing. Invasive candidiasis and candidemia is a growing concern in the ICU, apart from cases with positive blood cultures or fluid/tissue biopsy, diagnosis is neither sensitive nor specific. The diagnosis remains difficult and is usually based on the evaluation of risk factors.

**Keywords** Antifungal · Azole · *Candida* · Candidiasis ·

Echinocandins · Invasive candidiasis · Intensive care · Polyenes

#### Abbreviations

aPTT	Activated partial thromboplastin time
CAGT	<i>Candida albicans</i> germ tube
CI	Colonization index
DLY	Discounted life year
FIO <sub>2</sub>	Fraction of inspired oxygen
HwP1	Hyphal wall protein 1
ICU	Intensive care unit
INR	International normalized ratio
MAP	Mean arterial blood pressure
OR	Odds ratio

PaO <sub>2</sub>	Partial pressure of arterial oxygen
PCR	Polymerize chain reaction
SBP	Systolic blood pressure
SD	Standard deviation
SDD	Selective digestive decontamination
SICU	Surgical intensive care unit
SIRS	Systemic inflammatory response syndrome
SvO <sub>2</sub>	Mixed venous oxygen saturation
WBC	White blood cell

## Introduction

Among documented invasive fungal infections, candidemia and invasive candidiasis are encountered with increasing incidence in nosocomial settings [1]. These infections cause considerable morbidity and mortality. Several studies have estimated that 6–11% of all positive nosocomial bloodstream infections could be attributed to *Candida* spp. [1, 2]. However, a recent US study showed that between 1991 and 2003, the mortality rate associated with invasive candidiasis decreased slightly over time [2]. *C. albicans* has remained the main pathogen overall, although the frequency of *C. glabrata* increases with age.

Data from a US surveillance study found that over a 7-year period *Candida* spp. accounted for 4.6 bloodstream infections per 10,000 admissions and 9% of all bloodstream infections [1], whereas the incidence may vary between centers. The estimated incidence of candidemia also varies between countries. In Europe, Denmark has reported the highest incidence with 11.0 cases/100,000/year compared with a study carried out in Finland which only recorded 1.9 cases/100,000/year in the hospital population [3–5]. *Candida* spp. are generally reported to be the fourth-most prevalent pathogen isolated in blood cultures or deep-site infections although this prevalence varies depending on the population surveyed [1, 2]. In intensive care units (ICUs), a slightly higher incidence is usually observed; in one study carried out in the ICU setting, candidemia accounted for 10.1% of blood stream infections compared with 7.9% on the general ward [1]. Luzzati et al. [6] reported a study showing that candidemia occurred more frequently in ICUs than on either surgical or general medical wards. The infection rates were cited as 15.8/10,000 patient-days in ICUs versus 0.15/10,000 on medical wards and 0.69/10,000 patient-days on surgical wards. Bougnoux et al. [7] observed a

mean incidence of candidemia of 6.7/1,000 admissions in ICU patients in France, and candidemia occurred more frequently in non-neutropenic patients than in patients with neutropenia [1, 7]. Invasive candidiasis and candidemia are associated with increased ICU and hospital stay of 12.7 and 15.5 days, respectively, and increased total costs [8–10].

Overall, ICU candidiasis represent one-third of all invasive candidiasis and is associated with a high mortality rate [11]. A recent study carried out in an adult ICU in France showed a 61.8% crude mortality [7]. A perhaps more clinically relevant parameter is the attributable mortality. This parameter estimates the excess of mortality attributable to the fungal infection compared with the mortality rate in patients matched for underlying disease and other risk factors. Thus, attributable mortality may estimate how mortality may be decreased by effective antifungal therapy. Attributable mortality of candidiasis was evaluated retrospectively between 1997 and 2001 in 108 matched pairs [12], the crude mortality among case patients was 61% compared with 12% in controls; the resulting “attributable mortality” was therefore estimated to be 49%. A study performed in the US evaluating candidemia associated with septic shock and multiple organ failure showed that, although relatively infrequent in the non-immunocompromized patient, it was associated with a very high mortality rate [13]. Although not statistically significant, the mortality rate at 28 days in this study was 60% in candidemic septic shock patients, compared with 46% in bacteremic septic shock patients. Falagas et al. [14] also assessed the impact of candidemia on hospital mortality in a systematic review of seven matched cohort and case–control studies. The mortality attributed to candidemia, in the reviewed studies, ranged from 5 to 71%, and for six, the difference in mortality between cases and controls was statistically

significant. The authors concluded that despite the methodological heterogeneity, these data suggest that candidemia is associated with considerable mortality. In another study recently published, Tumbarello et al. [15] retrospectively studied the risk factors for mortality of patients with candidemia. The multivariate analysis identified three factors associated with mortality: inadequate antifungal therapy, infection with biofilm-forming *Candida* species, and Apache III score.

The increasing incidence of non-albicans *Candida* species could be important, as a prospective study in a medical–surgical ICU suggested that candidemia due to non-albicans species was associated with higher mortality [16]. Blot et al. [17] compared critically ill patients with fungemia due to *C. albicans* and *C. glabrata*. They found that patients infected by *C. glabrata* were significantly older and showed a trend toward a higher mortality. In cancer patients, Viscoli et al. [18] also suggested that *C. glabrata* was associated with a higher mortality rate. Comparing fluconazole-susceptible with resistant strains in 161 patients, Kovacicova et al. [19] found a significantly higher attributable mortality in patients infected with a fluconazole-resistant strain. On the contrary, crude mortality was not different between patients infected by *C. glabrata* or *C. albicans* (respectively 41 vs. 44%,  $P = 0.7$ ) in a recent case control study [20], suggesting that uncertainty exists around the relative mortality of different *Candida* species, requiring well-controlled studies.

Despite the overwhelming evidence identifying the increasing mortality and morbidity burden of invasive candidiasis and candidemia, and its adverse impact on morbidity and mortality of critically-ill patients, the optimal management, even in the high-risk ICU patient, is still debated in the medical literature.

The aim of this article is to summarize the current management of invasive candidiasis and candidemia in adult non-neutropenic ICU patients based on a review of the international literature.

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### ***Candida* spp. epidemiology in the intensive care unit**

Only a limited number of studies have specifically focused on *Candida* spp. encountered in the ICU. In one study carried out over a 4-year period, Aliyu et al. [21] investigated 92 episodes in 90 patients, *C. albicans* was the most-frequently isolated fungal species, *C. glabrata* was second. All isolated *Candida* spp. were susceptible to amphotericin B, and only 87% were susceptible to fluconazole.

A larger study conducted over a 5-year period in Italy recorded 182 episodes of ICU candidemia, with an average incidence of 2.22 episodes/10,000 patient-days/year [22]. The authors observed an increased incidence of

candidemia over the years: overall, 40% of cases were due to *C. albicans* followed by *C. parapsilosis* (23%), *C. glabrata* (15%), *C. tropicalis* (9%), and other species (13%). The results of this study reflected a shift toward an increased rate of infection with non-albicans *Candida* species. This observation correlated with the increasing use of azoles for prophylaxis or empirical treatment, which will be discussed later in this review although this finding has not been corroborated by Shorr et al. in a recently published study [23]. The influence of azole prophylaxis on *Candida* epidemiology has not been clearly elucidated yet.

A hospital-based study conducted in England and Wales reported 18.7 episodes of candidemia/100,000 finished consultant episodes, 45.4% of which occurred in the ICU. *C. albicans* was isolated in 64.7% of confirmed cases [24].

In a large European study, Tortorano et al. [25] showed that *Candida albicans* was responsible for more than half of the cases in all patient populations. *Candida glabrata* was the most frequent non-*albicans* isolate in surgical (16%) patients. These authors concluded that there was a limited role of species with decreased susceptibility to azoles in causing bloodstream infections and a low proportion of antifungal resistance.

In a study from Turkey, 302 isolates from 270 ICU patients were collected from various samples; *C. albicans* was the most frequent species detected (65.6%) followed by *C. parapsilosis* (11.3%) and *C. glabrata* (8.8%) [26]. Of all the isolates, 92.9% were susceptible to fluconazole. In Canada, 409 *Candida* isolates were recovered during a 1-day point-prevalence study in 35 ICUs [27]. *C. albicans* accounted for 72% of the isolated species, followed by *C. glabrata* (16%). Only 4% of the isolates were resistant to fluconazole and/or itraconazole.

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### **Diagnosis of invasive candidiasis and candidemia**

The diagnosis of candidiasis is still a major challenge in the ICU, and it is often made late in the course of the infection. This can be explained by several factors: clinical manifestations are non-specific, blood cultures are usually not positive until late in the course of infection, and, in approximately 50% of patients, blood culture sample size may be inadequate, i.e., not performed according to guidelines with a sample size  $\geq 20$  mL of blood [28, 29]. Finally, serological tests and cultures, apart from blood cultures, are non-specific and their diagnostic accuracy is still debated [29–31]; as a result, clinicians often disregard a potential diagnosis of candidiasis. An additional diagnostic hurdle relates to the fact that ICU patients may have received prophylactic doses of fluconazole (e.g., 100 mg) which may render samples negative at the time of testing.

A diagnosis usually requires clinical, microbiological, and biochemical evidence of infection, which even if positive may not be sufficient or specific enough to guide optimal treatment. One of the main features in diagnosis is the evaluation of risk factors for infection. Possible risk factors have been evaluated in several studies and used to identify patients in need of pre-emptive or empiric treatment [32, 33]. The optimal timing of these therapeutic options has still not been completely elucidated. Most frequently this latter objective was achieved by calculating a clinical risk score derived from identification of pre-determined risk factors in patients suspected of having a fungal infection. It is appropriate to describe these risk factors first before commenting on clinically relevant risk scores. The specific role of colonization will then be discussed before assessing the relevance of biological tests.

#### Assessment of risk factors

Commonly recognized risk factors for invasive *Candida* infection are listed in Table 1 [2, 34, 35]. Several authors have used multivariate analyses in an attempt to assess independent risk factors associated with invasive candidiasis [28, 32, 33]. Using a case control study, Wey et al. [36] identified four factors associated with high risk of candidiasis: number of antibiotics received prior to infection (odds ratio (OR), 1.73 per unit increase); isolation of *Candida* spp. from sites other than blood (OR, 10.37); previous hemodialysis (OR, 18.13), and prior use of a Hickman catheter (OR, 7.23). Possible risk factors must be analyzed with extreme caution as they also depend on the study population: in one study, surgical ICU (SICU) patients with severe acute pancreatitis who did develop invasive candidiasis could not be differentiated from those who did not become infected when evaluated according to classical parameters such as Apache II score or previous antibiotic treatment [37]. In another study focusing on *Candida* peritonitis in a SICU, four variables could be identified: the Apache II score, respiratory failure on

**Table 1** Commonly recognized risk factors for invasive *Candida* infection [2, 34, 35]

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#### Risk factors

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Neutropenia  
 Cancer chemotherapy  
 Colonization with *Candida* spp.  
 Broad-spectrum antibiotic use  
 Presence of a central venous catheter  
 Hemodialysis or renal failure  
 Severity of illness (Apache score)  
 Parenteral nutrition  
 Mechanical ventilation  
 Prior surgery  
 Age

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admission, upper gastrointestinal tract site peritonitis, and positive results for *Candida* following direct testing of peritoneal fluid [38]. These observations were confirmed in a recent study in 59 consecutive multidisciplinary ICU patients where both high colonization index and recent extensive gastro-abdominal surgery were correlated with invasive candidiasis and candidemia [39]. Other risk factors have also been identified, such as the presence of a central venous catheter [21] or hemodialysis [40]. In a multicenter study on risk factors in surgical patients, the incidence of fungal infections increased from 0.98/1,000 to 1.42/1,000 SICU days when a central venous catheter was in place [34]. Another major factor associated with an increased risk of invasive candidemia is the length of stay in the ICU; in a small study, Pelz et al. [41] showed a clear increase in risk beyond the seventh day of stay.

#### Prediction rules

In an attempt to improve this risk factor driven approach, several authors have tried to develop models to identify independent factors that are predictive of invasive candidiasis, and use these factors to build clinically relevant scores that may help clinicians to identify, implement and adapt an optimal therapeutic approach. In a two-stage study, Michalopoulos et al. [42] identified independent predictive factors and prospectively validated them in two centers. Independent predictors were ongoing invasive mechanical ventilation  $\geq 10$  days, hospital-acquired bacterial infection and/or bacterium, cardiopulmonary bypass duration  $> 120$  min, and diabetes mellitus. Of these, the first two factors were the strongest predictors. This study needs, however, to be analyzed cautiously because it only involved 19 patients with candidemia. In another study, Leon et al. [28] described a clinical score based on four parameters derived from a logit model: surgery, multifocal colonization, total parenteral nutrition, and severe sepsis. A cut-off value of 2.5 was associated with a sensitivity of 81% and a specificity of 74%. Using a less formal approach, Ostrosky-Zeichner et al. attempted to identify patients at high risk for invasive candidiasis in the ICU. The best-performing rule was  $\geq 1$  day of systemic antibiotic therapy or presence of a central venous catheter, and at least two of the following: total parenteral nutrition, any form of dialysis, any major surgery, pancreatitis, any use of steroids, or use of an immunosuppressive agent [33].

#### Clinical diagnostic criteria

Of all the risk factors discussed in the previous section, *Candida* colonization should be highlighted. Invasive *Candida* infections represent a growing challenge in the ICU and as a consequence treatment of high-risk patients is more frequently initiated pre-emptively or empirically.



One of the main concerns in the ICU, therefore, is how to identify these patients and propose appropriate treatment algorithms, with the presumption that, in most cases, the risk of invasive candidiasis and candidemia is related to the density and extent of fungal colonization over time. One of the most important questions, which if answered positively would support the rationale for prophylaxis, is whether colonizing species portend subsequent fungal infection. An earlier study by Petri et al. [43] showed that 64% of ICU patients were colonized, and that all infected patients had been previously colonized. A related question as yet unanswered is whether colonization of certain sites carries more predictive impact versus other colonization sites.

Fungal burden was also found to be an independent risk factor in a multivariate analysis carried out on predictors of fungal infections found in ICU patients [41]. More recent studies using microsatellite markers have confirmed that, in most cases, the fungal acquisition was mainly endogenous [44, 45].

In a pioneer study, Pittet et al. [46] proposed a clinical colonization index to assess fungal colonization in high-risk SICU patients. In this 6-month prospective cohort study, the investigators evaluated 29 patients. Of these, 11 (38%) developed severe infections (8 candidemia); the others were heavily colonized but did not require specific therapy. The results of this study identified two independent factors that predicted subsequent invasive *Candida* infection: the severity of illness as assessed by the Apache II score, and the intensity of *Candida* spp. colonization defined as the colonization index (CI). In this study the colonization index was defined as the number of distinct non-blood body sites (dbs) colonized by *Candida* spp. over the total number of distinct sites tested per patient. The results of this study led the authors to conclude that systematic screening of critically ill patients with risk factors had the potential to identify those requiring so-called pre-emptive therapy with the threshold for intervention set at a CI of 0.5. The authors developed a corrected index (product of the CI times the ratio of the number of dbs showing heavy growth to the total of dbs growing *Candida* spp.) which was associated with a 100% sensitivity and specificity.

#### Laboratory diagnosis of invasive candidiasis and candidemia

As mentioned previously, diagnosis of invasive candidiasis and candidemia remains a great challenge, since symptoms and signs are usually non-specific, microbiological cultures are difficult to analyze, and histological specimens require invasive procedures [29, 30, 46].

A positive blood culture or the isolation of *Candida* spp. from a normally sterile site (except urine) provides test results that are easy to analyze, but all too often this

level of positive evidence is not available to the clinician. Several techniques have recently been proposed to assist the clinician and improve the diagnostic accuracy.

#### Surrogate markers

*(1 → 3)-β-D-glucan.*  $(1 \rightarrow 3)\text{-}\beta\text{-D-glucan}$  is a component of the cell wall of many fungi and has been proposed as a non-specific marker for invasive fungal infections. Using commercially available assays (colorimetric or kinetic), this method was evaluated to add another element to the diagnostic panel for invasive candidiasis. Sensitivity and specificity have been estimated to be 69.9 and 87.1%, respectively [47], as there are a high number of false positive results. Furthermore the specificity of the test is hampered by  $\beta$ -glucan contamination of certain antibiotics and materials, such as surgical gauzes, requiring further validation of the assay in the appropriate ICU setting before routine use can be recommended.

*Mannans and other markers.* Like glucans, mannans are major components of the *C. albicans* cell wall, but in contrast to glucans, mannans are non-covalently bound at the cell surface and are highly immunogenic [48]. The use of mannan antigenemia has been suggested to facilitate the diagnosis of invasive candidiasis; the most important limitation was rapid clearance of the antigen from the patient's sera [49]. To improve test performance, Sendid et al. suggested combining antigen and antibody detection. This possibility was explored using 162 serum samples selected from 63 patients with clinically proven candidiasis, compared with 98 control samples [50]. Combined analysis showed a sensitivity and specificity of 80 and 93%, respectively, suggesting a potential value in clinical practice. This test was also effective with non-*albicans Candida* species [51]. A second test based on the detection of beta-linked oligomannoses was subsequently developed and associated with the analysis of alpha-linked oligomannoses. The results showed a slight improvement in specificity to 95%, with a sensitivity of 90% [52]. The routine use of these tests could be valuable to increase early diagnosis, but does not, by itself, offer a definitive solution for diagnosis.

Other tests have also been evaluated. A *C. albicans* germ tube antibody (CAGTA) detection test was evaluated and compared to a standard test in a retrospective study [53]. Using 172 sera from 51 hematological and intensive care patients, *Candida albicans* IFA IgG test showed a sensitivity of 84.4% and a specificity of 94.7%, while the standard test showed a sensitivity of 78.1% and a specificity of 100%. Several other antigens expressed on the *C. albicans* cell wall have been recently identified. Specific antibodies directed toward the hyphal wall protein 1 (Hwp1) were developed and compared with CAGT antibodies [54]. Detection of these antigens needs additional clinical confirmation.

**Polymerase chain reaction.** The amplification of genomic sequences through polymerase chain reaction (PCR) testing has mostly been developed for invasive aspergillosis but is not routinely used in invasive candidiasis. A recent Japanese publication describes a novel PCR assay directed to five common *Candida* spp. [55]. A recent study evaluated prospectively, in non neutropenic ICU patients, three TaqMan-based polymerase chain reaction assays and the results showed a 90.9% sensitivity, and 100% specificity suggesting a potential usefulness of this method [56]. These results need further evaluation.

## Conclusion

ICU patients have many risk factors for developing invasive candidiasis or candidemia. For the specialist, the management of invasive candidiasis and candidemia, from diagnosis to selection of the therapeutic protocol, is often a challenge. Apart from cases with positive blood cultures or fluid/tissue biopsy, diagnosis is neither sensitive nor specific. It relies on many different factors including clinical and laboratory findings, but there is clearly a need for more specific diagnostic markers.

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from Astellas, MSD, Swedish Orphan, Pfizer, Schering Plough and Cephalon and a research grant from Pfizer, and Schering Plough. Georg Auzinger received honoraria from Pfizer for advisory activities. Elie Azoulay has received research grants from Pfizer France and honorarium for lectures from Pfizer and Gilead. Marcio Borges Sá received honoraries as a speaker from MSD, Cephalon, Pfizer, Astra-Zeneca and Wyeth. Elisabeth Johnson received speakers honoraria from Gilead, MSD, Pfizer and Schering Plough, consultant honoraria from Gilead, MSD, Pfizer and Schering-Plough and research funding from Gilead. Eckhard Müller was speaker and received consultation fees for Astra Zeneca, Sanofi-Aventis Germany, Bayer Vital, Biosyn Arzneimittel, Biotest AG, Fresenius Medical Care, MSD Sharp & Dohme, Novartis Pharma, Pfizer Pharma, Wyeth Pharma and participated to Advisory Boards of Caspofungin (Fa. MSD Sharp & Dohme GmbH; Merck, USA), Voriconazol (Fa. Pfizer Pharma GmbH), Anidulafungin (Fa. Pfizer, Germany; Fa. Pfizer, Europa), and Posaconazol (Fa. Essex Pharma). Coleman Rotstein received Grants/Research Supports from Astellas, Basilea, Johnson & Johnson, Merck, Pfizer, Wyeth; was consultant for Astellas, Bayer, Merck, Pfizer, Wyeth and belonged to the speakers Bureau of Bayer, Merck, Pfizer, Wyeth. Gabriele Sganga received honoraries as a speaker from Pfizer, Gilead and Wyeth. Mario Venditti received honoraries as a speaker from Angelini, Aventis, Bayer, Glaxo, Novartis, Pfizer, Wyeth and as a consultant from Novartis and Wyeth. Bart Jan Kullberg was consultant for Basilea, Novartis, and Pfizer. The other authors do not declare any conflict of interest.

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